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The inverse association between the apolipoprotein E ε4 allele and C-reactive protein levels is stronger in persons with obesity and diabetes

Lasse Melvaer Giil[1,2] | **Silja Hanseth**[1] | **Ognjen Bojovic**[3] | **Jan Erik Nordrehaug**[2] | **Per Magne Ueland**[4] | **Klaus Meyer**[4] | **Grethe S. Tell**[5]

[1]Neuro-SysMed, Department of Internal Medicine, Haraldsplass Deaconess Hospital, Bergen, Norway

[2]Department of Clinical Science, University of Bergen, Bergen, Norway

[3]Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway

[4]Bevital AS, Bergen, Norway

[5]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Correspondence
Lasse Melvaer Giil, Øvre Kråkenes 7A, Bønes 5152, Norway.
Email: lassegiil@gmail.com

Abstract

Background: C-reactive protein (CRP) is lower in patients who carry the apolipoprotein E *epsilon* 4 allele variant (APOEε4) of the *APOE* gene. This could however be explained by other factors observed in APOEε4 carriers, such as lower body mass index (BMI), possibly less diabetes and more use of statins, all associated with CRP concentrations.

Objectives: To assess the association between CRP and APOEε4 stratified by BMI, statin use and diabetes.

Methods: We included 2700 community-dwelling older adults from the Hordaland health study with genotyping of the APOE gene by a one-step polymerase chain reaction and CRP measured using immuno-MALDI-TOF MS. Differences in CRP concentrations by APOE (ε4 vs no ε4) were assessed using the Mann–Whitney *U* tests, also stratified by statin use, diabetes and BMI categories. Finally, we performed linear regression with log (CRP) as the outcome and APOEε4 together with statin use, diabetes, BMI and their respective interactions.

Results: CRP was higher in APOEε4 carriers irrespective of BMI, diabetes and statin use. In APOEε4 non-carriers, CRP was elevated with diabetes and obesity as expected. However, this was attenuated or even reversed in APOEε4 carriers. Such differences were not observed for statin use.

Conclusions: Statin use, obesity or diabetes did not confound the known association between the APOEε4 allele and lower CRP. Our data suggest that CRP is less responsive to inflammatory cues involved in diabetes and obesity in APOEε4 carriers. Epidemiological studies should take note of these relationships, as CRP, APOEε4, diabetes and obesity are both linked to neurodegenerative and cardiovascular disease.

1 | INTRODUCTION

Lower C-reactive protein (CRP) concentrations have been described by independent investigators in persons heterozygous or homozygous for the apolipoprotein E (APOE) ε4 allele variant of the *APOE* gene.[1–4] Both elevated CRP and APOEε4 portend adverse health outcomes such as neurodegenerative disease, cardiovascular disease and all-cause mortality, pointing to the potential importance of this association.[5–7] Furthermore, CRP correlates positively with body mass index (BMI),[8] which is reduced in persons with APOEε4.[9]

APOE is predominantly expressed in the liver and brain, although lower expression levels are also found in adipose tissue and immune cells.[10] The human *APOE* gene has three alleles, namely *epsilon* 2 (ε2), ε3, and ε4, where ε3 is the most frequent and ε2 the rarest.[11] Both hetero- and homozygous combinations occur.[12] The most well-established function of APOE is lipid transport,[13,14] and carriers of the APOEε4 allele have higher total cholesterol and LDL concentrations compared to ε3 and particularly ε2 carriers.[15] Besides its role in lipid transport, APOE plays an increasingly recognized role in both innate and adaptive immune responses[16] where APOEε4 is linked to a pro-inflammatory phenotype with a reduced ability to suppress inflammation.[16–18] Notably, APOEε4 is the major genetic risk factor for Alzheimer's disease.[19]

Despite the consistent association between lower CRP and APOEε4, the reasons for this association remain obscure.[2] It seems prudent to stratify by statin use, as APOEε4 carriers are more likely to be treated with statins,[20] and statins tend to lower CRP.[21] Persons with the APOEε4 allele variant have lower BMI,[9] and this is frequently observed in older individuals.[22] Further, obesity exacerbates the risk of Alzheimer's disease and exacerbates inflammation in persons with APOEε4.[23] Experimentally, insulin resistance induced in mice by feeding a high-fat diet has more severe consequences for cognition in APOEε4 mice.[24]

In this study, we aimed to determine whether the relationship between CRP and APOEε4 was confounded or modified by BMI, statin use or diabetes in community-dwelling older adults.

2 | MATERIALS AND METHODS

2.1 | Study participants

The Hordaland Health Study (HUSK) is a community-based interdisciplinary study whose overall aim is to investigate the epidemiology of chronic disease and how these are affected by lifestyle risk factors and blood-based biomarkers. Participants were invited based on their year of birth and place of residence in a previous survey in 1992–93 (The Hordaland Homocysteine study) where all residents in a specific geographical region born 1925–27 had been invited. The place of residence included Bergen and three surrounding municipalities. In 1997–99, all participants were re-invited for a new survey, and this time, also blood sampling (The HUSK study). Although several age groups were involved, this study focuses on the subcohort of older adults who were born 1925–27 and participated in HUSK 1997–99, when they were 71–74 years old. Of the 4338 who were invited, 3328 (76.7%) agreed to participate.

The letter of invitation included a self-report questionnaire on education, smoking habits, use of medications, physical exercise, alcohol consumption and history of angina pectoris, myocardial infarction, stroke, phlebitis, thrombosis and hypertension. Additionally, the participants answered a 7-item subscale for depression from the Hospital Anxiety and Depression Scale and a comprehensive food-frequency questionnaire. During the clinical examination, study nurses collected blood samples, recorded height, weight, waist circumference, upper-arm circumference and blood pressure.[25] For this study, 2700 participants were included who had APOE genotypes, CRP concentrations and BMI measured.

2.2 | Measures

2.2.1 | Body mass index

Height (to the nearest 1 cm) and weight (to the nearest 0.5 kg) of participants (wearing light clothing and no shoes) were measured by trained study staff according to standard protocols. BMI was calculated as weight in kilograms divided by the square of height in meters.[26] Participants with a BMI > 30 were considered obese.

2.2.2 | Diabetes and statin use

Diabetes was assessed using a questionnaire with the item "have you, or have you had diabetes" and items concerning antidiabetic treatments. Participants answering affirmative were classified according to the type of antidiabetic treatment as (1) un-medicated diabetes (no use of antidiabetic drugs), (2) orally treated diabetes (with or without the use of insulin) and (3) insulin-treated diabetes (and no oral antidiabetic agents). Antidiabetic medications and statin use were classified using the 1997 anatomical therapeutic chemical classification system. This included all drugs classified as A10A (insulins), A10B (for example

metformin, glibenclamide, chlorpropramide, and acarbose), and AX2 (glimeperide). The sensitivity and specificity of self-reported diabetes range between 58.5%–70.8% and 95.6%–96.8%, respectively.[27] Additionally, plasma glucose was measured and used to make a diagnosis of diabetes in cases with high non-fasting plasma glucose, as previously described.[28]

2.3 | Biomarkers and APOE genotyping

CRP was measured using an immuno-MALDI-TOF MS approach, as previously described.[29] The limit of detection for CRP was 0.2 μg/mL, and within- and between-day coefficients of variation were 5.5–8.4 and 7.0–11.7, respectively. The biochemical analyses were performed at the laboratory of Bevital AS (Bergen, Norway, https://bevital.no). Genotyping of the *APOE* gene was carried out using a one-step polymerase chain reaction, as previously described.[30,31]

2.4 | Statistics

Normally distributed continuous variables were described by their means and standard deviations (SDs), whereas continuous variables that deviated from normality were described by their medians and interquartile ranges (IQRs). In the case of normality, differences in continuous variables between two groups were tested using *t*-tests, and Mann–Whitney *U* tests (MWUT) with deviation from normality (Kruskal–Wallis test with more than two groups). Differences between groups in categorical variables were tested using the Pearson chi-square test and correlation involving categorical variables was determined using tetrachoric correlations.

The distribution of CRP was positively skewed and thus log transformation was performed after adding a constant of one (Figure S1) prior to any parametric analysis. However, QQ plots and histograms revealed that although the log (CRP + 1) distribution was closer to normality, it was still somewhat positively skewed. More complex power transformations did not perform better. Thus, robust analyses using MWUT were used for most of the study. To facilitate the interpretation of this non-parametric test, we report the Mann–Whitney effect size (MWES), equivalent to the Area Under the Curve (AUC). It reports the probability that a value in group one is higher than in group zero where no effect is 0.5 (50%), a positive effect could be 0.6 (60%) and a negative effect 0.4 (40%).[32] As the MWUT is a univariate analysis, we performed linear regression for multivariable analysis with standardized log (CRP + 1) as the outcome and APOEε4 as the predictor with and without adjustment for obesity, diabetes and statin use. Due to the residual positive skewness of log (CRP + 1) and thus of the residuals from the model, we estimated robust standard errors using the Huber/White sandwich estimator.[33,34]

Assessment of effect modification was performed qualitatively by gauging the AUC for APOEε4 on CRP stratified by subgroups and formally by introducing interactions in linear regression with CRP as the outcome. The linear regressions were estimated as $\log(\mathrm{CRP}+1)=\beta_0+\beta_1$ APOEε4 $+\beta_2$ Variable $+\ \beta_3$ APOEε4*Variable $+\ \varepsilon$. Here, β_0 represents the intercept and ε the error (or residuals). We ran three separate linear regression models where "Variable" was either obesity, diabetes or statin use. We were unable to statistically adjust for all three two-way interactions with APOEε4 as, for example, only nine persons with APOEε4 had both diabetes and obesity. We calculated adjusted *P*-values, *q*-values (Q (Stata package: qqvalue, method: Simes)), using the Benjamini–Hochberg approach accepting a false discovery rate (FDR) of 0.05.[35] The *m* number of tests were all test involving differences according to the presence of allele variation in the *APOE* gene. A *q*-value <0.05 was thus considered statistically significant. For all tests included in the total of tests used to estimate the FDR, *q*-values are listed in the results. All analyses were conducted in Stata 16. StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

3 | RESULTS

3.1 | Study participants of the Hordaland Health Study, Norway

Table 1 lists the descriptive statistics. The study participants were invited according to their year of birth and thus the age range was narrow, spanning from 71 to 74 years of age. There were no differences in age according to the presence of at least one APOEε4 allele. About 55–56 per cent of the participants were women, irrespective of the presence of the APOEε4 allele. The mean BMI was 26.1 (SD 3.9) kg/m^2 and was slightly higher in participants without the APOEε4 allele (mean 26.2 SD 3.9) compared to those with the allele (mean 25.8, SD 3.8), $Q=0.017$. Overall, 13.6% were obese (BMI ≥30 kg/m^2), 12.7% with the APOEε4 allele and 14.0% without the ε4 allele, although these differences were not statistically significant. Fewer study participants with the APOEε4 allele had diabetes but this did not reach statistical significance (overall 6.6%, no APOEε4 7.0%, APOEε4 5.5%, $Q=0.072$). Overall, 12.6% of the participants were using statins; 11.3% of APOEε4 non-carriers and 15.7% of APOEε4 carriers ($Q=0.002$).

TABLE 1 Study participants overall an according to one or more APOEε4 alleles.

	All	No APOEε4	APOEε4		
	N **= 2700**	***n*** **= 1858**	***n*** **= 842**	***P*-value**	***q*-Value[c]**
Age, years					
71, *n* (%)	412 (15.3)	277 (14.9)	135 (16.0)		
72, *n* (%)	930 (31.4)	647 (34.8)	283 (33.6)		
73, *n* (%)	909 (33.7)	633 (34.1)	276 (32.8)		
74, *n* (%)	449 (16.6)	301 (16.2)	148 (17.6)	.643[b]	
Women, *n* (%)	1519 (56.3)	1055 (56.8)	464 (55.1)	.416[b]	
BMI kg/m^2, m ± SD	26.1 ± 3.9	26.2 ± 3.9	25.8 ± 3.7		0.017*,[d]
Obese, *n* (%)[a]	367 (13.6)	260 (14.0)	107 (12.7)		0.428[b]
Diabetes, *n* (%)	177 (6.6)	130 (7.0)	42 (5.0)		0.072[b]
Using statins, *n* (%)	341 (12.6)	209 (11.3)	132 (15.7)		0.002*,[b]
CRP, μg/mL, Mdn ± IQR	2.17 ± 3.40	2.41 ± 3.60	1.73 ± 2.85		<0.001**,[e]

Abbreviations: APOEε4, apolipoprotein E gene epsilon 4 allele (one or two); BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; m, mean; Mdn, median; *N*, number of participants; SD, standard deviation.

[a]BMI ≥30.

[b]Pearson chi-square test.

[c]Multiple-comparisons adjusted *q*-values were estimated from all relevant study *P*-values by the Benjamini-Hochberg False Discovery rate (see statistics for details).

[d]Student's *t*-test.

[e]Mann–Whitney *U* test.

*Q < 0.05.; **Q < 0.001.

The median (Mdn) CRP concentration was 2.17 μg/mL (IQR 3.40). The tetrachoric correlation between diabetes and obesity was 0.26 ($P < .001$), diabetes and statin use 0.20 ($P < .001$) and obesity and statin use 0.02 ($P = .612$).

3.2 | CRP concentrations according to *APOE* gene

CRP was lower in participants with the APOEε4 allele (Mdn 1.73 μg/mL, IQR 2.85) than without the allele (Mdn 2.4 μg/mL, 1 IQR 3.60, see Table 1) and this difference was significant (AUC 0.41, $Q < 0.001$, see Table 4). The median difference in CRP concentrations was 0.7 μg/mL (Table 4). This corresponded to a standardized β of −0.30 in unadjusted linear regression and −0.29 in linear regression adjusted for diabetes, statin use and obesity (Table 2).

Assessing all alleles, there was significant variation in CRP according to *APOE* alleles (Kruskal–Wallis $P < .001$), see Table 3 for a summary. Using the most frequent ε3ε3 allele as a reference, only participants with the ε3ε4 allele had significantly lower CRP (MWUT $Q < 0.001$). However, compared to a median CRP of 2.41 μg/mL (IQR 3.70) in participants with the ε3ε3 allele, all groups with at least one ε4 allele had relatively similarly lower CRP concentrations (ε4ε4 Mdn 1.61 IQR 3.13, ε3ε4 Mdn 1.72 IQR 2.82, ε2ε4 Mdn 1.81 IQR 3.51). The lowest CRP concentrations observed in participants homozygous for *epsilon* four. Accordingly, the concentration was 0.80, 0.69 and 0.60 μg/mL lower in ε4ε4, ε3ε4 and ε2ε4 relative to participants homozygous for *epsilon* three with a corresponding AUC of 0.38, 0.41, and 0.44, respectively (Table 2). Of note, the sample size was low for some alleles (ε2ε4: 67, ε4ε4: 83, ε2ε2: 9) and thus a "at least one ε4 allele" was used for further analyses (ε2ε4, ε3ε4, and ε4ε4).

3.3 | Effect modification of the APOEε4–CRP association by obesity and diabetes

Participants with the APOEε4 allele had lower CRP than persons without APOEε4. This difference was observed to a higher degree in persons with higher BMI. According to whether a person was underweight (BMI < 18.5), normal (18.5–24.9), pre-obese (25–29.9), obese class I (30–34.9) or obese classes II–III (BMI ≥ 35), the median CRP was 0.1, 1.3, 2.0, 2.3 and 3.3 μg/mL lower in APOEε4 carriers compared to non-carriers with the respective AUC 0.47, 0.41, 0.42, 0.36 and 0.30 (Table 4). This interaction (APOEε4*Obese [BMI< or ≥30]) was significant using ($Q = 0.047$) linear regression (Figure 1 and please see Table 5 for details).

Similarly, the median CRP was 0.7 μg/mL lower in APOEε4 carriers compared to non-carriers without

TABLE 2 C-reactive protein concentrations by APOEε4, obesity, diabetes and statin use.

	Univariate analyses			Multivariate analysis		
	β[a]	95% CI	q-value[b]	β[a]	95% CI	q-value[b]
APOEε4	−0.30	−0.38, −0.22	<0.001	−0.29	−0.37, 0.21	<0.001
Obesity	0.50	0.40, 0.61	<0.001	0.49	0.40, 0.59	<0.001
Diabetes	0.14	−0.03, 0.41	0.105	0.05	−0.11, 0.22	0.517
Statin use	−0.10	−0.21, 0.01	0.065	−0.09	−0.19, 0.02	0.118

Abbreviations: *APOE, apolipoprotein E gene*; CI, confidence interval.

[a]Linear regression with Huber/White sandwich standard errors.[34] CRP was standardized prior to analysis so that the mean was zero and one standard deviation one (z-score).

[b]Multiple-comparisons adjusted q-values were estimated from all relevant study P-values by the Benjamini–Hochberg False Discovery rate (see statistics for details).

TABLE 3 C-reactive protein concentrations by APOE genotypes.

APOE	*N*	CRP	Diff. from ε3ε3[a]	AUC	q-value[b,c]
ε2ε2	9	2.04 ± 1.98	−0.37	0.45	0.626
ε2ε3	260	2.40 ± 3.53	−0.01	0.49	0.683
ε3ε3	1589	2.41 ± 3.70	Reference		Reference
ε2ε4	67	1.81 ± 3.51	−0.60	0.44	0.148
ε3ε4	692	1.72 ± 2.82	−0.69	0.41	<0.001**
ε4ε4	83	1.61 ± 3.13	−0.80	0.38	0.114

Abbreviations: *APOE, apolipoprotein E gene*; AUC, area under the curve; CRP, C-reactive protein (μg/mL); ε, epsilon, *N*, number of participants.

[a]Median CRP with other alleles – median CRP in APOEε3ε3 carriers.

[b]Mann–Whitney U test (Kruskal–Wallis testing CRP variation in all groups: $P < .001$).

[c]Multiple-comparisons adjusted q-values were estimated from all relevant study P-values by the Benjamini-Hochberg False Discovery rate (see statistics for details).

diabetes (AUC 0.42) and 1.5 μg/mL lower in APOEε4 carriers compared to non-carriers with diabetes (AUC 0.31), see Table 4. The APOEε4*diabetes interaction term was also significant using linear regression ($Q = 0.048$, see Table 5 and Figure 1). Notably, CRP was the lowest in APOEε4 carriers with diabetes and the highest in participants without APOEε4 but with diabetes (Table 4). There was no effect modification by statin use (Tables 4, 5 and Figure 1).

4 | DISCUSSION

In this study on community-dwelling older adults we confirm the association between the ε4 allele of the *APOE* gene and lower CRP concentrations, also after stratifying by the use of statins (more frequent among APOEε4 carriers) and for obesity and diabetes. APOEε4 carriers had a slightly but significantly lower BMI. Expanding on previous results,[1–4] we find that the tendency for lower CRP among APOEε4 carriers is more pronounced in persons with higher BMI or diabetes. This suggest that CRP may be less responsive to underlying cues of chronic inflammation in APOEε4 carriers.

In our study, we observed that CRP concentrations were lower in participants with the APOEε4 allele, independent of statin use, diabetes and obesity where statin use is an important additional analysis adding on previous works.[1–4] The tendency for CRP to be higher in obesity and diabetes was less pronounced in APOEε4 carriers than in non-carriers. Further, the higher CRP in diabetic compared to non-diabetic persons[36–38] was not observed in APOEε4 and was indeed reversed. The association between APOEε4 and the risk of diabetes remains controversial.[39] In our data, without adjusting for BMI, APOEε4 carriers had marginally less diabetes compared to non-carriers, although this was not significant following adjustment for multiple comparisons and would likely be less significant in an adjusted analysis.

A study by März and associates have addressed the possibility that the lower CRP in APOEe4 carriers is influenced by the mevalonate pathway in the liver.[1] This is based on the observation that the mevalonate pathway is

TABLE 4 C-reactive protein according to APOEε4 by BMI, diabetes and statin use.

	No APOEε4	APOEε4			
	CRP	CRP	Diff.	AUC	*q*-Value[j,k]
Overall	2.4 ± 3.6	1.7 ± 2.9	−0.7	0.41	<0.001**
BMI class					
Underweight[a]	1.0 ± 1.8	0.9 ± 6.0	−0.1	0.47	0.760
Normal[b]	1.8 ± 2.9	1.3 ± 2.3	−0.5	0.41	<0.001**
Pre-obese[c]	2.5 ± 3.4	2.0 ± 3.0	−0.5	0.42	<0.001**
Obese class I[d]	3.7 ± 5.7	2.3 ± 2.7	−1.4	0.36	<0.001**
Obese class II–III[e]	5.5 ± 5.5	3.3 ± 3.5	−2.2	0.30	0.031*
Diabetes					
No[f]	2.4 ± 3.5	1.7 ± 2.9	−0.7	0.42	<0.001**
Yes[g]	3.0 ± 5.9	1.5 ± 2.3	−1.5	0.31	<0.001**
Statin use					
No[h]	2.4 ± 3.4	1.8 ± 3.1	−0.6	0.42	<0.001**
Yes[i]	2.3 ± 3.4	1.5 ± 1.8	−0.8	0.37	<0.001**

Abbreviations: APOEε4, epsilon 4 alleles of the apolipoprotein E gene; AUC, area under the curve; BMI, body mass index; CRP, C-reactive protein (median concentrations in μg/mL ± interquartile range); Diff., APOEε4 group median – no APOEε4 group median; IQR, interquartile range; Mdn, median.

[a]BMI <18.5, $n = 36$.

[b]BMI 18.5–24.9, $n = 1061$.

[c]BMI 25–29.9, $n = 1236$.

[d]BMI 30 to 34.9, $n = 299$.

[e]BMI ≥35, $N = 68$.

[f]$n = 2487$.

[g]$n = 177$.

[h]$n = 2359$.

[i]$n = 341$.

[j]Mann–Whitney *U* test.

[k]Multiple comparisons adjusted *P*-values (see statistics).

downregulated in APOEε4 carriers compared to APOEε2,[1] combined with the finding that statins, which inhibit the mevalonate pathway through HMG–CoA, not only reduce cholesterol but also CRP.[40–42] However, in our study, statins did not modify the association between APOEε4 and CRP. Further, APOEε2 carriers had similar CRP concentrations to APOEε3 carriers. Thus, our data suggest an altered CRP response to metabolic inflammation in obesity and diabetes rather than changes in the melavonate pathway.

The relationship between APOEε4 and CRP has implications for our understanding of the risk associated with CRP in epidemiological studies on several levels. First, it has already been shown that CRP might be protective with regards to cognitive function in persons carrying APOEε4[3] but associated with risk in persons without APOEε4. For all outcomes where both CRP and APOEε4 are associated with the risk of that outcome, such as all-cause mortality, cardiovascular disease and neurodegenerative disorder, several dilemmas arise. As APOEε4 causes CRP lowering and not vice versa, it is not a confounding relationship that can be easily resolved by adjustment. Further, our study suggests that if adjustment for BMI and diabetes is to be performed for an end-point associated with CRP, this confounding adjustment might also be different according to the presence of APOEε4. Thus, we would suggest carefully considering the analytic approach when assessing the predictive value of CRP in relation to allele variation in the *APOE* gene, obesity and diabetes. In clinical practice, median differences of 0.8 μg/mL (ε3ε3 vs ε4ε4) could be relevant when assessing high-sensitivity CRP with cut-offs as low as 3 or 5 μg/mL,[43] and more so with obesity (Tables 4 and 5).

Our study has limitations. More extensive immune and metabolic profiling of markers linked to obesity and diabetes might have been revealing. For example, the correlation of CRP with biomarkers of insulin resistance and adipokines could have been informative, as could interleukin-6, which induces CRP synthesis. Further, the subgroups of patients with obesity and diabetes were small, making more detailed analyses complicated and we did

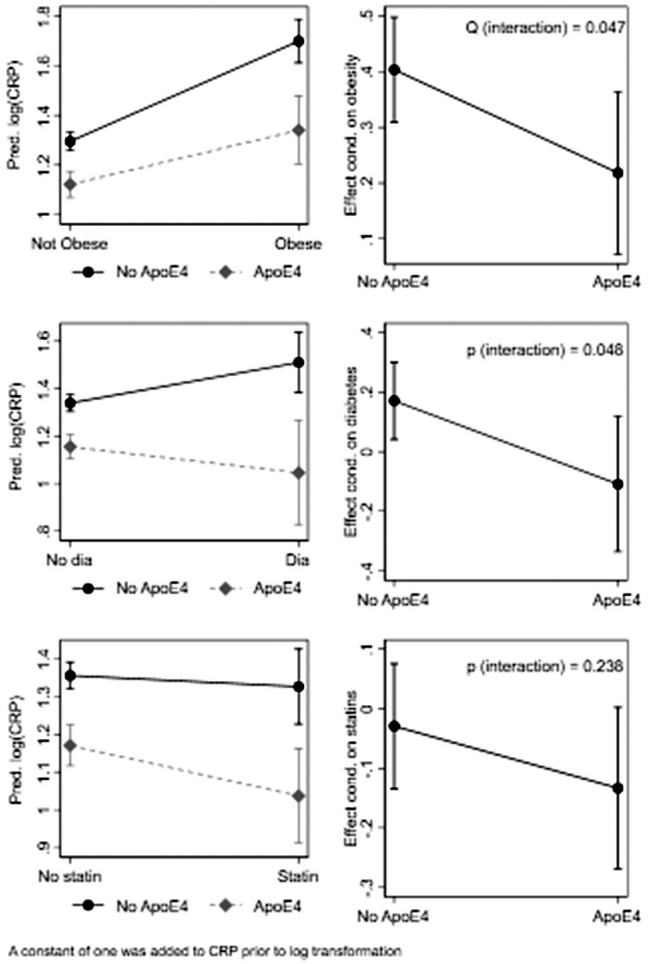

FIGURE 1 Effect modification of obesity, diabetes and statins on the APOEε4-CRP association. Linear regression with CRP as the outcome, and one or two APOEε4 alleles vs other alleles as the predictor, together with either obesity (first row), diabetes (second row) or statins (third row) with the corresponding interaction. The left-hand side displays the effect size by group and the right-hand side displays the conditional effect, meaning the difference in effect size of APOEε4 on CRP due to the presence of obesity, diabetes or statin use. ApoE4, epsilon 4 alleles of the apolipoprotein gene; Dia, diabetes.

not have statistical power to adjust the interaction analyses for other interactions. CRP did not follow a log-normal distribution and thus there are some risks of bias using linear regression although sample size should to a large degree protect against highly influential cases. Further, a sensitivity analysis (data not shown) supported this conclusion.

In conclusion, we demonstrate that CRP is lower in community-dwelling older adults who are carriers of the APOEε4 allele variant of the *APOE* gene independent of the lower BMI, diabetes and more frequent use of statins in persons with this variant. The tendency for CRP to be higher in persons with a higher BMI or diabetes was less pronounced in APOEε4 carriers compared to non-carriers,

TABLE 5 Effect modification of the CRP–APOEε4 association by obesity and diabetes.[a]

	β	95% CI	*q*-Value[b]
Obese	0.55	0.42, 0.68	<0.001
APOEε4	−0.24	−0.32, −0.15	<0.001
Obese* APOEε4	−0.25	−0.39, −0.04	0.047
Diabetes	0.23	0.05, 0.42	0.025
APOEε4	−0.25	−0.33, −0.17	<0.001
Diabetes* APOEε4	−0.38	−0.72, −0.04	0.048
Statins	−0.04	−0.18, 0.10	0.626
APOEε4	−0.25	−0.34, −0.16	<0.001
Statins* APOEε4	−0.14	−0.36, 0.07	0.238

Abbreviations: *APOE, apolipoprotein E gene*; CI, confidence interval; Obese, body-mass index < or ≥30.

[a]Three separate linear regression models with Huber/White sandwich standard errors.[34] CRP was standardized prior to analysis so that the mean was zero and one standard deviation one (*z*-score).

[b]Multiple comparisons adjusted *q*-values were estimated from all relevant study *P*-values by the Benjamini–Hochberg False Discovery rate (see statistics for details).

suggesting that CRP responds less to underlying dysmetabolism related to insulin resistance and inflammation in APOEε4 carriers.

AUTHOR CONTRIBUTIONS

L.M.G. contributed to the conception of the study, data analysis, interpretation of data, gave final approval to the submitted manuscript and agreed to be accountable to all aspects of the work. S.H. contributed to the interpretation of data, critically revised the manuscript, gave final approval to the submitted manuscript and agreed to be accountable to all aspects of the work. O.B. contributed to the interpretation and analysis of the data, critically revised the manuscript, gave final approval to the submitted manuscript and agreed to be accountable to all aspects of the work. J.E.N. contributed to the conception of the study, interpretation of data, gave final approval to the submitted manuscript and agreed to be accountable to all aspects of the work. P.M.U. contributed to the conception of the study, data acquisition (CRP measurement), interpretation of data, gave final approval to the submitted manuscript and agreed to be accountable for all aspects of the work. K.M. contributed to data acquisition (CRP measurement), interpretation of data, gave final approval to the submitted manuscript and agreed to be accountable for all aspects of the work. G.S.T. contributed to the conception of the study, data handling, and interpretation of

data, gave final approval to the submitted manuscript and agreed to be accountable to all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors report no disclosures.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Regional Committee for Medical and Health Research Ethics Western Norway approved the study protocol (REC number: 2016/2208) and all participants provided signed informed consent.

ORCID

Lasse Melvaer Giil https://orcid.org/0000-0003-3520-7530

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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