APOE4

- Overview
- Evaluation
- Implications
  - Risk Management for APOE4 carriers
  - APOE4 & Paleo
- Discussion
  - General Reading
  - Cholesterol & Cardiovascular Disease
  - APOE4, Saturated Fat & LDL-C
  - APOE4, Saturated Fat & LDL Particle Size
  - APOE4, MUFAS, Carbohydrates & LDL-C/P/Size
  - APOE4 & Dietary Cholesterol
  - APOE4, Fish Oil & LDL / HDL
  - APOE4, Saturated Fat & CRP
  - APOE4 & Exercise
  - APOE4 & Heavy Metal Toxicity
  - APOE4 & Alcohol
  - APOE4, Quercetin & HDL
  - Lack of evidence

Overview

APOE is the gene responsible for coding Apolipoprotein E, a key player in our lipid metabolism. APOE comes in 3 significant variants: APOE2, APOE3 & APOE4. Since we have two copies of each gene, there are six permutations we can carry: APOE 2/2, 2/3, 2/4, 3/3, 3/4 & 4/4.

There are numerous implications of carrying one or two copies of the E4 variant to our health, particularly concerning saturated fat, fish oil, and heavy metal detox.

APOE4 is famous for its association with a significantly higher risk for Alzheimer's disease, but numerous other conditions have been linked to it, including other forms of dementia and cardiovascular disease (CVD).

In the general population in Europe / USA, roughly 75% of people are APOE3/3, and the APOE3/4 or 4/4 variants are present in 20 - 25 % of us.

Evaluation

There are multiple, mostly adverse effects associated with carrying one or two copies of APOE4

Consuming saturated fatty acids (SFAs) can

- substantially raise LDL particle count (LDL-P) which is the major risk factor in our cholesterol profile for CVD
- raise c-reactive protein (CRP), which is a risk factor for CVD
- increase LDL particle size, which in itself is cardioprotective. However, this is outweighed by the rise in LDL-P
- substantially raise LDL cholesterol (LDL-C) which is not correlated with CVD

Consuming monounsaturated fatty acids (MUFAs) like in olive oil, avocados, etc. can

- decrease LDL-P which is very cardioprotective
- decrease LDL particle size, which is a risk factor for CVD. However, this is outweighed by the decrease in LDL-P
- decrease LDL-C which is not correlated with CVD

Consuming DHA & EPA (e.g., from fish oil) above a certain, quite low level produces significant adverse health effects

Consuming DHA can

- substantially increase LDL-P (bad)
- reduce LDL particle size (bad)
- significantly increase LDL-C (irrelevant)

Consuming EPA can

- lower HDL-C (bad)
• lower HDL-P (bad)

• Consuming alcohol can increase triglycerides
• Consuming small amounts of alcohol has no cardioprotective effect (only works for APOE2)
• Impaired heavy metal detoxification capabilities particularly for lead and mercury
• Increased susceptibility to the detrimental effects of a sedentary lifestyle regarding increased Alzheimers Disease (AD) risk
• A substantially higher risk of late-onset AD

Implications

Regarding the high probability to be an APOE4 carrier and it's far-reaching consequences we think that everybody should have their APOE status checked (e.g., using 23andme.com).

The good news is that once we know if we carry APOE4 we can modify our diet and lifestyle accordingly and counter the risk factors that come with this genetic variant.

Risk Management for APOE4 carriers

• APOE4 carriers should carefully monitor their cholesterol profile, especially LDL-P measured with NMR which is strongly correlated with increased CVD risk
• APOE4 carriers usually do better on a diet very low in SFAs, low in PUFAs, low but sufficient protein with a focus on moderate amounts of MUFAs and low GI carbohydrates

• Keep saturated fat intake as low as possible
• Avoid palm oil, coconut oil, coconut milk, butter and ghee
• Avoid bulletproof coffee
• Consume nuts with care. Of all nuts, almonds are the lowest in SFAs (3.7%) - Nuts in Comparison
• Unfortunately, dark chocolate and raw cacao nibs are high in saturated fat (up to 40%)
• 50% of fat in animal meat is saturated
• Avoid fatty animal meats like bacon
• If consuming animal meat, go for the lowest fat option like lean chicken
• If possible, go for fish or crustaceans which are low in saturated fat
• Limit EHA + DHA to a max. of 500mg /day which would be appr. 2g of fish oil
• If possible, avoid fish oil to lower the risk of consuming oxidized fat
• consume EHA & DHA in their natural form by eating fatty fish
• Keep intake of PUFAs on the lower side. Unfortunately, there is not much research on the effect on PUFAs in general for APOE4, but the research on EHA and DHA (both PUFAs) shows that more might not be better
• Good sources of MUFAs are avocados and olive oil
• Good sources of low GI carbs are lentils & sweet potatoes

With all general guidelines and medical research on APOE4 and nutrition, we should keep in mind that the reaction of our metabolism to dietary changes is highly individual. Determining the right balance of macronutrients, especially balancing MUFAs and carbohydrates for an optimal cholesterol profile requires personal experimentation and frequent retesting

• Take care to get appropriate amounts of exercise to counter the adverse effects of a sedentary lifestyle for APOE4 carriers

It is hard to say what a sufficient amount of training should be since all studies are just correlating the amount of physical activity (mostly self-reported) and the occurrence of AD. We think that three times of vigorous exercise a week (45 min) in combination with as much physical activity as possible such as daily walking, using a standing/walking desk, regular yoga and stretching is a good place to start

• closely monitor levels of mercury, lead and heavy metal toxicity in general
• take appropriate measures to detox mercury and other heavy metals

APOE4 & Paleo
Paleo style diets often emphasize liberally consuming saturated fatty acids (SFAs) from coconut oil, palm oil, butter, ghee, fatty meat, dark chocolate, etc. which are nowadays deemed safe for consumption.

If we view the population as a statistical whole, switching from an unhealthy diet to a clean paleo diet even if it is high in SFAs on average lowers the risk for CVD. Unfortunately, if we break down the numbers according to APOE status, this remains only true for those of us that don't carry the APOE4 gene.

For carriers of the APOE4 gene consuming saturated fatty acids can substantially raise the risk of CVD

Unfortunately, the wider Paleo community has not yet realized this critical fact and still promotes the consumption of SFAs to everyone, potentially putting people in harm's way.

However, Paleo at its core is not about SFAs but about eating clean and healthy food that our bodies were designed for by evolution. We can easily do a low SFA variant of Paleo.

Discussion

General Reading

A collection of documents that give a rough overview of the topic. However, they are sometimes not entirely accurate or specific in every detail.

High cholesterol and the APOE gene - gbhealthwatch.com

Reducing Risk For APOE4 Genotypes - youniquegenomics 2014

A brief overview and some links to useful studies

The Perfect Gene Diet: Use Your Body's Own APO E Gene to Treat High Cholesterol, Weight Problems, Heart Disease, Alzheimer's...and More! - amazon.com

Gives an overview of the issues one is facing with APOE4. However, the nutritional advice is a bit dated, and several of the claims she makes about APOE4 are not backed by science. (like the connection between APOE, muscle fiber type, and exercise). In general, the author does not supply scientific backup for the claims she is making — not very scientific, which may be due to her background as a nurse and not a scientist.

Cholesterol & Cardiovascular Disease

Since APOE has such a strong impact on our lipid metabolism, cholesterol profile and our CVD risk profile we have added this section for the interested.

The straight dope on cholesterol - Peter Attia

Probably the best introduction to cholesterol and the real significance of the individual markers in our cholesterol profile for CVD

APOE4, Saturated Fat & LDL-C

There is a correlation between APOE4, the amount of fat of saturated consumed and LDL-C. It looks like it is primarily the amount of saturated fat that drives total LDL and not MUFAs and PUFAs.

Why Does LDL Skyrocket When Doing Paleo? It could be ApoE - paleohacks.com

For the remaining 35% of the population, about 25% include type 4; e.g., 4-3, 3-4 or 4-4. These people’s LDL may skyrocket on a fat-heavy diet, especially saturated fat. And the LDL increase may be in the form of Pattern B (the small, dense ones that are supposed to be dangerous). These people tend to thrive on a low-fat diet, as their LDL would be managed best by keeping saturated fat low. For example, eating coconut oil might increase their LDL significantly, while it would not affect the Apo E 3-3 type. Fish oil could also increase the LDL of these people.

Interview with Joe D. Goldstrich, MD - Goldstrich 2011

People that carry the 4 allele, either one occurrence of it as in 3,4 or in double occurrence as in 4,4, those folks seem to get huge increases in their LDL, especially their small dense LDL, when they eat fat, especially saturated fat, but all fat seems to play a role.
The maximum amount of fish oil that someone who’s an Apo E4 carrier should take in my opinion is 500 mg of EPA plus DHA.

Anecdotal example of highly elevated LDL on saturated fat consumption due to bulletproof diet - bayesianinvestor.com

Saturated Fat: Healthful, Harmful, or Somewhere In Between? - thepaleomom.com

Even though saturated fat has pretty much been redeemed on the heart disease front, there’s one subset of the population that might genuinely need to limit their intake for the sake of heart-health: ApoE4 carriers!

Gene-nutrient interactions: dietary behavior associated with high coronary heart disease risk particularly affects serum LDL cholesterol in apolipoprotein E epsilon4-carrying free-living individuals - Loktionov 2000

In the e4-expressing subjects:

- Alcohol intake was positively correlated with triacylglycerol concentration.
- Positive correlations between diet and blood lipids were found for total fat intake and total and LDL cholesterol and for saturated fat intake and total and LDL cholesterol.
- Monounsaturated fat consumption was also positively correlated with total and LDL cholesterol concentrations, whereas it was inversely related with HDL cholesterol. There were also inverse associations between HDL cholesterol and polyunsaturated fat. However, when energy was controlled for by expressing intakes as a percentage of total energy, only the relation between saturated fat and LDL cholesterol remained significant.

APOE4, Saturated Fat & LDL Particle Size

The increase of LDL-C observed for APOE4 when consuming SFAs seems to result from increasing both the particle size of the individual particles and LDL particle count (LDL-P).

APOE4, MUFAS, Carbohydrates & LDL-C/P/Size

There is evidence that MUFAS decrease LDL particle size APOE4 carriers but also decrease LDL-P.

It is important to realize that LDL-P is the single most relevant CVD risk factor in our whole cholesterol profile. Therefore a higher amount of MUFAs might be better since it produces a more significant decrease in LDL-P for APOE4 carriers.

Unfortunately, we could not find any further studies that examine diets with even higher amounts of MUFAs than Moreno (below) and whether they improve the cholesterol profile even further. This probably is very individual anyhow, and studies can only give us a general hint on ways to try to optimize our diet to lower our CVD risk factors. On a personal level, nothing saves us from experimenting with different macro ratios and retesting frequently.

Apolipoprotein E isoform phenotype and LDL subclass response to a reduced-fat diet - Dreon 1994

This study finds that a low-fat diet will reduce LDL size and the decrease in size is bigger for APOE 3/4 & 4/4 than 3/3 and that ApoB, however, remained unchanged.

The Effect of Dietary Fat on LDL Size Is Influenced by Apolipoprotein E Genotype in Healthy Subjects - Moreno 2004

Even though a MUFA-rich diet increases LDL size compared with a CHO-rich diet, this effect is dependent on apoE genotypes. Thus, the replacement of a CHO diet by a MUFA diet increases LDL size in apoE 3/3, whereas it decreases it in apoE 4/3 subjects.
Moreno shows that for APOE3/4 a MUFA based diet produces a greater increase in HDL-C and a reduction in Triglycerides, LDL-C, and ApoB (a proxy for LDL-P) than a Carbohydrate (CHO) based diet.

<table>
<thead>
<tr>
<th>SFA</th>
<th>MUFA</th>
<th>PUFA</th>
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<td>12%</td>
<td>6%</td>
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<tr>
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<td>12%</td>
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<tr>
<td>10%</td>
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<th>HDL-C</th>
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<td>0.52 ± 0.15c</td>
<td>25.69 ± 0.31</td>
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**APOE4 & Dietary Cholesterol**

APOE4 carriers seem to have a higher uptake of dietary cholesterol than APOE 2 & 3

*Apolipoprotein E polymorphism and atherosclerosis - Davignon 1988*

> When the response of an E3/3 phenotype was used for comparison, individuals with an E3/2 phenotype had a lower rate of intestinal absorption of cholesterol, while those with an E4/3 phenotype had a higher rate

**APOE4, Fish Oil & LDL / HDL**

There is evidence that for APOE4 carriers the DHA in fish oil can substantially increase LDL-C, reduce LDL particle size, increase LDL-P and EPA can lower HDL-C and HDL-P.

A daily intake of a total of 500 mg of EHA & DPA for APOE4 carriers is probably safe.

*PubMed: apoe4 ldl (omega-3 or fish oil or dha or epa) not mice*
*PubMed: apoe4 (omega-3 or fish oil or dha or epa) not mice*
*Google Scholar: apoe4 ldl omega-3 OR "fish oil" OR dha OR epa -mice*
*SNPedia: 4.2 Omega-3 (n-3) fatty acids*

*ApoE Polymorphism and Fish Oil Supplementation in Subjects With an Atherogenic Lipoprotein Phenotype - Minihane 2000*

> In apoE4 individuals, a significant increase in total cholesterol and a trend toward a reduction in HDL-C relative to the common homozygous E3/E3 profile was evident.

*Contribution of apolipoprotein E genotype and docosahexaenoic acid to the LDL-cholesterol response to fish oil - Olano-Martin 2009*
High dose DHA supplementation is associated with increases in total cholesterol in E4 carriers, which appears to be due to an increase in LDL-C and may in part negate the cardioprotective action of DHA in this population subgroup.

**APOE genotype modifies the association between plasma measured omega-3 fatty acids and plasma lipids in the Multi- Ethnic Study of Atherosclerosis (MESA) - Liang 2013**

Significant gene-EPA interactions were found with HDL-C, and particle concentrations of large and total HDL. The lipid targets were positively associated with EPA in the E2 groups, whereas negative trends were observed among the E4 participants. Gene-DHA interactions were noted for small LDL particle concentrations alone, where a positive trend was found among E4 but not E2 or E3 participants.

**Effect of sex and genotype on cardiovascular biomarker response to fish oils: the FINGEN Study - Caslake 2008**

In contrast with our previous study, in which an effect of genotype on the LDL cholesterol response was evident—7% increases were observed in the group as a whole, and 3%, 1%, and 16% increases were observed in E2, E3, and E4 subgroups, respectively, after 3 g EPA DHA/d — there was no significant effect of genotype in the current study (0.7g/d & 1.8g/d). Taken together, these data suggest that the effect of APOE genotype on the LDL-cholesterol response may be dose dependent.

**APOE4, Saturated Fat & CRP**

There is evidence that consuming saturated fat increases c-reactive protein (CRP) for APOE4 carriers.

**APOE genotype influences triglyceride and C-reactive protein responses to altered dietary fat intake in UK adults - Carvalho-Wells 2012**

We provide novel evidence of a divergent CRP response to SFA according to APOE genotype, with a significant increase in CRP concentrations after increased SFA intakes evident only in APOE4 carriers.

**APOE4 & Exercise**

There is lots of evidence that regular exercise can counter the risk posed by carrying APOE4. A sedentary lifestyle increases the risk of cognitive decline and Alzheimer's.

PubMed: [apoex exercise not (mice or mouse or rat or monkey)]

Google: [apoex exercise -mice -mouse -rat -monkey]

**Exercise, APOE genotype, and the evolution of the human lifespan - Raichlen et al.**

There is growing evidence that physical activity, exercise, and aerobic fitness significantly reduce CAD risk and improve cognitive aging and biomarkers of AD pathology in APOE e4 carriers.

**Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition - Neurol 2012**

Collectively, these results suggest that cognitively normal sedentary APOE 4-positive individuals may be at augmented risk for cerebral amyloid deposition.

**Physical Activity May Modulate Effects of ApoE Genotype on Lipid Profile - Bernstein 2002**

Increasing physical activity may compensate for the potentially deleterious effects of the apoE4 genotype on the lipid profile, at least in western (European) populations. It appears that this protection may be obtained by performing any high-intensity physical activity (ie, expending 4 times the BMR or more), such as brisk walking or sports.

**Physical activity reduces hippocampal atrophy in elders at genetic risk for Alzheimer's disease - Smith 2014**

Participants who endorsed one of the two items indicating two or fewer days of low intensity PA (ranging from no PA to slow walking or light chores) were classified as physically inactive (Low PA). Participants endorsing one of the remaining three items describing moderate to vigorous intensity PA three or more days per week (ranging from brisk walking, jogging or swimming for 15 min or more, or moderately difficult chores for 45 min, to regular jogging, running, bicycling or swimming for 30 min or more, or playing sports such as handball or tennis for an hour or more) were classified as physically active (High PA).
... change from baseline to 18-month follow-up. A significant interaction was observed between Risk and PA for the hippocampus. Hippocampal volume decreased 3% in the High Risk/Low PA group, whereas the volumetric changes in the remaining three groups were negligible.

APOE4 & Heavy Metal Toxicity

APOE4 carriers have a substantially reduced capacity for heavy metal detox (both mercury and lead) which might be a primary reason for the higher AD risk since mercury is high neurotoxic.

- APOE2 can transport two atoms of mercury out of the brain
- APOE3 can transport one atom of mercury out of the brain
- APOE4 can not transport mercury out of the brain

<table>
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<th>HM Detox Capability</th>
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<td>APOE 3/2</td>
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<td>APOE 3/3</td>
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<td>APOE 3/4</td>
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<td>APOE 4/4</td>
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Amalgam fillings (which should be removed anyhow) in combination with periodontitis and anaerobic bacterial infected teeth (teeth with root canals) pose an even higher health risk due to the toxic mercury compounds that are created by simple chemical reactions directly in the mouth and then absorbed by the body. This is especially so for APOE4 carriers.

Apolipoprotein E genotyping as a potential biomarker for mercury neurotoxicity - Godfrey 2003

Only 2 (with two cysteine-SH groups), and to a lesser extent 3 (with one cysteine-SH group), are able to bind and remove mercury from the brain and cerebrospinal fluid.

Susceptibility Factors in Mercury Toxicity: Immune Reactivity, Detoxification System Function, Enzymatic Blockages, Synergistic Exposures

The biochemical difference between APO E2 and APO E4 is that APO E2 has two additional thiol groups, capable of binding and removing mercury (and ethyl mercury) that APO E4 does not have. The second highest concentration of APO E proteins is in the cerebrospinal fluid. Therefore, the protective effects of APO E2 is due to its ability to protect the brain from exposure to oxidants like mercury and ethyl mercury by binding these toxicants in the cerebrospinal fluid and keeping them from entering the brain.

The relationship of the toxic effects of mercury to exacerbation of the medical condition classified as Alzheimer’s disease - Haley 2007

Anyone with periodontal disease, anaerobic bacterial infected teeth, and mercury containing fillings would be exposed daily to these very toxic compounds.

APOE4 & Alcohol

There is evidence that APOE4 carriers do not profit from the protective effect of small amount of alcohol like APOE2 carriers do. Consuming alcohol can increase triglycerides for APOE4. APOE4 carriers probably do best without alcohol.

SNPedia: 4.3 Alcohol consumption

Gene-nutrient interactions: dietary behaviour associated with high coronary heart disease risk particularly affects serum LDL cholesterol in apolipoprotein E epsilon4-carrying free-living individuals - Loktionov 2000

In the e4-expressing subjects alcohol intake was positively correlated with triacylglycerol concentration.
Saturated fat intake and alcohol consumption modulate the association between the APOE polymorphism and risk of future coronary heart disease: a nested case-control study in the Spanish EPIC cohort - Corella 2011

We have found a strong association between the APOE polymorphism and LDL-C concentrations as well as a dietary modulation in determining CHD risk. In addition to their lower LDL-C concentrations, E2 carriers have a lower incidence of CHD than E3/E3 subjects, with the greater CHD risk in E4 carriers not reaching the statistical significance compared to E3/E3, although it does so in comparison with E2 carriers. Moreover, we have observed that saturated fat intake modulates CHD risk in such a way that in the lower consumption stratum (<10% of energy), the genetic effect was not observed, whereas in the higher consumption stratum, the differences in CHD risk between E2 and E4 carriers were magnified. Our results also suggest that moderate alcohol consumption may be more favorable in E2 carriers both on plasma lipids and CHD risk.

Apolipoprotein E, alcohol consumption, and risk of ischemic stroke: The Framingham Heart Study revisited - Djoussé 2009

Our data do not provide evidence for an interaction between E4 allele and alcohol consumption on the risk of ischemic stroke in this population. Furthermore, ApoE polymorphism did not influence the alcohol-HDL relation.

APOE4, Quercetin & HDL

There is inconclusive evidence whether Quercetin lowers HDL for APOE4 carriers or not. However, the later, 2nd study suggests quercetin is a suitable supplement for APOE4 carriers.

Serum Lipid and Blood Pressure Responses to Quercetin Vary in Overweight Patients by Apolipoprotein E Genotype - Egert 2009

In conclusion, reanalysis of our data according to apoE phenotype showed that daily supplementation of the diet with 150 mg quercetin may have beneficial cardiovascular effects in overweight-obese carriers of the apoE 3/3 genotype but may be of little value in apoE4 carriers, who had reductions in HDL cholesterol and apoA1, but not in SBP, due to quercetin supplementation. Our results are, however, based on a relatively small number of 4 allele carriers (especially homozygous 4/4) of a retrospectively genotyped cohort.

Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms - Pfeuffer 2011

In some previous human studies quercetin or a quercetin-rich grape concentrate decreased triacylglycerol concentrations, but not in other studies. In this study quercetin increased also HDL-C, as observed before for a grape concentrate. Triacylglycerol concentrations are usually inversely related to HDL-C. TC and LDL-C were not decreased, consistent with two but contrary to other previous reports. None of these effects were APOE genotype-dependent, while Egert et al. found adverse effects of quercetin on HDL-C and the LDL-C/HDL-C ratio only in APOE4 subjects, and adverse effects on apolipoprotein A-I only in APOE3 subjects. Their study subjects were obese, of a wide age range and both sexes which might have resulted in gender or age bias.

Lack of evidence

Claimed effects for which there was no evidence

- APOE influences the muscle fiber type distribution and thus affects optimal training strategies (as claimed in "The Perfect Gene Diet")