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Preface

This Practical Guide is part of Forever Healthy’s "Maximizing Health" initiative that seeks to review the world’s leading medical knowledge on various health-related topics and turn it into actionable information.

Section 1: Overview

Motivation

APOE is the gene responsible for coding Apolipoprotein E, a key player in our lipid metabolism. APOE comes in 3 significant variants: 2, 3 & 4. Since humans carry two copies of the gene, there are six possible permutations: APOE 2/2, 2/3, 2/4, 3/3, 3/4 & 4/4. In Europe / USA, roughly 75% of people are APOE3/3, and the APOE3/4 or 4/4 variants are present in 20 - 25 %.

The 4 variant is well known for its association with a significantly higher risk of Alzheimer's disease. Numerous other conditions have been linked to it including different forms of dementia, cardiovascular disease (CVD), and decreased longevity. There are several important implications for carriers of one or two copies of the 4 variant, particularly concerning saturated fat and heavy metal detox.

Key Questions

This analysis seeks to answer the following questions:

- Which risks are involved in carrying one or two 4 alleles?
- What are the potential risk mitigation strategies?
- Who should be tested for APOE4?

Impatient readers may choose to skip directly to Section 4 for the summary of findings and tips on risk management.

Section 2: Methods
Literature search

A literature search was conducted on PubMed, Google, Google Scholar, and SNPedia using the search terms shown in Table 1. Titles and abstracts of the resulting studies were screened and relevant articles downloaded in full text. The references of the full-text articles were manually searched to identify additional trials that may have been missed by the search terms.

Table 1: Literature Search (as of 27 Jul 2020)

<table>
<thead>
<tr>
<th>Search terms</th>
<th>Number of publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed: apoe4 ldl (omega-3 or fish oil or dha or epa) not mice</td>
<td>7</td>
</tr>
<tr>
<td>PubMed: apoe4 (omega-3 or fish oil or dha or epa) not mice</td>
<td>77</td>
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<tr>
<td>PubMed: apoe exercise not (mice or mouse or rat or monkey)</td>
<td>30</td>
</tr>
<tr>
<td>Google Scholar: apoe4 ldl omega-3 OR &quot;fish oil&quot; OR dha OR epa -mice</td>
<td>434</td>
</tr>
<tr>
<td>PubMed: apoe e4 OR APOE4 filter: clinical trials</td>
<td>318</td>
</tr>
</tbody>
</table>

Other searches

Google: apoe exercise -mice -mouse -rat -monkey
SNPedia: 4.2 Omega-3 (n-3) fatty acids
SNPedia: 4.3 Alcohol consumption

Other sources

A manual search of the reference lists of the selected papers

Recommended Reading/Viewing

The following sites and documents offer information on APOE4 at a consumer level and are useful as an introduction to the topic. However, sometimes they are not entirely accurate or specific in every detail.

- High cholesterol and the APOE gene - gbhealthwatch.com
- Reducing Risk For APOE4 Genotypes (pdf)
  A brief overview and links to some relevant studies
- The straight dope on cholesterol - Peter Attia
  Since APOE has such a strong impact on lipid metabolism, cholesterol profile, and our CVD risk profile we have included this reference. A good introduction to cholesterol and the significance of the individual markers for CVD.

Abbreviation list

<table>
<thead>
<tr>
<th>Abbr.</th>
<th>Full text</th>
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<tbody>
<tr>
<td>LDL</td>
<td>Low-Density Lipoprotein</td>
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<tr>
<td>LDL-P</td>
<td>LDL Particle Number</td>
</tr>
<tr>
<td>LDL-C</td>
<td>LDL Cholesterol</td>
</tr>
<tr>
<td>HDL</td>
<td>High-Density Lipoprotein</td>
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Section 3: Review of APOE4’s influence on metabolism & disease

Saturated Fat & LDL-C

There is a correlation between APOE4, the amount of fat consumed, and low-density lipoprotein cholesterol (LDL-C). It appears that it is primarily the amount of saturated fatty acids (SFA) that drives total LDL-C and not monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA).

Interview with Joe D. Goldstrich, MD (Goldstrich, 2011)

People that carry the 4 alleles, 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.

An anecdotal example of severely elevated LDL on saturated fat consumption due to the 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 et al., 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 to 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.

Saturated Fat & LDL Particle Size
The increase of LDL-C observed in APOE4 carriers when consuming saturated fat seems to result from an increase in both the size and number of LDL particles (LDL-P).

**Gene-diet interactions and plasma lipoproteins: Role of apolipoprotein E and habitual saturated fat intake** (Campos et al., 2001)

Higher saturated fat intake was associated with smaller LDL particles (-2%, P < 0.05) in APOE2 carriers, and larger LDL particles (+2%, P < 0.05) in APOE4 carriers, but the gene-diet interaction was not statistically significant (P = 0.09).

**Saturated Fat & CRP**

There is evidence that consuming saturated fat increases C-reactive protein (CRP), a marker of systemic inflammation, in APOE4 carriers. Multiple studies have reported a lower baseline CRP in APOE4 carriers.

**APOE genotype influences triglyceride and C-reactive protein responses to altered dietary fat intake in UK adults** (Carvalho-Wells et al., 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.

**Impact of the Apolipoprotein E (epsilon) Genotype on Cardiometabolic Risk Markers and Responsiveness to Acute and Chronic Dietary Fat Manipulation** (Rathnayake et al, 2019)

In conclusion, this study has confirmed previous findings that the APOE genotype is associated with fasting lipid profile and CRP. Additionally, serum CRP was lower in E4 carriers, a finding that has also been observed in other studies.

**Mono-unsaturated Fat, Carbohydrates, LDL Particle Size & Particle Count**

Elevated LDL particle number (LDL-P) and decreased LDL particle size are both significant CVD risk factors.

There is evidence that MUFA decrease both LDL particle number (good) and LDL particle size (problematic) in APOE4 carriers.

Reduced-fat (particularly saturated fat) diets with low glycemic index carbohydrates appear to have positive effects on the metabolic profile. However, this is probably very individual, 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, it is important to experiment with different macro ratios and retest frequently.

**Apolipoprotein E isoform phenotype and LDL subclass response to a reduced-fat diet** (Dreon et al., 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 et al., 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.

**Diets used in the Moreno Study**

<table>
<thead>
<tr>
<th></th>
<th>SFA</th>
<th>CHO</th>
<th>MUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>SFA</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>MUFA</td>
<td>12%</td>
<td>12%</td>
<td>22%</td>
</tr>
<tr>
<td>PUFA</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>CHO</td>
<td>47%</td>
<td>57%</td>
<td>47%</td>
</tr>
</tbody>
</table>
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.

**APOE4 Genotype Exerts Greater Benefit in Lowering Plasma Cholesterol and Apolipoprotein B Than Wild Type (E3/E3), After Replacement of Dietary Saturated Fats With Low Glycaemic Index Carbohydrates** (Griffin et al., 2018)

... there was evidence of a significant diet x genotype interaction with significantly greater decreases in TC (p = 0.02) and apo B (p = 0.006) among carriers of E4 when SFA was replaced with low GI carbohydrate on a lower-fat diet (TC -0.28 mmol/L, p = 0.03; apo B -0.1 g/L, p = 0.02), and a relative increase in TC (in comparison to E3/E3) when SFA was replaced with MUFA and high GI carbohydrates (TC 0.3 mmol/L, p = 0.03).

**Dietary Cholesterol**

APOE4 carriers seem to have a higher uptake of dietary cholesterol than APOE 2 & 3. There is evidence that they also experience greater decreases in total cholesterol and apo B when saturated fats are replaced with low GI carbohydrates on a lower-fat diet.

**Apolipoprotein E polymorphism and atherosclerosis** (Davignon et al., 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 Genotype Exerts Greater Benefit in Lowering Plasma Cholesterol and Apolipoprotein B than Wild Type (E3/E3), after Replacement of Dietary Saturated Fats with Low Glycaemic Index Carbohydrates** (Griffin et al., 2018)

Following intervention, there was evidence of a significant diet x genotype interaction with significantly greater decreases in TC (p = 0.02) and apo B (p = 0.006) among carriers of E4 when SFA was replaced with low GI carbohydrate on a lower fat diet (TC -0.28 mmol/L, p = 0.03; apo B -0.1 g/L, p = 0.02), and a relative increase in TC (in comparison to E3/E3) when SFA was replaced with MUFA and high GI carbohydrates (TC 0.3 mmol/L, p = 0.03).

**Fish Oil & LDL / HDL**

Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) are the main omega-3 essential fatty acids in fish oil and are generally considered to have a number of important health benefits. However, there is some evidence that for APOE4 carriers, DHA supplementation may be less effective and can substantially increase LDL-C, reduce LDL particle size, and increase LDL-P. Additionally, EPA may also lower HDL-C and HDL-P.

APOE4 carriers exhibit disturbances in DHA metabolism. This results in an inability to maintain an appropriate balance between the arachidonic acid and DHA/EPA content in phospholipids that the body creates or modifies. This imbalance leads to an inflammatory state that may contribute to the development of several diseases.

DHA and EPA clearance from plasma is also faster than in non-carriers. Lower levels of DHA (baseline and post-supplementation) in APOE4 carriers have been reported by several studies.

There is, however, also a significant amount of evidence that APOE4 carriers do profit from anti-inflammatory effects, and lowering of triglycerides (TG) & very-low-density LDL (VLDL) following DHA supplementation and that the negative effects may be dose-dependent.

Consumption of DHA/EPA between the amount of 700 - 1,800 mg/day appears to have net positive effects.

**Disturbance in uniformly 13C-labelled DHA metabolism in elderly human subjects carrying the apoE e4 allele** (Chouinard-Watkins et al., 2013)

In E4+, mean plasma [13C]DHA was 31 % lower than that in E4-, and cumulative b-oxidation of [13C]DHA was higher than that in E4- 1–28 d post-dose (P<0.05). A genotype time interaction was detected for cumulative b-oxidation of [13C]DHA (P 0·01). The whole-body half-life of [13C]DHA was 77 % lower in E4+ compared with E4- (P 0·01).

**Effect of APOE Genotype on Plasma Docosahexaenoic Acid (DHA), Eicosapentaenoic Acid, Arachidonic Acid, and Hippocampal Volume in the Alzheimer’s Disease Cooperative Study-Sponsored DHA Clinical Trial** (Tomaszewski et al., 2020)

The preferential binding of APOE4 compared to APOE 3 (APOE3) and APOE2 alleles (APOE4 > APOE3 > APOE2) with larger fat-containing particles contributes to altered lipid and cholesterol metabolism. For example, DHA and EPA are transported on chylomicrons to the liver following absorption, and APOE4 carriers have faster DHA and EPA clearance from plasma compared to non-carriers.
ApoE Polymorphism and Fish Oil Supplementation in Subjects With an Atherogenic Lipoprotein Phenotype (Minihane et al., 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-Martín et al., 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 et al., 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 et al., 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.

...the greatest hypotriacylglycerolemic effects were evident in apoE4 males: 15% (P 0.004) and 23% (P 0.001) reductions in TAG concentrations were evident after the 8-wk 0.7FO and 1.8FO intervention periods, respectively, in the male E4 subgroup

At a population level, the overall clinical significance of the 0–10% TAG, cholesterol, and HDL and LDL size changes may be modest, but, for certain persons, such as males with an APOE4 genotype (11% of whites), the lipid-modulatory effects observed at these EPA-DHA doses are likely to have a significant effect on CVD risk

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

Also, we have reported that the commonly observed LDL-cholesterol– raising effect of high-dose fish oils, particularly DHA, is most evident in APOE4 carriers. A significant 10% increase in LDL cholesterol was observed in this subgroup after supplementation with a DHA-rich oil (3.7 g DHA /d) as was a modest reduction evident in the wild-type APOE3/E3 group, which was broadly consistent with the findings of an earlier study

In contrast with our previous findings, in the current study (against a background diet high in total fat and SFA) we observed no increase in total and LDL cholesterol in the APOE3/E4 group after high-dose DHA supplementation

In conclusion, our data indicate that, in normolipidemic individuals, heterozygous APOE4 status is unlikely to be a major population determinant of the fasting cholesterol responses to altered fat intakes, but conferred greater sensitivity to the hypotriglyceridemic actions of DHA

Disrupted fatty acid distribution in HDL and LDL according to apolipoprotein E allele (Dang et al., 2015)

...young E4+ participants already had a tendency toward lower baseline-DHA levels in LDL particles as well as a more atherogenic -6/-3 PUFA ratio in LDL pre- and post-supplementation.

Interaction between BMI and APOE genotype is associated with changes in the plasma long-chain–PUFA response to a fish-oil supplement in healthy participants (Chouinard-Watkins et al., 2013)

Our findings indicate that apolipoprotein E genotype and BMI may be important variables that determine the plasma long-chain PUFA response to dietary fat manipulation. APOE4 carriers with BMI 25.5 may need higher intakes of DHA for cardiovascular or other health benefits than do noncarriers

The effect of APOE genotype on the delivery of DHA to cerebrospinal fluid in Alzheimer’s disease (Yassine et al., 2016)

Baseline CSF A42 levels were significantly lower in 4 carriers than in 4 noncarriers (p = 0.01). Participants carrying the 4 allele (n = 25) demonstrated a less pronounced increase in CSF DHA level compared with noncarriers (n = 4), APOE 4 allele and lower CSF A42 levels were associated with less transport of DHA to CSF.
Apolipoprotein E genotype status affects habitual human blood mononuclear cell gene expression and its response to fish oil intervention (Matu alatupauw et al., 2016)

Interestingly, 6 months of fish-oil supplementation decreased IFN-related gene expression in APOE4 carriers. The increased expression of genes in the IFN signaling pathway and IFN-regulated genes in PBMCs of APOE4 carriers at baseline may point toward a systemic pro-inflammatory state.

Motor Function

There is inconclusive evidence on a correlation between APOE4 and motor function. Some studies have reported a relationship between the presence of an APOE4 allele and the decrease of motor function in healthy adults while others found no such association.

The Association of APOE 4 Status with Lower Limb Function and Handgrip strength in older Adults (Maltais et al., 2019)

Some studies have found a possible relationship between the presence of an ApoE 4 allele and the decrease of motor function in healthy older adults. No significant cross-sectional or prospective associations were found between ApoE 4 status, lower-limb function, and handgrip strength in our study.

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. However, a study has also shown that exercise is less effective in improving brain function in APOE4 carrying individuals than in those carrying APOE2 or E3 alleles.

Exercise, APOE genotype, and the evolution of the human lifespan (Raichlen et al., 2014)

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 et al., 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 et al., 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 et al., 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.

Effect of aerobic exercise on cognition in younger adults A randomized clinical trial (Stern et al., 2019)

Controlling for age and baseline performance, individuals with at least one APOE 4 allele showed less improvement in executive function with aerobic exercise.
Neurodegeneration & Multiple Sclerosis

A correlation between APOE4 and increased risk of various types of neurodegeneration and other diseases of the CNS has been shown in several studies. There is also evidence that ApoE isoforms control A production (a key pathological finding in AD).

APOE and Alzheimer’s Disease: Evidence Mounts that Targeting APOE4 may Combat Alzheimer’s Pathogenesis (Uddin et al., 2018)

It has been found that 40 to 80% of people with AD have at least one APOE4, and it increases the risk of AD in heterozygotes and homozygotes by 3 and 15 times, respectively.

Relative effect of APOE e4 on neuroimaging biomarker changes across the lifespan (Gonneaud et al., 2016)

There was no significant effect of APOE or APOE x age interaction on gray matter volume and glucose metabolism, although decreases with age tended to be stronger in noncarriers than in carriers. In contrast, -amyloid (A) deposition was significantly higher in carriers compared with noncarriers in a largely distributed network, and there was a significant APOE x age interaction such that A deposition increased nonlinearly with age in APOE 4 carriers only.

Apolipoprotein E e4 allele frequency in patients with Lewy body dementia, Alzheimer’s disease and age-matched controls (St Clair et al., 1994)

There was a 3-fold increase in the epsilon 4 allele frequency in both LBD and AD groups compared with controls. These results indicate that LBD and AD share the epsilon 4 allele of ApoE as a major risk factor for the development of disease and suggest a similarity in disease aetiology.

Apolipoprotein E 4 Is Associated with Rapid Progression of multiple sclerosis (Fazekas et al., 2001)

The authors found no significant differences in the distribution of genotypes between patients with MS and controls. However, patients with MS with the epsilon4 allele (n = 85) had a significantly higher progression index of disability (0.46 +/- 0.4 versus 0.33 +/- 0.26; p < 0.004) and a worse ranked MS severity score (5.1 +/- 1.9 versus 5.7 +/- 1.7; p = 0.05) than their non-epsilon4 counterparts.

Apolipoprotein E 4 Is Associated with Neuronal Loss in the Substantia nigra in Alzheimer’s Disease (Camicioli et al., 1999)

Among 31 prospectively assessed subjects with pathologically confirmed AD (without Lewy bodies), epsilon4+ subjects had a longer duration of disease (by 2.8 years, p = 0.04). Only cell loss in the substantia nigra (p = 0.002) was associated with epsilon4. Neither neurofibrillary tangles nor plaque counts were associated with epsilon4.

Regional brain atrophy in cognitively intact adults with a single APOE 4 allele (Wishart et al., 2006)

The epsilon3/epsilon4 participants showed lower gray matter density than the epsilon3/epsilon3 participants in right medial temporal and bilateral frontotemporal regions as well as other areas.

White Matter Lesions in Alzheimer Patients Are Influenced by Apolipoprotein E Genotype (Bronge et al.,1999)

The patients with the APOE genotype sigma4/4 had more extensive WMLs in the deep white matter than patients with genotypes sigma3/3 and sigma3/4. There was a correlation with age for WMLs in the deep white matter in patients with the APOE sigma3/3 genotype. In patients carrying at least one sigma4 allele, the WMLs showed no age correlation.

Roles of apolipoprotein E4 (ApoE4) in the pathogenesis of Alzheimer’s disease: lessons from ApoE mouse models (Huang et al., 2011)

Based on our studies, we hypothesize that the A and plaque-independent effects of apoE4 on neuronal and behavioural deficits are caused by neurotoxic effects of the apoE fragments.

Traumatic Brain Injury

There is some evidence that APOE4 carriers have enhanced EEG abnormalities and worse functional outcomes following traumatic brain injury (TBI).

Different quantitative EEG alterations induced by TBI among patients with different APOE genotypes (Jiang et al., 2011)
But in the TBI group, APOE4 carriers had more focal or global irregular slow wave activities than APOE4 non-carriers. APOE gene did not influence brain electrical activity under normal conditions, but TBI can induce different alterations among different APOE gene carriers, and APOE4 allele enhances the EEG abnormalities at the early stage of TBI.

**Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury** (Friedman et al., 1999)

The odds ratio of more than 7 days of unconsciousness was 5.69 in those with the APOE-epsilon4 allele compared with those without the epsilon4 allele (95% CI, 1.69 to 20.8; p = 0.001). Only 1 of 27 subjects (3.7%) with the epsilon4 allele had a good functional outcome compared with 13 of 42 (31.0%) of those without the epsilon4 allele (p = 0.006).

**Telomeres**

There is evidence that APOE4 carriers may have an accelerated rate of telomere shortening.

**Accelerated Cell Aging in Female APOE-e4 Carriers: Implications for Hormone Therapy Use** (Jacobs et al., 2013)

...the odds of an APOE-4 carrier exhibiting telomere shortening (versus maintenance/growth) over the 2-year study were more than 6 (OR = 6.26, 95% CI = 1.02, 38.49) times higher than a non-carrier, adjusting for established risk factors and potential confounds. Despite the high-functioning, healthy mid-life status of study participants, APOE-4 carriers had marked telomere attrition during the 2-year study window, the equivalent of approximately one decade of additional aging compared to non-carriers.

**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 Alzheimer’s risk since they are both highly neurotoxic.

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

<table>
<thead>
<tr>
<th>HM Detox Capability</th>
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<tbody>
<tr>
<td>APOE 3/2</td>
<td>150 %</td>
</tr>
<tr>
<td>APOE 3/3</td>
<td>100 %</td>
</tr>
<tr>
<td>APOE 3/4</td>
<td>50 %</td>
</tr>
<tr>
<td>APOE 4/4</td>
<td>0 %</td>
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Amalgam fillings (which should be removed anyhow) in combination with periodontitis and anaerobic bacterially 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 et al., 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** (Windham)

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 APOE2 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.

Cardiovascular Disease

APOE4 is associated with an increased risk of CVD including coronary heart disease, intracerebral hemorrhage, and atherosclerotic cerebral infarction.

APOE Gene Polymorphism and Risk of Coronary Stenosis in Pakistani Population (Cheema et al., 2015)

The frequency of APOE4 carriers (3/4 and 4/4 genotypes) was significantly higher in severe stenosis group (70%) as compared to mild group (<30%) (22.8% versus 13.01%; P = 0.01). In multiple regression, the odds ratio for APOE4 carriers to develop 70% stenosis was 2.16 (95% CI: 1.29-3.79; P < 0.005). In conclusion, the presence of APOE4 allele is a significant risk factor to develop severe coronary stenosis (>70%) among Pakistanis.

APOE genotype, ethnicity, and the risk of cerebral hemorrhage (Tzourio et al., 2008)

In Asian patients, the risk of ICH for epsilon 2 or epsilon 4 carriers was 2.11 (95% CI = 1.28 to 3.47) and 1.48 (95% CI = 0.76 to 2.87) in Europeans. Carriers of the epsilon 2 or epsilon 4 allele had an increased risk of both incident and recurrent ICH, and both cortical and deep ICH and most risk estimates were higher in Asians than in Europeans.

Apolipoprotein E Epsilon 4 Enhances the Association between the rs2910164 Polymorphism of miR-146a and Risk of Atherosclerotic Cerebral Infarction (Zhong et al., 2016)

ApoE4 may function through attenuating miR-146a expression to enhance ACI susceptibility. This study provides new information about the possible relationship between miR-146a and ApoE4 in the development of ACI, with potentially important therapeutic implications.

Polymorphism of the apolipoprotein E gene and early carotid atherosclerosis defined by ultrasonography in asymptomatic adults (Cattin et al., 1997)

The echographic measurements of carotid IMT showed increasing values from E2 to E4 carriers. After adjustment for total and LDL cholesterol serum levels, triglycerides, ratio of LDL to HDL cholesterol, age, sex, and body mass index, ANCOVA showed that the common carotid IMT was significantly greater (P = .029) in subjects with E4 allele compared with E3 carriers. Our data confirm the influence of apoE4 on cholesterol levels and clearly show that apoE genotype affects carotid atherosclerosis in its early stages in middle-aged asymptomatic subjects.

Insulin Resistance

There is evidence that APOE4 carriers with metabolic syndrome and a high intake of SFA have a significantly increased risk of developing type 2 diabetes.

APOE Genotype Influences Insulin Resistance, Apolipoprotein CII and CIII According to Plasma Fatty Acid Profile in the Metabolic Syndrome (Faillaize et al., 2017)

A detrimental association between high plasma SFA and insulin resistance in E4 carriers at baseline was observed. ... we observed that a high proportion of plasma palmitic acid was associated with greater insulin resistance in E4 carriers with MetS, ...

Glucose

A correlation between APOE4 and an accelerated rate of increasing plasma glucose has been demonstrated.

apoE4 allele and the natural history of cardiovascular risk factors (Scuteri et al., 2005)
apoE4 was independently associated with accelerated changes over time in fasting plasma glucose (+9.5% vs. no change in those without apoE4 in the 6th age-decade over 10 yr). No significant effect of apoE4 on longitudinal changes in total or HDL-cholesterol, triglycerides, or blood pressures was observed. In conclusion, apoE4 influences fasting plasma glucose and its changes over time.

**Metabolic Phenotype & Increased Disease Risk**

There is evidence that APOE4 carrying women with poor metabolic phenotype are more likely to have higher levels of subclinical atherosclerosis compared with ApoE4- women.

**Effect of ApoE4 Genotype on the Association Between Metabolic Phenotype and Subclinical Atherosclerosis in Postmenopausal Women (Sripraser et al., 2019)**

In a cross-sectional analysis, ApoE4+ women with poor metabolic phenotype had the highest CIMT compared with all other groups. In ApoE4- women, CIMT was significantly lower in those classified as healthy compared with high blood pressure phenotype (p = 0.004). In ApoE4+ women, CIMT was significantly higher in those with poor metabolic phenotype compared with healthy (p = 0.0003) and high blood pressure (p = 0.001) phenotypes.

**Toward a personalized lifestyle intervention approach to prevent Alzheimer’s disease (Maki, 2018)**

In a general population of postmenopausal women, association between poor metabolic profile with reduction in cognitive performance is more apparent in women who carry an ApoE4 allele. These data indicate a window of opportunity for interventions to reverse the trajectory of the preclinical phase of Alzheimer’s disease.

**Sex**

There is evidence of sex-related differences in carriers of APOE4. Women carrying one APOE4 allele had reduced hippocampal volume whereas men only showed a reduction when they were carrying two copies of APOE4. Statistically significant age-associated memory impairment was only observed in women carrying APOE4.

**Sex, Apolipoprotein E 4 Status, and Hippocampal Volume in Mild Cognitive Impairment (Fleisher et al., 2005)**

...women with 1 or 2 APOE*E4 alleles were found to have significantly reduced hippocampal volume, whereas men only showed a significant reduction in hippocampal volume when carrying 2 APOE*E4 alleles

**Apolipoprotein E Gender Effects on Cognitive Performance in Age-Associated Memory Impairment (Bartrés-Faz et al., 2002)**

Among 100 individuals with age-associated memory impairment (AAMI), APOE E4 carriers performed worse on memory. However, when subjects were considered by gender, this effect was only observed in females. APOE E4 may have a more robust cognitive influence on female than on male individuals with AAMI.

**Longevity**

Carriage of the APOE4 allele is the only major genetic determinant of survival into old age.

**A genome-wide association study confirms APOE as the major gene influencing survival in long-lived individuals (Nebel et al., 2011)**

...fully explicable by linkage disequilibrium with the APOE allele 4, the only variant hitherto established as a major genetic determinant of survival into old age. Our GWAS failed to identify any additional autosomal susceptibility genes. One explanation for this lack of success in our study would be that GWAS provide only limited statistical power for a polygenic phenotype with loci of small effect such as human longevity. A recent GWAS in Dutch LLI independently confirmed the APOE-longevity association, thus strengthening the conclusion that this locus is a very, if not the most, important genetic factor influencing longevity.

**Bone Mineral Density**
There is evidence that post-menopausal APOE4 carrying women have decreased spinal mineral bone density, with a 2-fold higher rate of bone loss.

Apolipoprotein E Gene Polymorphism and Bone Loss: Estrogen Status Modifies the Influence of Apolipoprotein E on Bone Loss (Salamone et al., 2000)

Spine bone loss was significantly greater in peri- and postmenopausal women having an APOE*4 allele than in women without this allele (-1.75 +/- 1.15% per year vs. -0.98 +/- 1.4% per year, respectively, p = 0.018). Among peri- and postmenopausal women currently using hormone replacement therapy (HRT), there were no differences in the annualized percentage rate of change in spine BMD; whereas, among non-HRT users, there was a 2-fold higher rate of spine bone loss in women with an APOE*4 allele compared with women without this allele (-2.31 +/- 1.5% per year vs. -1.27 +/- 1.3% per year, respectively, p = 0.033; APOE*4 x HRT interaction, p = 0.076).

Apolipoprotein E 4 allele is associated with low bone density in postmenopausal women (Zajícková et al., 2003)

Women with Apo E 4 allele had significantly lower BMD at the lumbar spine than women with no Apo E 4 allele (p<0.003, ANCOVA). In contrast, there were no significant differences in BMD at the hip comparing women with or without the Apo E 4 allele. To conclude, these data may support the importance of Apo E 4 allele in determining postmenopausal spine bone mass.

Gut Microbiome

Several studies have implicated a link between the gut microbiome, short-chain fatty acids (SCFA), and the development of AD. There is evidence that gut microbiota composition in humans differs by APOE genotype. This results in a changed production of amino acids and SCFA, potentially contributing to Alzheimer's pathology.

APOE genotype influences the gut microbiome structure and function in humans and mice: relevance for Alzheimer’s disease pathophysiology (Tran et al., 2019)

We observed that the relative abundance of the phylum Firmicutes and order Clostridiales was higher in subjects of the APOE2/E3 genotype than in APOE3/E4 or APOE4/E4. Furthermore, at the bacterial family level, the abundance of Ruminococcaceae (a family of fermentative anaerobes associated with fiber degradation and SCFA production) was higher in APOE2/E3 than in APOE3/E3 (P = 0.004), APOE3/E4 (P = 0.002), or APOE4/E4 (P = 0.072). On the other hand, the abundance of Prevotellaceae was lower in APOE2/E3 than the other 3 APOE genotypes (APOE3/E3, P = 0.008; APOE3/E4, P = 0.085; APOE4/E4, P = 0.015) and was slightly more abundant at close to significant levels (P = 0.088) in APOE3/E4 compared with APOE4/E4 with mean of relative abundance of 1.79 vs. 1.40%. The abundance of Clostridium cluster IV was lower in APOE3/E3 than in APOE2/E3 (P = 0.027) and APOE4/E4 (P = 0.039), whereas the abundance of Clostridium cluster XIVa was higher in APOE4/E4 than in APOE2/E3 (P = 0.044) and APOE3/E4 (P = 0.078).

Alcohol

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

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 et al., 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 et al., 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 (b10% 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 et al., 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.

**Quercetin & HDL**

There is inconclusive evidence regarding the effect of Quercetin on HDL-C in APOE4 carriers. One study reported that quercetin lowered HDL-C, while a more recent study reported that quercetin increased HDL-C. There is, however, also evidence that Quercetin's beneficial effects of lowering oxLDL and TNFα also extend to APOE4 carriers.

**Serum Lipid and Blood Pressure Responses to Quercetin Vary in Overweight Patients by Apolipoprotein E Genotype** (Egert et al., 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.

Quercetin decreased systolic blood pressure by 3.4 mm Hg (P < 0.01) in the apoE3 group, whereas no significant effect was observed in the apoE4 group. Quercetin decreased serum HDL cholesterol (P < 0.01) and apoA1 (P < 0.01) and increased the LDL:HDL cholesterol ratio (P < 0.05) in the apoE4 subgroup, whereas the apoE3 subgroup had no significant changes in these variables. Quercetin significantly decreased plasma oxidized LDL and tumor necrosis factor-alpha in the apoE3 and apoE4 groups, whereas no significant inter-group differences were found. Serum C-reactive protein and nutritional status (body weight, waist circumference, fat mass, fat-free mass) were unaffected compared with placebo.

**Effect of quercetin on traits of the metabolic syndrome, endothelial function, and inflammation in men with different APOE isoforms** (Pfeuffer et al., 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.

Quercetin moderately but significantly reduced BMI, body weight, and waist circumference in APOE3/3 but not in APOE4 subjects.

**Cholesterol-lowering Substances**

There is conflicting evidence on the effects of consuming plant sterols in APOE4 carriers with one study reporting increased cholesterol-lowering effects, and another studying reporting decreased effects. Varying responses to statins have also been reported.

**CYP7A1-rs3808607 and APOE isoform associate with LDL cholesterol lowering after plant sterol consumption in a randomized clinical trial** (MacKay et al., 2015)

In response to PS consumption, participants with the APOE e4 isoform had greater LDL cholesterol lowering (20.31 6 0.07, P < 0.0001, n = 23) than did APOE e3 participants (20.13 6 0.05, P = 0.0370, n = 40).

**Serum Lipid and Antioxidant Responses in Hypercholesterolemic Men and Women Receiving Plant Sterol Esters Vary by Apolipoprotein E Genotype** (Sanchez-Muniz et al., 2008)

During sterol consumption, TC, LDL-C, and ApoB concentrations and the TC:LDL-C and LDL-C:HDL-C ratios decreased in only E2 and E3 subjects and TAG decreased in only E2 subjects. Thus, responses to plant sterols vary by apoE genotype and may be of little value in apoE4 carriers.

**Apolipoprotein-E polymorphism and response to pravastatin in men with coronary artery disease (REGRESS)** (Maitland-Van Der Zee et al., 2006)

There was a significant interaction between treatment (placebo/pravastatin) and APOE genotype when lipid levels were considered. APOE2 carriers exhibited the largest improvement of HDL levels (+0.15mmol/l) and LDL/HDL ratios (-0.60) compared with APOE3 (+0.06mmol/l, -0.043, respectively) and APOE4+ carriers (+0.07mmol/l, -0.04).
Evolutionary / Ancestral / Paleo Style Diets

These diets often emphasize liberally consuming saturated fat from coconut oil, palm oil, butter, ghee, fatty meat, dark chocolate, etc., which are nowadays deemed safe for consumption.

Viewing the population as a whole, switching from an unhealthy diet to a clean ancestral diet lowers the risk for CVD, even if it is high in saturated fat. Unfortunately, if broken down according to APOE status, this remains true only for those that don’t carry the APOE4 variant.

For carriers of the APOE4 variant, consuming saturated fatty acids can substantially raise the risk of CVD.

Sadly, most of the proponents of this lifestyle have not yet realized this critical fact and still promote the consumption of saturated fat to everyone, putting a significant percentage of the population in harm's way.

However, these diets at their core are not about saturated fat but about eating clean and healthy food. A modified variant of these diets that is low in saturated fat is easily achievable.

Section 4: Summary of Findings

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

- Decreased longevity
- A substantially higher risk of late-onset AD and other forms of dementia, worse outcomes following traumatic brain injury, & accelerated progression of MS
- A substantially higher risk of CVD including coronary heart disease, intracerebral hemorrhage, and atherosclerotic cerebral infarction
- Severely impaired heavy metal detoxification capabilities, particularly for lead and mercury
- Increased susceptibility to the detrimental effects of a sedentary lifestyle regarding increased AD risk
- Accelerated telomere shortening
- Greater risk of disease when found in combination with a poor metabolic profile
- Reduced hippocampal volume and increased age-related memory impairment (females)
- Lower bone density (females)

Consuming saturated fats can:
- Substantially raise LDL-P which is a major risk factor for CVD
- Raise CRP, which is a risk factor for CVD, however, APOE4 carriers have lower baseline levels of CRP
- Increase LDL particle size, which is itself, is cardioprotective. However, this may be outweighed by the rise in LDL-P
- Substantially raise LDL-C
- Result in insulin resistance & an increased risk of diabetes

Consuming MUFA found in olive oil, avocados, etc. can:
- Decrease LDL-P which is cardioprotective
- Decrease LDL particle size, which is a risk factor for CVD. However, this may be outweighed by the decrease in LDL-P
- Decrease LDL-C

Consuming DHA & EPA (e.g., from fish oil) produces many health benefits but can also result in adverse health effects if consumed in high doses

- Consuming DHA can
  - Increase LDL-P (bad)
  - Reduce LDL particle size (bad)
  - Increase LDL-C (bad)
  - Decrease inflammatory gene expression (good)
  - Decrease triglycerides (good)

- 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)

• Consuming plant sterols may result in a greater LDL-C lowering effect (good)
• Pravastatin may be less effective in lowering cholesterol

Section 5: Risk Management

Testing APOE Status

Regarding the high probability of being an APOE4 carrier and its far-reaching consequences, everybody should have their APOE status checked (e.g., using 23andme.com).

The good news is that once APOE status is known, diet and lifestyle can be modified in order to counter the risk factors that come with the E4 variant.

Basic Risk Management for APOE4 Carriers

• Closely monitor levels of mercury, lead and heavy metal toxicity in general
• Take appropriate measures to detox mercury and other heavy metals
• Carefully monitor the cholesterol profile, particularly LDL-P measured with NMR, which is strongly correlated with increased CVD risk
• APOE4 carriers usually do better on a diet low in SFA, low in PUFA, low but sufficient protein with a focus on moderate amounts of MUFA 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 SFA (3.7%)
• Unfortunately, dark chocolate and raw cacao nibs are high in saturated fat (up to 40%)
• Since 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 EPA + DHA to a max. of 1800 mg/day
• Consume EHA & DHA in their natural form by eating fatty fish
• Keep the intake of PUFA on the lower side. Unfortunately, there is not much research on the effect on PUFA in general for APOE4, but the research on EHA and DHA (both PUFA) shows that more might not be better
• Good sources of MUFA 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, keep in mind that the reaction of the metabolism to dietary changes is highly individual. Determining the right balance of macronutrients, especially balancing MUFA 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 just correlate the amount of physical activity (mostly self-reported) and the occurrence of AD. 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.

• Oral supplementation of anserine/carnosine may help preserve cognitive functions in APOE4 carrying older adults (Masuoka et al., 2019).
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