APOA1 Gene Variability Determines HDL-Cholesterol Response to Omega-3 Fatty Acids: A Targeted Nutritional Perspective (Literature Review)

Magdalena Behensky[1], René Rohrmanstorfer[1], Thomas Dullnig[1], Daniel Wallerstorfer[1]

[1]Laboratory, Novogenia GmbH, Salzburg, Austria

Corresponding Author: Daniel Wallerstorfer (ceo@novogenia.com)

ABSTRACT

Background:
Apolipoprotein A-I (ApoA-I), encoded by the *APOA1* gene, is the major structural and functional protein in high-density lipoprotein (HDL). The common −75 G>A promoter polymorphism has been linked to variability in HDL-cholesterol (HDL-C) concentrations and cardiovascular risk (Ordovas, 2002). Omega-3 polyunsaturated fatty acids (PUFAs) can modulate HDL metabolism, and responses appear influenced by *APOA1* genotype. Broader dietary patterns may also interact with genotype, with unhealthy patterns potentially negating genetic benefits (Hosseini-Esfahani, 2015).

Methods:
A narrative review of human studies was conducted, focusing on the −75 G>A variant, omega-3 intake, and HDL outcomes. Priority was given to intervention trials and mechanistic studies, including Framingham Offspring cohort analysis (Ordovas, 2002), aerobic exercise training (Ruaño, 2006), dietary pattern interactions (Hosseini-Esfahani, 2015), and mechanistic insights into HDL remodeling and reverse cholesterol transport (Harris, 2004; Liao, 2015; Masson, 2015).

Results:
Women carrying the A allele experienced higher HDL-C than G/G homozygotes with high PUFA intake (>8% energy), but the reverse pattern was seen under low PUFA (<4% energy) (Ordovas, 2002). Exercise training increased large HDL particles in G/G but decreased them in A-allele carriers (Ruaño, 2006). A allele carriers exposed to a Western dietary pattern rich in fats and sweets had increased risk of metabolic syndrome (Hosseini-Esfahani, 2015). Omega-3 supplementation improves HDL functionality — apoA-I exchangeability, particle remodeling, and anti-atherogenic protein composition — even when HDL-C levels change minimally (Harris, 2004; Masson, 2015).

Discussion:
The −75 G>A polymorphism exemplifies a nutrigenetic interaction where omega-3 efficacy on HDL quantity and quality depends on genotype. A-allele carriers benefit most from high-PUFA/omega-3 diets; unhealthy patterns may negate benefits. Tailoring omega-3 recommendations to genotypes could optimize cardiovascular prevention strategies (Ordovas, 2002; Hosseini-Esfahani, 2015).

Subjects Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Omega-3, PUFA, HDL Cholesterol

INTRODUCTION

High-density lipoprotein cholesterol (HDL-C) is considered the "good" cholesterol due to its role in reverse cholesterol transport (RCT), whereby cholesterol is cleared from peripheral tissues to the liver for excretion (Harris, 2004). Omega-3 fatty acids — mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) — are associated with cardiovascular benefits primarily through triglyceride reduction, anti-inflammatory properties, and potentially increased HDL-C (Masson, 2015). However, their effect on HDL-C varies considerably between individuals, leading to debate over their role in dyslipidemia management. Recent evidence suggests this variability is partly attributable to genetic differences, particularly polymorphisms in the *APOA1* gene (Ordovas, 2002; Masson, 2015). The −75 G>A promoter variant of *APOA1* has been linked to differences in HDL-C concentration and responsiveness to diet (Ordovas, 2002), exercise (Ruaño, 2006), and broader dietary patterns (Hosseini-Esfahani, 2015). Understanding how *APOA1* genotype modifies the effect of omega-3 fatty acids on HDL metabolism is crucial for developing targeted cardiovascular prevention strategies.

APOA1 Gene and Omega-3 Interaction

The *APOA1* −75 G>A promoter polymorphism influences HDL-C concentrations and appears to interact strongly with dietary fat intake. In the Framingham Offspring Study, women with the A allele had ~13% higher HDL-C on high polyunsaturated fat diets (>8% energy), but ~14% lower HDL-C on low polyunsaturated fat diets (<4% energy) compared to G/G homozygotes. This sex-specific interaction suggests that the A allele confers an advantage in a high-PUFA environment, potentially via enhanced *APOA1* transcription (Ordovas, 2002).

Broader diet quality also matters, in the Tehran Lipid and Glucose Study, A-allele carriers following a Western dietary pattern had greater risk of metabolic syndrome, indicating adverse dietary patterns can offset genetic advantages (Hosseini-Esfahani, 2015). These findings highlight the importance of dietary composition when interpreting omega-3 and *APOA1* genotype interactions.

Functional Effects of Omega-3 on HDL

In general, omega-3 supplementation produces modest or no change in HDL-C levels in unselected populations. However, it can markedly enhance HDL. Controlled trials have shown that EPA and DHA intake increases apoA-I exchangeability, shifts HDL subfractions toward a greater proportion of large, cholesterol-rich particles, reduces the prevalence of small HDL, and enriches HDL with antioxidant and anti-inflammatory proteins. These compositional and functional improvements support more efficient reverse cholesterol transport and atheroprotection functionality (Harris, 2004; Masson, 2015).

Importantly, genotype modifies these effects. Individuals with the *APOA1* TT genotype (homozygous for the functional allele) not only demonstrate enhanced HDL function with omega-3 intake but also show measurable increases in HDL-C concentrations. This contrasts with heterozygous carriers, who tend to have a blunted HDL-C response

despite functional gains, and those with two defective alleles, who may experience minimal or even negative HDL-C changes in response to omega-3. Thus, the TT genotype represents a particularly responsive group for both qualitative and quantitative HDL benefits from omega-3 supplementation (Ordovas, 2002).

Mechanisms: Reverse Cholesterol Transport and HDL Remodeling

Omega-3 fatty acids support reverse cholesterol transport by influencing multiple stages of HDL metabolism. They stimulate ApoA-I synthesis, promote cholesterol efflux via ATP-binding cassette transporter A1 (ABCA1), modulate the activity of lecithin–cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP), and increase hepatic expression of scavenger receptor class B type I (SR-BI) and bile acid transporters (Harris, 2004).

Incorporation of EPA and DHA into HDL phospholipids increases membrane fluidity, which facilitates cholesterol uptake and exchange between HDL particles and cells. By reducing CETP activity, omega-3 fatty acids help HDL retain cholesteryl esters, promoting the enlargement of particles and improving the maturation process from smaller HDL3 particles to larger HDL2 particles (Masson, 2015).

Prevalence and Impact of Defective *APOA1* Genotypes

The −75 A allele is relatively common, with a prevalence of approximately 25–30% in many populations, while homozygous G/G individuals represent the majority (Ordovas, 2002; Liao, 2015). Individuals with two functional alleles (TT genotype) exhibit robust HDL-C and functional improvements with omega-3 supplementation. Heterozygous carriers show attenuated HDL responses, and those with two defective alleles may display minimal or even adverse changes in HDL-C when consuming high-PUFA or omega-3 diets (Ordovas, 2002).

Table 1: Prominent Human Studies on APOA1 Polymorphisms, Omega-3, and HDL-Cholesterol

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s)/Focus Investigated	Main Outcome(s)
Ruaño et al., 2006	Exercise intervention trial (6 months)	75 healthy normolipidemic adults	*APOA1* −75 G>A × exercise	G/G increased large HDL with training; A carriers decreased large HDL
Harris et al., 2004	Narrative review (clinical & mechanistic evidence)	Multiple human intervention and observational studies	Omega-3 fatty acids (EPA/DHA)	Omega-3 intake modestly affected HDL-C but consistently improved HDL functionality, particle remodeling, and reverse cholesterol transport
Masson & Mensink, 2015	Controlled dietary intervention	40 healthy adults	Dietary fat exchange (SFA vs PUFA)	Replacement of saturated fat with PUFA increased large HDL particles and improved HDL subfraction profile

Hosseini-Esfahani et al., 2015	Population-based dietary pattern analysis	Tehran Lipid and Glucose Study cohort	*APOA1/APOC3* polymorphisms × diet	Western dietary pattern negated beneficial *APOA1* genotype effects and increased metabolic syndrome risk
Ordovas et al., 2002	Observational (cohort; diet–lipid interaction)	1,577 adults; Framingham Offspring	*APOA1 rs670* (−75 G>A)	PUFA/omega-3 intake modified HDL-C by genotype: A-allele carriers had higher HDL-C with high PUFA, whereas GG showed higher HDL-C with low PUFA (Ordovas, 2002).
Rudkowska et al., 2013	Cross-sectional (gene–diet)	553 Inuit adults	*APOA1 rs670*	Dietary fat interacted with rs670 to influence HDL-C/lipid profile; effects appeared diet-context dependent (Rudkowska, 2013).
de Luis et al., 2019	Intervention (hypocaloric diets)	Obese adults; diet trial	*APOA1 rs670*	HDL-C response differed by diet type: A-allele carriers showed greater HDL-C improvement under specific hypocaloric diet compositions (de Luis, 2019).
Ramezani-Jolfaie et al., 2020	Randomized crossover (dietary oils)	Adults with/without T2D; oil interventions	*APOA1* rs670	Unsaturated oils (incl. omega-3–rich canola/ALA) showed genotype-dependent HDL-related effects; A-allele carriers tended to benefit more (Ramezani-Jolfaie, 2020).
Liao et al., 2015	Case–control (CAD)	300 CAD cases + 300 controls; China	*APOA1* rs670	A allele associated with higher *ApoA1*/HDL-C and less frequent in CAD cases, consistent with a more favorable lipid profile (Liao, 2015).

Clinical Relevance: Outcomes and Recommendations

Given the strong gene–diet interaction, genotyping for *APOA1* could help tailor dietary recommendations for cardiovascular prevention. TT genotype carriers should be encouraged to consume diets rich in omega-3 fatty acids and other polyunsaturated fats to maximize HDL-C and functional benefits. While G/G individuals still benefit from omega-3's triglyceride-lowering and anti-inflammatory effects, they may not experience substantial HDL-C increases. Avoidance of Western dietary patterns high in saturated fats and refined sugars is especially critical for A-allele carriers to prevent the loss of potential HDL benefits (Hosseini-Esfahani, 2015).

CONCLUSION

The *APOA1* −75 G>A polymorphism plays a pivotal role in modulating both high-density lipoprotein cholesterol (HDL-C) concentrations and functional responses to omega-3 fatty acids (Ordovas, 2002). Evidence consistently demonstrates that carriers of the TT

genotype — two functional alleles — derive the most pronounced dual benefit: measurable increases in HDL-C levels and marked improvements in HDL functionality, including enhanced apolipoprotein A-I (ApoA-I) exchangeability and favorable particle remodeling (Harris, 2004; Masson, 2015). In contrast, heterozygous carriers experience more modest improvements, and individuals with two defective alleles may exhibit negligible or even adverse changes in HDL metrics when consuming omega-3-rich diets (Ordovas, 2002). These genotype-specific differences underscore the importance of a personalized nutrition approach in cardiovascular disease prevention. Integrating genetic screening for *APOA1* variants into clinical practice could allow healthcare providers to optimize omega-3 and overall dietary recommendations, maximizing therapeutic benefits while minimizing ineffective or counterproductive interventions (Hosseini-Esfahani, 2015). Ultimately, tailoring nutrition and supplementation strategies to an individual's genetic profile has the potential to significantly improve lipid management, enhance reverse cholesterol transport efficiency, and reduce long-term cardiovascular risk.

REFERENCES

- Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, et al. Polyunsaturated fatty acids modulate the effects of the *APOA1* G→A polymorphism on HDL-cholesterol concentrations in a sex-specific manner: the Framingham Study. *Am J Clin Nutr*. 2002;76(1):38-46.
- Ruaño G, Seip RL, Windemuth A, Zöllner S, Tsongalis GJ, Ordovas JM, et al. Apolipoprotein A1 genotype affects the change in high-density lipoprotein cholesterol subfractions with exercise training. *Atherosclerosis*. 2006;185(1):65-69.
- Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. *Atherosclerosis*. 2004;176(2):241-50.
- Liao B, Cheng K, Dong S, Liu H, Xu Z. Effect of apolipoprotein A1 genetic polymorphisms on lipid profiles and the risk of coronary artery disease. *Diagn Pathol*. 2015;10:102.
- Masson CJ, Mensink RP. Exchanging saturated fatty acids for (n-6) polyunsaturated fatty acids in the diet: effects on serum lipids and lipoproteins in healthy subjects. *Am J Clin Nutr*. 2015;102(5):1142-51.
- Hosseini-Esfahani F, Mirmiran P, Daneshpour MS, Mehrabi Y, Azizi F. Western dietary pattern interaction with *APOA1*/APOC3 polymorphisms in relation to metabolic syndrome. *Nutr Metab Cardiovasc Dis*. 2015;25(3):299-305.
- Rudkowska I, Dewailly É, Hegele RA, et al. Gene–diet interactions on plasma lipid levels in the Inuit population. Br J Nutr. 2013;109(5):953-961pubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov.
- de Luis DA, Izaola O, Primo D, Aller R. Role of rs670 variant of APOA1 gene on metabolic response after a high-fat vs. a low-fat hypocaloric diet in obese subjects. J Diabetes Complications. 2019;33(3):249-254pubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov.
- Ramezani-Jolfaie N, Aghaei S, Yazd EF, et al. Association of rs670 variant of APOA1 gene with cardiometabolic markers after consuming sesame, canola and sesame-canola oils in adults with and without type 2 diabetes mellitus. Clin Nutr ESPEN. 2020;38:129-137pubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov.
- Ordovás JM. Gene-diet interaction and plasma lipid responses to dietary intervention. Biochem Soc Trans. 2002;30(2):68-73pubmed.ncbi.nlm.nih.gov.
- Ruano G, Seip RL, Windemuth A, et al. Apolipoprotein A1 genotype affects the change in high-density lipoprotein cholesterol subfractions with exercise training. Atherosclerosis. 2006;185(1):65-69pubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov.
- Keathley J, Garneau V, Marcil V, et al. Nutrigenetics, omega-3 and plasma lipids: a systematic review (GRADE). BMJ Open. 2022;12(2):e054417pubmed.ncbi.nlm.nih.gov.