World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

NOS3 rs1800779 and endothelial dysfunction: Gene diet interactions in cardio metabolic health and personalised nutrition

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World Journal of Biology Pharmacy and Health Sciences, 2025, 23(01), 085-089

Publication history: Received on 27 May 2025; revised on 05 July 2025; accepted on 07 July 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.23.1.0657

Abstract

The endothelial nitric oxide synthase gene (*NOS3*) plays a central role in vascular health by regulating nitric oxide (*NO*) synthesis, a molecule vital for endothelial function and cardiovascular integrity. Among its polymorphisms, *rs1800779 (−922A>G)*, located in the promoter region, has been linked to altered gene expression and reduced *NO* bioavailability. This review explores the influence of the *rs1800779* variant on endothelial function and its associations with cardiovascular, metabolic, and respiratory disorders. Emerging evidence suggests that carriers of the *G* allele (*AG* or *GG* genotypes) exhibit diminished *NOS3* expression and increased susceptibility to endothelial dysfunction, hypertension, insulin resistance, and impaired lung function. The review further examines gene diet interactions involving this polymorphism, highlighting how specific dietary components such as nitrates, omega-3 fatty acids, antioxidants, and nutraceuticals may mitigate the negative effects associated with reduced *NO* synthesis. Personalised dietary strategies based on genotype may offer promising avenues to restore vascular health and reduce chronic disease risk. Integrating nutrigenomic insights into clinical and public health practices holds potential for developing targeted nutritional interventions that support endothelial function and improve long-term health outcomes.

Keywords: *NOS3; Rs1800779* Polymorphism; Endothelial Dysfunction; Nitric Oxide; Gene Diet Interaction; Personalised Nutrition

1. Introduction

Genetic factors significantly influence endothelial function, particularly through genes involved in nitric oxide (*NO*) synthesis and regulation. The *NOS3* gene encodes endothelial nitric oxide synthase (*eNOS*), a crucial enzyme responsible for producing nitric oxide (*NO*), a key mediator in maintaining vascular homeostasis. *NO* regulates endothelial function by modulating vascular tone, inhibiting platelet aggregation, and preventing leukocyte adhesion; malfunction in this pathway is central to the pathogenesis of cardiovascular and metabolic diseases [1].

The *rs1800779* polymorphism, located within the promoter region of *NOS3*, involves an adenine (*A*) to guanine (*G*) substitution that can alter transcriptional efficiency and, consequently, *NO* bioavailability. Promoter variations such as this affect *eNOS* expression and are implicated in endothelial dysfunction, hypertension, type 2 diabetes mellitus, and other cardio metabolic conditions [2].

Emerging research using molecular and clinical approaches has highlighted the functional impact of *rs1800779*. In a lung tissue study, individuals carrying the *AG/GG* genotype exhibited significantly reduced *NOS3 mRNA* and protein expression compared to *AA* carriers [3]. Moreover, functional variants in the *NOS3* promoter region, including *rs1800779*, have been associated with altered *NO* formation and increased risk of hypertensive disorders such as preeclampsia, reinforcing the physiological relevance of promoter *SNP*s in vascular health [2].

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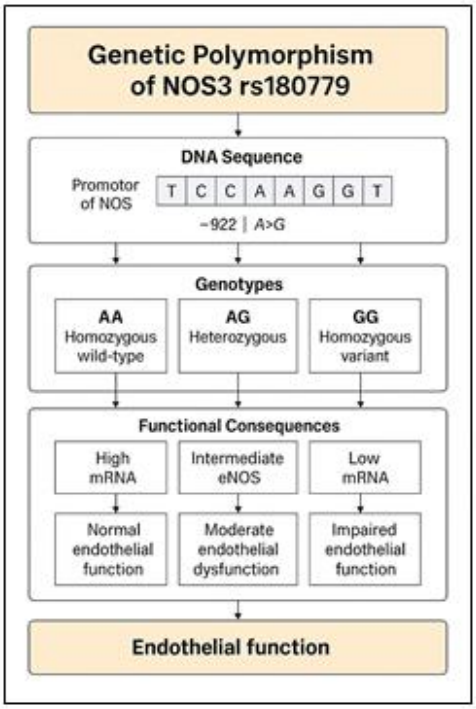
Similarly, diet gene interactions involving *NOS3* polymorphisms have gained considerable attention within the precision nutrition field. Recent evidence demonstrates that polymorphic variations within *NOS3*, when combined with nutritional interventions, can substantially influence cardio metabolic risk profiles [4]. Such findings emphasis the potential of genotype guided dietary strategies to improve individualised health outcomes. Therefore, by integrating molecular data with clinical trials and nutritional research, this review establishes a foundation for translating *rs1800779* genotype knowledge into precision nutrition strategies tailored to maintain endothelial and cardiovascular integrity.

This review aims to:

- Explore the structure and function of the *NOS3* gene, focusing on the *rs1800779* polymorphism and its effects on endothelial function.
- Evaluate the association between *rs1800779* genotypes and the risk of cardio metabolic and respiratory disorders.
- Explore the role of *rs1800779* in personalised nutrition and its interaction with dietary components.
- Propose genotype specific dietary recommendations to support vascular health.

2. Structure and Function of the *NOS3* Gene and the *rs1800779* Polymorphism

The *NOS3* gene, located on chromosome *7q36.1*, encodes endothelial nitric oxide synthase, an enzyme critical for the production of nitric oxide (NO), a vasodilator and signaling molecule essential for vascular homeostasis. *eNOS* is primarily expressed in endothelial cells, where it catalysis the conversion of L-arginine to L-citrulline, generating *NO* in the process, which plays a vital role in regulating endothelial functions.



Source- illustration created by the author based on data from [5, 6, 7]

Figure 1 Genetic polymorphism of NOS3 rs 180779

The *rs1800779* polymorphism *(−922A>G)* is located in the promoter region of the *NOS3* gene and involves a substitution of adenine (*A*) with guanine (*G*). This variant does not alter the amino acid sequence of the protein but influences gene transcription by modifying transcription factor binding affinity. Several studies have reported that individuals carrying the *G* allele exhibit reduced *eNOS* gene expression, leading to diminish *NO* production and compromised endothelial function [5, 6].

Reduced *NO* bioavailability due to this polymorphism has been associated with elevated risk of hypertension, impaired insulin signaling, and increased susceptibility to cardiovascular and respiratory diseases. Notably, *AG* or *GG* genotypes

may demonstrate intermediate or lower levels of *NO* synthesis compared to *AA* homozygotes, with effects modulated by environmental, epigenetic, and dietary factors [7].

The *rs1800779* polymorphism thus represents a functional genetic variant with potential clinical relevance in predicting endothelial health and guiding personalised interventions aimed at restoring *NO* balance.

3. Association Between *rs1800779* Genotypes and Disease Risk

The *rs1800779 (−922 A>G)* polymorphism in the *NOS3* gene has been widely studied for its influence on nitric oxide production and the consequent risk of cardio metabolic and respiratory disorders.

3.1. Cardiovascular Disorders

The rs1800779 polymorphism affects transcriptional activity of the *NOS3* gene, resulting in reduced *eNOS* expression and impaired *NO* bioavailability among *G* allele carriers. A pharmacogenetic study from the GenHAT project reported that individuals with *AG* or *GG* genotypes had a higher risk of heart failure (hazard ratio 1.10; 95 % CI, 1.00–1.21; $P = 0.046$), compared to *AA* homozygotes [8]. The same study found significant gene treatment interactions influencing stroke incidence and all-cause mortality, suggesting that *rs1800779* modifies cardiovascular outcomes in response to pharmacological interventions.

However, findings are not always consistent across populations. A 2022 study from Iraqi Kurdistan found no significant association between *rs1800779* genotypes and risk of myocardial infarction (MI) or circulating *NO* levels [9], suggesting that ethnicity, environmental exposure, and sample size may contribute to variability in genetic effects.

3.2. Metabolic Disorders

Although fewer studies have directly examined *rs1800779* and metabolic disease, reduced *NO* synthesis among *G* allele carriers is biologically linked to impaired endothelial insulin signaling. This may contribute to insulin resistance and increased susceptibility to type 2 diabetes mellitus [10]. Some evidence suggests *AG* heterozygotes might demonstrate a degree of protective endothelial insulin sensitivity, but results are not yet conclusive [11].

3.3. Respiratory Disorders

Another research demonstrated that *AG* and *GG* genotypes correspond to significantly lower *NOS3* protein expression in lung tissue. This finding implicates *rs1800779* in pulmonary endothelial dysfunction, which may contribute to the pathogenesis of chronic obstructive pulmonary disease (COPD), reduced lung function, and pulmonary hypertension. Although the Lung Health Study identified a potential link between the *G* allele and lower FEV_1 (Forced Expiratory Volume in 1 second) in COPD cases, the strength of association varied across ethnic groups and study designs [3, 12].

4. Role of *rs1800779* in Personalised Nutrition and Dietary Interactions

The concept of personalised nutrition, which involves tailoring dietary recommendations based on genetic variation, is increasingly recognised for its potential in preventing and managing complex diseases. In this context, the *NOS3* gene particularly the *rs1800779 (−922 A>G)* polymorphism has attracted attention due to its functional effects on endothelial nitric oxide synthase expression and nitric oxide availability. Although *rs1800779* does not alter the amino acid sequence of eNOS, it affects gene transcription, with the *G* allele associated with reduced *NOS3* expression and *NO* bioavailability [3].

4.1. Nutrient-Gene Interactions and Underlying Mechanisms

Nutrients that modulate vascular function, such as *omega-3 fatty acids*, polyphenols, nitrates, and antioxidants, have been proposed to interact with *NOS3* gene variants. Although direct studies on *rs1800779* are limited, research on related *NOS3* polymorphisms supports the existence of gene diet interactions, a recent research showed that *NOS3* variants modified lipid and vascular responses to *omega-3* supplementation, suggesting that *G* allele carriers may respond differently to cardio protective diets [13]. Another recent study also emphasised the role of antioxidant rich diets in supporting endothelial function by mitigating oxidative stress in individuals with reduced *eNOS* activity [14].

4.2. Genotype Guided Dietary Recommendations for rs1800779 Carriers

Carriers of the *G* allele (*AG* or *GG* genotypes) of the *NOS3 rs1800779* polymorphism are known to have reduced expression of endothelial nitric oxide synthase, which leads to lower nitric oxide availability. This diminished *NO*

synthesis has significant implications for endothelial function, vascular tone, and cardio metabolic health. Tailoring dietary interventions for these individuals can help compensate for their genetically impaired *NO* production and potentially reduce disease risk.

An increased intake of nitrate rich vegetables, such as beetroot, spinach, celery, rocket, and chard, is strongly advised. These vegetables contribute to *NO* production through the *nitrate–nitrite–NO* pathway, which can function independently of *eNOS*. Consumption of beetroot juice in particular typically in the range of 70 to 140 ml per day has been shown to improve vascular function in individuals with compromised *NO* production [15, 16].

Dietary *omega-3 fatty acids* also play an important role in supporting endothelial health. Fatty fish including salmon, mackerel, and sardines, as well as plant sources such as flaxseeds and walnuts, provide essential long chain *omega 3*. For individuals with the *G* allele, a regular intake of at least two servings of oily fish per week or 1000 mg per day of *EPA/DHA* supplements is recommended. Gene diet interaction studies have demonstrated that *NOS3* polymorphisms can modify the lipid lowering and vascular effects of *omega 3* intake, suggesting a genotype-dependent benefit [13, 17].

Antioxidant rich foods may offer additional benefits by protecting *NO* from oxidative degradation. A diet that includes citrus fruits, green leafy vegetables, berries, green tea, dark chocolate (containing at least 70% cocoa), and extra virgin olive oil can help reduce oxidative stress and preserve *NO* activity. Supplementation with *vitamin C* has been shown to restore endothelial function in individuals at cardiovascular risk [18]. Antioxidant support is particularly relevant for *G* allele carriers, who are more vulnerable to endothelial dysfunction under conditions of oxidative stress [14].

Modifying dietary fat and salt intake is also essential. A reduction in saturated fats and sodium is advised to improve endothelial function and overall vascular health. Evidence supports the adoption of a Mediterranean style or DASH (Dietary Approaches to Stop Hypertension) dietary pattern in individuals with impaired *NO* synthesis, due to the focus on plant based foods, unsaturated fats, and dietary fiber [19]. Physical activity should also be promoted, with at least 150 minutes of moderate intensity aerobic exercise per week shown to enhance endogenous *NO* production. Additionally, maintaining good oral hygiene and avoiding the use of antibacterial mouthwash around nitrate rich meals can support the activity of oral microbiota involved in nitrate reduction and subsequent *NO* synthesis [16].

For individuals whose diets are inadequate or who are at higher physiological demand, nutraceutical support may be beneficial. Supplements such as *L-arginine*, *L-citrulline*, and cofactors including *tetrahydrobiopterin (BH4),* riboflavin, magnesium, and iron may support *NO* synthesis and *eNOS* function [20].

In contrast, individuals with the *AA* genotype generally exhibit normal *NOS3* expression and *NO* production. For these individuals, a balanced diet adhering to standard nutritional guidelines is typically sufficient to maintain vascular health without the need for genotype-specific modifications.

4.3. Limitations and Future Directions

Despite rising interest in nutrigenetics, direct trials involving *rs1800779* are still rare. Most recommendations derive from studies on related *NOS3* variants. Furthermore, gene nutrient interactions are influenced by ethnicity, lifestyle, environment, and health status. As such, larger, diverse cohort interventions are needed to validate these genotype specific strategies.

5. Conclusion

The *NOS3* gene plays a critical role in vascular homeostasis through its regulation of endothelial nitric oxide production. The *rs1800779 (−922 A>G)* promoter polymorphism has been shown to influence *NOS3* gene expression, with the *G* allele generally associated with reduced *eNOS* levels and diminished *NO* bioavailability. This genetic variation has been implicated in a range of cardio metabolic and respiratory conditions, highlighting its clinical relevance. Insights from *NOS3* variants and emerging nutrigenomic research support the integration of genotype guided dietary interventions particularly those enhancing *NO* availability and reducing oxidative stress. Incorporating such genetic information into personalised care strategies may ultimately contribute to more effective prevention and management of chronic diseases through precision nutrition.

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