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# Influence of Known Genetic Risk Factors for Atherosclerosis on People with Different Racial Backgrounds

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**Abstract**
Atherosclerosis, a key contributor to cardiovascular diseases (CVD), presents significant health disparities among different racial groups due to variations in genetic risk factors. This review investigates the influence of Apolipoprotein E (*ApoE*) and Paraoxonase 1 (*PON1*) genes on atherosclerosis susceptibility across various racial backgrounds. *ApoE* polymorphisms, particularly the ε4 allele, are associated with elevated LDL cholesterol levels, contributing to higher atherosclerosis risk. PON1 activity, crucial for protecting lipoproteins from oxidative stress, also varies with racial background, influencing disease risk. A comprehensive literature search identified relevant studies, focusing on these genetic factors' prevalence and impact in different populations. The findings highlight significant racial differences in *ApoE* and *PON1* distributions, underscoring the need for tailored prevention and treatment strategies. Understanding these genetic disparities is vital for developing precision medicine approaches to mitigate CVD risk and improve health outcomes across diverse racial groups.

**Keywords**: atherosclerosis; cardiovascular disease; CVD; apolipoprotein E; ApoE; paraoxonase 1; PON1; racial disparities

## Introduction

Atherosclerosis, a chronic inflammatory condition characterized by the accumulation of lipids and fibrous elements in the large arteries, stands as a leading cause of cardiovascular disease (CVD) worldwide. This condition contributes significantly to morbidity and mortality rates, with severe implications such as myocardial infarction, stroke, and peripheral artery disease [1]. Understanding the multifaceted nature of atherosclerosis is critical, particularly its genetic underpinnings, as they play a pivotal role in individual susceptibility to the disease [2].

The pathogenesis of atherosclerosis involves a complex interplay of genetic, environmental, and lifestyle factors. The disease process begins with endothelium dysfunction, leading to increased permeability of the arterial wall and the subsequent infiltration of lipoproteins, particularly low-density lipoprotein (LDL) cholesterol [1]. Insulin insensitivity in the liver, skeletal muscle, and adipose tissue impairs the clearance of lipoproteins, resulting in their accumulation in the blood stream and deposition into abluminal spaces [1]. Oxidative modification of these lipoproteins triggers an inflammatory response, recruiting monocytes to the endothelium [1]. These monocytes differentiate into macrophages that engulf oxidized LDL, forming foam cells and leading to the development of fatty streaks [1]. Over time, these fatty streaks evolve into fibrous plaques characterized by a core of lipid-laden macrophages and a fibrous cap [1]. Plaque instability and rupture can result in acute clinical events such as myocardial infarction and stroke [1].

Genetic risk factors for atherosclerosis encompass a variety of genes that influence lipid metabolism, inflammation, and the function of endothelial cells. Notably, genes such as *Apolipoprotein E* (*ApoE*), and *Paraoxonase* 1 (*PON1*) have been identified as key players in the pathogenesis of this condition. *ApoE* is instrumental in lipid transport and metabolism, with its polymorphisms (ε2, ε3, ε4) being strongly associated with variations in plasma cholesterol levels and atherosclerosis risk [3, 4]. For instance, the *ApoE* ε4 allele is linked to higher LDL cholesterol levels and an increased risk of atherosclerosis, whereas the ε2 allele is associated with lower LDL cholesterol levels but may increase triglycerides

Meanwhile, *PON1*, an enzyme associated with HDL, protects lipoproteins from oxidative modification, thereby exerting an anti-atherogenic effect [5]. *PON1* hydrolyzes oxidized lipids in LDL and HDL, reducing oxidative stress and inflammation within the arterial wall. Genetic polymorphisms in PON1, such as Q192R and L55M, have been shown to affect enzyme activity and concentration, influencing an individual's susceptibility to atherosclerosis [5]. Due to its extensive research and clinical relevance; rich availability of data; and better comparative effectiveness, this

paper will be focusing on how *PON1* affects different racial groups in their risks of atherosclerosis.

The prevalence and impact of these genetic risk factors can vary significantly across different racial and ethnic groups due to genetic diversity [5]. It is well-documented that different racial groups exhibit varying risk profiles for CVD, influenced by a combination of genetic, socioeconomic, and lifestyle factors [6, 7]. For instance, African Americans have a higher prevalence of hypertension and stroke, while South Asians are more prone to diabetes and coronary artery disease [8]. These disparities highlight the importance of studying genetic factors within diverse populations to better understand and address health disparities in cardiovascular disease outcomes.

Our review aims to explore the mechanisms driving these differences, focusing specifically on two critical genetic factors: *ApoE*, and *PON1*. By examining the distribution and impact of these genetic variants, we seek to provide insights into tailored prevention and treatment strategies that consider genetic backgrounds. Understanding these genetic disparities is essential for developing effective public health strategies and clinical interventions tailored to specific populations, ultimately aiming to reduce the global impact of cardiovascular diseases. [9].

By summarizing current research on these genetic factors, we aim to provide a comprehensive overview of their role in atherosclerosis and how racial differences in *ApoE*, and *PON1* may influence disease risk and progression. This introduction sets the stage for a detailed exploration of the genetic landscape of atherosclerosis, emphasizing the need for continued research in this critical area of precision medicine. Our goal is to highlight the potential for personalized medicine approaches that consider genetic backgrounds, aiming to develop tailored prevention and treatment strategies that can more effectively address individual and population-specific cardiovascular disease risks.

## Methods

### Search Strategy

A comprehensive literature search was conducted using Ovid Medline to identify relevant studies examining the genetic risk factors of atherosclerosis among different racial groups. The search terms headers are used included "Atherosclerosis," "Racial Groups," "Classification, Ethnology, Genetics," "Proteins, " combined with filters for "English language" and "humans." These terms and filters were applied to capture a broad range of studies focusing on genetic variations in atherosclerosis-related proteins across various racial classifications.

### Inclusion and Exclusion Criteria

To ensure the relevance and quality of the studies included in this review, we applied the following inclusion and exclusion criteria:

**Table 1.** Inclusion and Exclusion Criteria Applied for the Study

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. Studies published in peer-reviewed journals.<br>2. Research involving human subjects.<br>3. Articles written in English.<br>4. Studies focusing on the genetic risk factors of atherosclerosis, specifically examining *ApoE* and *PON1*.<br>5. Research that includes data on racial or ethnic differences in the prevalence or impact of these genetic factors. | 1. Studies not involving human subjects.<br>2. Non-English language articles.<br>3. Articles without a clear focus on genetic risk factors or atherosclerosis.<br>4. Studies that do not provide specific data on racial or ethnic groups.<br>5. Review articles, commentaries, and editorials without original data. |

### Data Extraction

Relevant data were extracted from the selected studies using a standardized form. The extracted information included the study design, population characteristics, sample size, genetic variants studied (e.g., *ApoE* alleles, *PON1* polymorphisms), key findings related to atherosclerosis risk, and any reported racial or ethnic differences in these genetic factors [10].

### Quality Assessment

The quality of the included studies was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for observational studies [11]. The assessment criteria included:

1. Selection of study groups: Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at the start of the study.
2. Comparability of study groups: Control for confounding factors.
3. Outcome assessment: Adequacy of follow-up and use of validated outcome measures.

Studies were scored based on these criteria, and only those with a full score for all three aspects indicating satisfactory quality were included in the final review.

### Study Selection

The study selection process is illustrated in Table 1. Initially, 161398 studies were identified through the database search. After removing duplicates, 716 studies were screened based on their titles and abstracts. Of these, 37 studies were assessed for eligibility through full-text review, resulting in

the inclusion of nine. The rigorous methodology employed in this review ensures that the findings are based on high-quality evidence, providing a reliable overview of the genetic risk factors for atherosclerosis across different racial groups.

## Results

### Atherosclerosis is Representative of Cardiovascular Diseases

Cardiovascular disease (CVD) is a broad term, encompassing many medical conditions. In this review, CVD is defined as describing four conditions: coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease, and aortic atherosclerosis [12]. Therefore, the focus of this review will be on atherosclerosis, more specifically what genetic factors put individuals with different ethnicities at different risks for atherosclerosis. Atherosclerosis is representative of CVD due to the direct positive association between the degree of atherosclerosis and the frequency of CVD [13]. Further, atherosclerosis is easy to measure, and classification of severity is standardized; B-mode ultrasound can be used to monitor and measure atherosclerosis [13]. There is great variation in the rates of CVD between different ethnic groups [13], hence, this review aims to collect evidence from current academic literature to better understand the mechanistic drivers of these documented differences in CVD rates amongst various racial groups.

### How Racial Groups Affect an Individual's Cholesterol Profile, and Its Effects on Atherosclerosis

Cholesterol levels are a major factor in the prevalence of CVD. Studies show that South Asians currently have the highest prevalence of atherosclerosis compared to Europeans and Chinese (11%, 5%, and 2%, respectively) [13]. Interestingly, South Asians also exhibit the least favourable cholesterol and lipid profile for CVD, as compared to Europeans, and Chinese. Studies show that South Asians have higher total low-density lipoprotein (LDL) cholesterol, higher triglycerides, and lower high-density lipoprotein (HDL) cholesterol than Europeans and Chinese [13]. Triglycerides serve as the storage form of lipids in humans, and LDL cholesterols are often classified as the "bad cholesterol". LDL functions as cholesterol carriers that distribute cholesterol around the body. However, too much LDL can contribute to atherosclerotic plaque formation that obstructs arteries, eventually leading to atherosclerosis [15]. HDL, other than being cholesterol transporters, have several additional functional properties including anti-oxidant; anti-inflammatory; and immune-regulating activities [16]. Although HDL is generally considered the "good cholesterol", extremely high HDL levels are also associated with all-cause mortality [16].

To investigate the role of HDL in the differential susceptibility to atherosclerosis in different races, multi-ethnic studies were conducted [17, 18]. Montealegre et al. concluded that small HDL particles consistently do not retain their protective vascular effect in different races under controlled sex and age [17]. Their research team found that Apolipoprotein A-1, which is essential for the structure of HDL, also is a key determinate vascular protector protein [17]. Apolipoprotein C-III in contrast, is an important modulator of HDL function [17]. However, this research team did not find the apolipoprotein content within HDL to differ between races. Further research should be conducted to specifically investigate how the apolipoprotein content within HDL differs between races.

Samantha et al. focused on ethnicity's impact on HDL and how it affects atherosclerosis risks. Their Multi-Ethnic Study of Atherosclerosis (MESA) included four ethnic groups: White, Black, Hispanic, and Chinese [18]. Black individuals stood out with significantly higher systolic blood pressure, and fewer medium HDL particles compared to other ethnicities [18]. Hispanic individuals had significantly fewer large HDL particles, whereas White individuals had significantly more large HDL particles. Chinese individuals had significantly more small HDL particles compared to other races [18]. Within their study, Samantha et al. found that Black individuals stood out in another finding: the interaction between HDL concentrations and race for incident atherosclerosis was found significant only within Black participants. This means that the blunted levels of medium HDL particles in Black individuals were demonstrated to increase their risk of atherosclerosis significantly. It was also found that the interaction between the number of large HDL particles and race/ethnicity is also only significant ($p=0.05$) in Black participants [18]. The relationship is negative; hence Black individuals have a significantly lower number of large HDL particles, putting them at a higher risk of atherosclerosis again [18].

### Structure of *Apolipoprotein E* (*Apo E*) and its Consequences

With the understanding provided by previous research on LDL and HDL, it is essential to understand that any protein that impacts cholesterol metabolism would impact CVDs. *Apolipoprotein E* (*Apo E*) is discovered as a lipid transport protein and major ligand for LDL receptors, they are thus involved in cholesterol metabolism [3]. There are three different alleles for the *Apo E* gene, and they occur at different frequencies in humans, *Apo E2* at 5-10%, *Apo E3* at 65-70%, and Apo E4 at 15-20% [3]. A protein structural study revealed that although the *Apo E* alleles only differ by one amino acid, *Apo E2* binds defectively to LDL receptors because it has a cysteine at residue 158 instead of arginine that alters side chain conformation [3]. *Apo E3* contains Arginine-158 which forms a salt bridge with Aspartic acid-154 allowing optimal binding [3]. Although Apo E4 also contains Arginine-158, it has an arginine at residue 112 that interacts ionically with glutamic acid 255 in the carboxyl-terminal domain [3]. This ionic interaction in *Apo E4* is very strong, hence its lipoprotein binding preference is the large Very Low-

Density Lipoprotein (VLDL) that leads to elevated LDL levels and increases the risk for atherosclerosis [3].

*Apo E* has Major Implications in AD, Can We Translate That into Atherosclerosis

It is interesting to note that most literature investigates the importance of *Apo E* in Alzheimer's disease, a neurodegenerative disease [4]. In this context, Belloy et al. assessed *Apo E* genotypes in four ethnic groups: East Asian, non-Hispanic White, non-Hispanic Black, and Hispanic [4].

Although we cannot extract data to interpret how different *Apo E* genotypes affect atherosclerosis risk, we can establish an understanding of how *Apo E* genotypes vary between races. It was demonstrated that the East Asian group consistently shows a higher odds ratio for *Apo E* genotypes 4/4, 3/4, 2/4, and 2/2+2/3 compared to Non-Hispanic White, Non-Hispanic Black, and Hispanic groups [4]. This means the likelihood of having AD with *Apo E* genotypes 4/4, 3/4, 2/4, and 2/2+2/3 is higher compared to other racial groups (non-Hispanic White, non-Hispanic Black, and Hispanic) [4]. Non-Hispanic White and Black groups show similar odds ratios for the genotypes listed, but higher than the Hispanic group [4]. The Hispanic group consistently has the lowest odds ratio across all *Apo E* genotypes, thus the lowest risk of developing AD [4]. This data is valuable as it suggests that we may conduct experiments to find Odds ratios for *Apo E* genotypes and atherosclerosis in different racial groups. It is extremely dangerous to extrapolate data so we must not assume the odds ratios are the same for AD and CVD.

*Paraoxonase* gene (*PON*) and its Implications

Another genetic factor under investigation for its involvement in atherosclerosis is the paraoxonase (*PON*) gene. Interestingly, the genetic profiles for *PON* differ between racial groups [19]. Due to single nucleotide polymorphisms [SNPs], there are 3 isoforms of *PON* in humans: *PON1*, *PON2*, and *PON3* [19]. Each *PON* isoform prevents oxidative stress serves anti-inflammatory functions, and is therefore central in human illnesses, including atherosclerosis [20]. *PON1* is a calcium-dependent esterase and is 43-45 kDa in size [20]. Although present in the majority of tissues, *PONs* are mainly synthesized in the liver and circulate in the body within HDL particles [20]. *PON1* is evident in protecting LDL from oxidative stress and reducing macrophage foam cell formation, therefore reducing the risk of atherosclerosis [20]. *PON2* does not associate with HDL molecules but also serves as an antioxidant that protects humans from atherosclerosis, albeit through unknown mechanisms [20]. However, there lack of understanding of how this is achieved, *PON3* has a similar expression as *PON1*, it delays LDL oxidation but is less effective than *PON1* [20].

The Role of the *Paraoxonase* (*PON*) Gene in Atherosclerosis and Racial Differences

Kang et al. researched a group of 538 Han Chinese patients to evaluate the association of the *PON1* gene and their susceptibility to atherosclerosis [21]. These authors found that the polymorphism in *PON1* -126 C>G substitution showed a significant association with CAD/atherosclerosis risk. The presence of the minor allele G is associated with a decreased risk of atherosclerosis, shown by its statistically significant odds ratio (0.42), and adjusted P value (0.0127) [21].

The relationship between the *PON1* genotype and major adverse cardiac events (MACE) is also closely related to atherosclerosis risk. The *PON1* Q192R genotype shows a marginally significant association with risk of MACE within one year represented by its adjusted P value of 0.0487 and an FDR of 0.0974 [21]. This suggests that in presence of the minor allele [G] may increase the risk of MACE thus representing an increased risk of atherosclerosis [21].

With these results, Kang et al. deduced that the *PON1* Q192R polymorphism is associated with a lower risk of atherosclerosis, and the *PON1* -126C allele is associated with a higher risk of atherosclerosis [21].Black individuals have been impacted by the greatest burden of atherosclerosis, more than any other race, as they have a 52% greater hazard compared to all other races, and a 1.24 times greater hazard compared to whites [19]. *PON* has been identified as a major factor that could explain this phenomenon, as it plays an important role in inhibiting the arterial formation of cholesterol plaques that lead to atherosclerosis development [19]. Bhattacharyya et al. found in participants 55 years and older, those with the lowest *PON1* activity had 3.4 times greater risk for atherosclerosis [22].

Coombes et al. conducted a study including 80 African Americans and 120 Caucasians, with an equal number of males and females in each group [23]. It was found that the *PON1* 192RR genotype is more common amongst Black individuals, whereas the *PON1* 192QQ genotype exhibited a greater proportion in Caucasians [23]. The *PON1* 192RR genotype most common in Black individuals represents a lower *PON1* activity compared to the 192QQ genotype prevalent in Caucasians, as measured by POaseNA; DZOase; POase; and PhAc activity [23]. Lower *PON1* activity associated with the 192RR genotype in the Black participants offers less protection against oxidative stress; this finding helps to explain the increased atherosclerosis risk in Black individuals. Although lower in all other measures of *PON1* activity, African American females had significantly higher POaseNa activities than Caucasian females and males [23]. This contrasting data is not consistent with the other results.

However, the observed increase in POaseNa activity among African American females is insufficient to compensate for the overall lower *PON1* activity. Future studies should replicate this experiment to verify the consistency of POaseNa activity results. Coombes et al. confirmed in their studies that increased levels of *PON1* activity were associated with a lower risk of developing atherosclerosis [23].

Davis et al. investigated the *PON1* Q192R polymorphism and *PON1* activity in 200 adult males and females in Black and Caucasian participants (50 in each race/sex class) [24]. The allele frequency of the *PON1* Q192R gene differs significantly between African Americans and Caucasians. Distribution of functional genotypes in African Americans: QQ (15%), QR (34%), and RR (44%) [24]. In Caucasians: QQ (60%), QR (31%), RR (7%) [24]. Breaking this data down to allele frequencies, Caucasians had a *PON1* 192Q allele frequency of 0.77 and *PON* 192R allele frequency of 0.23 [24]. In contrast, African Americans had a *PON1* 192 Q allele frequency of 0.34, and *PON1* 192R allele frequency of 0.66 [24]. POase and DZOase activities were used to measure *PON1* activities. African Americans have a significantly lower DZOase activity, but a significantly higher POase activity, with a significantly lower DZOase/POase ratio [24]. Lower DZOase activity in African Americans indicates a reduced ability to hydrolyze certain substrates compared to Caucasians, which could imply a diminished protective effect against atherosclerosis. The elevated POase activity in African Americans suggests a compensatory mechanism for oxidative stress/lipid metabolism, however it is not as effective as DZOase activity [24]. These findings are consistent with other literature discussed above, which provides additional strength to this important discovery. The significantly lower DZOase/POase ratio in African Americans suggests a less efficient overall enzyme activity of *PON1*, thus helping to explain why they have an increased susceptibility to atherosclerosis [24].

## Discussion

### Future Research Implications

As genetic association studies for atherosclerosis continue to be performed, there are emerging researchers discovering new genetic factors that are correlated with atherosclerosis risks in various ethnic groups. However, more research is essential to better understand the genetic risk factors contributing to the differential CVD risk exhibited by different races.

Cannone et al. suggested a minor G allele of the atrial natriuretic peptide (ANP) genetic variant rs5068 that tends to have a varied profile in different racial groups and lowers the risk of atherosclerosis [25]. There is a slight variation in allele frequencies among the participants of this study, but future research is needed to elaborate on this difference [25].

It was suggested that individuals harbouring the AG + GG genotypes have higher HDL cholesterol levels (54 vs. 50 mg/dl, $p = 0.006$); lower triglyceride levels (80 vs. 91 mg/dl, $p = 0.01$); lower insulin levels (4.8 vs. 5.7 μU/ml, $p = 0.02$); lower incidences of diabetes (8% vs. 18%, $p = 0.01$) and metabolic syndrome (23% vs. 38%, $p = 0.002$) [25]. Differences in this genotype and its effect need to be more heavily researched to determine a causal relationship with atherosclerosis risks.

Another interesting genetic predisposition that should be further investigated for its implications in atherosclerosis is the apolipoprotein L1 gene (APOL1). Current literature has focused on how APOL1 impacts kidney functions but has recently revealed that it could be related to atherosclerosis risk as well. The APOL1 gene is one of the six APOL gene families and contains two risk variants: the G1 risk factor contains the two amino acid substitutions S342G and I384M; the G2 risk factor contains the two amino acid deletions, del1388N389Y [26]. The non-risk allele of the APOL1 gene is simply named G0 [26]. Limited research has suggested that hypertension in Black individuals may respond differently to angiotensin-converting enzyme inhibitors due to the APOL1 genotype, contributing to their increased risk of atherosclerosis [26]. Mukamal et al., upon a 13-year follow-up study with 91 African Americans with the 2 risk alleles, has concluded that African Americans without the 2 risk alleles do not differ significantly in risk of atherosclerosis or mortality from whites [1].

### Limitations

This review encountered several limitations. Firstly, the heterogeneity in the design and methodologies of the studies reviewed made direct comparisons between studies challenging. Variations in sample sizes, study populations, and genetic analysis techniques contributed to inconsistencies in the reported associations between genetic factors and atherosclerosis across different racial groups. Secondly, the majority of the studies included were observational, limiting the ability to establish causal relationships. Additionally, many studies did not account for potential confounding factors such as socioeconomic status, lifestyle, and environmental influences, which could impact both gene expression and disease risk.

Another limitation is the underrepresentation of certain racial groups in genetic research. Many studies predominantly focused on populations of European descent, leading to a potential bias in the findings and limiting the generalizability of the results to other ethnicities. There is a need for more diverse genetic studies that include a broader range of racial groups to fully understand the genetic contributions to atherosclerosis and cardiovascular disease.

Furthermore, the review primarily relied on published literature, which may be subject to publication bias. Studies with significant findings are more likely to be published, while those with null or negative results might be underreported. This could skew the overall interpretation of the genetic factors influencing atherosclerosis.

Lastly, the complexity of gene-environment interactions was not fully addressed in this review. Atherosclerosis is influenced by a combination of genetic predispositions and environmental factors [12]. The interplay between these elements is intricate, and isolating the effect of individual genetic factors can be challenging. Future research should aim to incorporate more comprehensive models that consider the multifactorial nature of atherosclerosis, including gene-environment interactions and epigenetic modifications.

## Conclusions

Atherosclerosis, a key feature of CVD including conditions such as coronary artery disease (CAD) and peripheral artery disease, reveals significant ethnic disparities in disease prevalence and severity [12, 13]. This review has examined how genetic factors, particularly variations in cholesterol metabolism and *Apolipoprotein E* (*Apo E*) alleles, as well as *paraoxonase* (*PON*) genes, contribute to differential susceptibilities among ethnic groups.

South Asians, who display higher LDL cholesterol and triglycerides alongside lower HDL cholesterol levels, exhibit an elevated risk of atherosclerosis compared to Europeans and Chinese. This highlights the importance of lipid profiles in disease development [13]. Additionally, variations in *Apo E* alleles and HDL composition underscore the influence of genetic factors on atherosclerosis risk, with implications for personalized cardiovascular risk management [3, 17, 18].

Recent research into *PON* genes, specifically *PON1*, *PON2*, and *PON3*, reveals their significant roles in protecting against oxidative stress and inflammation. Ethnic differences in *PON1* activity and polymorphisms have been linked to varying atherosclerosis risks, providing new insights into how these genetic factors contribute to disease disparities among different populations [4, 19]. The interactions between *Apo E* and *PON* gene variants further elucidate the complex genetic landscape influencing cardiovascular health.

To address these disparities and improve cardiovascular outcomes, it is essential to advance comprehensive, multi-ethnic research. This will help validate current findings, explore additional genetic and environmental risk factors, and inform targeted interventions. By understanding the diverse genetic influences on atherosclerosis, we can develop more effective strategies for managing cardiovascular risk and promoting health across varied populations.

## List of Abbreviations Used

CVD: cardiovascular disease
*ApoE*: *Apolipoprotein E*
*PON1*: *Paraoxonase 1*
LDL: low-density lipoprotein

## Conflicts of Interest

Both authors declare that they have no conflict of interests.

## Ethics Approval and/or Participant Consent

This review article doesn't require ethics approval and participant consent.

## Authors' Contributions

YS: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
HY: contributed to study design and planning, assisted with the collection and analysis of data, and gave final approval of the version to be published.

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