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Diet-Derived Circulating Antioxidants and Functional Outcome after Ischemic Stroke: A Two-Sample Mendelian Randomization Study

Hanlin Cao[1,a], Junting Yang[1,b], Furong Zheng[2,c], Gongwei Jia[1,d,*]

[1]Department of Rehabilitation, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, China
[2]Hubei Maternal and Child Health Hospital, Wuhan, Hubei, 430070, China
[a]1134041073@qq,com, [b]3519115010@qq.com, [c]15281346578@163.com, [d]jiagongwei@hospital.cqmu.edu.cn
**Corresponding Author*

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Abstract: Oxidative stress may contribute to post-stroke injury, but whether circulating diet-derived antioxidants influence functional recovery remains uncertain. We used two-sample Mendelian randomization to examine associations of genetically predicted absolute or metabolite concentrations of ascorbate, retinol, β-carotene, lycopene, α-tocopherol, and γ-tocopherol with poor functional outcome after ischemic stroke. Outcome summary statistics were obtained from the GISCOME genome-wide association study. Inverse-variance weighted analysis was the primary method; weighted median, MR-Egger, heterogeneity, and pleiotropy analyses were performed where instrument numbers permitted. Most estimates showed no clear association. Higher genetically predicted absolute retinol was nominally associated with lower odds of poor outcome (OR 0.094, 95% CI 0.012–0.710; P=0.022), although this estimate was based on only two variants. No clear associations were observed for the other antioxidants or metabolite measures. These findings do not support a general protective association; the retinol signal requires replication with stronger instruments and independent outcome data.

1. Introduction

Stroke remains a leading cause of death and long-term disability worldwide, and ischemic stroke accounts for most incident events [1]. For survivors, functional recovery rather than recurrence alone determines independence, care needs, and rehabilitation burden. The modified Rankin Scale (mRS) is widely used to characterize global disability after stroke, and poor outcome is commonly defined as mRS 3-6 at approximately 3 months. Although acute reperfusion therapy has improved outcomes for selected patients, effective strategies that modify the biological processes of recovery are limited.

The clinical question is not whether an antioxidant molecule can scavenge reactive species in vitro, but whether a higher endogenous circulating level is linked to a clinically meaningful difference in

disability after an ischemic event. This distinction matters in rehabilitation medicine. Global disability reflects the combined consequences of acute brain injury, neural repair, medical complications, and access to rehabilitation. Nutritional interventions may be relevant to recovery, but they must be evaluated against the competing influence of stroke severity and the many determinants of function. An etiologic analysis can therefore help distinguish promising hypotheses from associations that arise because more severely affected patients eat differently or have altered metabolism.

Oxidative stress is implicated in ischemia-reperfusion injury through reactive oxygen species generation, mitochondrial dysfunction, lipid peroxidation, inflammatory signaling, and cell-death pathways [2-4]. Diet-derived antioxidants, including vitamin C, vitamin E, retinoids, and carotenoids, are biologically plausible modifiers of these processes. Observational studies, however, are difficult to interpret because antioxidant concentrations reflect diet, smoking, adiposity, comorbidity, acute illness, and treatment. Reverse causation is particularly relevant after stroke because dysphagia, catabolism, and disability may themselves alter diet and circulating nutrient concentrations.

MR does not remove every source of uncertainty. Its interpretation depends on three assumptions: the selected variants must be associated with the antioxidant phenotype, must not be associated with confounders of the exposure-outcome association, and must influence outcome only through the exposure of interest. When these conditions are met, alleles are assigned before disease onset and are less susceptible to the behavioral and clinical changes that occur after stroke. The design is particularly useful here because functional disability could affect both nutritional intake and measured antioxidant concentrations in conventional observational cohorts.

Mendelian randomization (MR) uses genetic variants associated with an exposure as instrumental variables and can reduce confounding and reverse-causation bias under specific assumptions [5]. Previous work has largely addressed antioxidant status and stroke incidence or experimental neuroprotection, whereas evidence for post-stroke functional outcome remains limited [6,7]. Small observational studies have examined circulating carotenoids and oxidative-stress markers in relation to early outcome after ischemic stroke [8,9], and a review has summarized the limitations of these peripheral markers [10]. Small intervention studies have also evaluated vitamin E or combined vitamins A and D after ischemic stroke [11,12]. However, these findings do not establish whether lifelong differences in circulating antioxidant concentrations influence post-stroke disability. We therefore conducted a two-sample MR analysis to assess whether genetically predicted concentrations of diet-derived circulating antioxidants and related metabolites were associated with poor functional outcome after ischemic stroke.

The exposure phenotypes were intentionally analyzed as separate traits. Absolute circulating concentrations represent measured levels in blood, whereas metabolite data represent relative abundances generated by high-throughput profiling. These measures differ in assay platform, transformation, genetic architecture, and biological interpretation. Consequently, concordance between the two categories would strengthen confidence, whereas discordance should not be assumed to be contradictory.

2. Materials and Methods

This two-sample MR study used publicly available GWAS summary statistics. The exposures were absolute circulating concentrations of ascorbate, retinol, β-carotene, and lycopene, and relative metabolite concentrations of α-tocopherol, γ-tocopherol, ascorbate, and retinol. The outcome was poor functional outcome after ischemic stroke, defined as mRS 3-6, from the Genetics of Ischaemic Stroke Functional Outcome (GISCOME) network. The published GISCOME meta-analysis included 6,165 patients from 12 cohorts and evaluated functional outcome 60-190 days after stroke onset [13]. The primary IVW estimates are presented in Figure 1.

Before MR estimation, exposure and outcome associations were harmonized so that effect alleles corresponded to the same allele in both datasets. Palindromic variants with ambiguous allele frequencies were handled conservatively. Several variants were unavailable in the outcome GWAS and were removed when a suitable proxy could not be identified. The final analysis therefore used the harmonized instrument sets shown in Table 1 rather than all SNPs reported by the original exposure GWASs.

Absolute antioxidant instruments were selected at $P<5 \times 10{-}8$ with LD clumping at $r^2<0.001$ within 10,000 kb. Metabolite instruments were selected at $P<1 \times 10{-}5$ using the same LD threshold because these metabolite GWASs had smaller discovery samples. GWAS sources for α-tocopherol, ascorbate, retinol, β-carotene, lycopene, and metabolite phenotypes have been described previously [14-20]. Variants absent from outcome data were removed unless an appropriate proxy was available. The final numbers of harmonized instruments are reported in Table 1. All retained SNPs had F-statistics above 10 based on the instrument calculations, reducing concern about weak-instrument bias.

Absolute alpha-tocopherol was retained in the source GWAS inventory for transparency but was excluded from the final MR analysis because no harmonized outcome estimate was retained; the main text and outcome tables therefore report eight analyzed phenotypes.

For each SNP, a ratio estimate was calculated by dividing the SNP-outcome association by the SNP-exposure association. IVW combines these estimates using inverse-variance weights. The weighted-median estimator can remain valid if at least half of the total weight is contributed by valid instruments, whereas MR-Egger can detect and adjust for some forms of directional pleiotropy under additional assumptions [21,22]. These approaches are informative only when an exposure has sufficient independent instruments and should not be interpreted as independent replications.

Table 1. Summary of instruments identified for circulating dietary-derived antioxidants as both absolute levels and metabolites.

Trait	Study type	No. of SNPs	Main mapped genes †	p-value	LD ‡	Unit	Explained variance (R^2) §	No. of participants	PMID
Absolute circulating antioxidants									
α-tocopherol*	GWAS	3	SCARB1, CYP4F2, BUD13/ZNF259/ APOA5	$5 \times 10{-}8$	0.001	mg/L in log-transformed scale	1.7%	5,006	21729881
Lycopene	GWAS	5	SETD7	$5 \times 10{-}8$	0.001	μg/dL	30.1%	441	26861389
β-carotene	GWAS	2	BCMO1	$5 \times 10{-}8$	0.001	μg/L in natural log-transformed scale	4.8%	2,344	23134893
Retinol	GWAS	2	TTR, RBP4	$5 \times 10{-}8$	0.001	μg/L in natural log-transformed scale	2.3%	5,006	21878437
Ascorbate	GWAS	10	-	$5 \times 10{-}8$	0.001	μmol/L	1.7%	52,018	33203707
Circulating antioxidants metabolites									
α-tocopherol	GWAS	11	-	$1 \times 10{-}5$	0.001	log10-transformed metabolites concentration	6.8%	7,725	24816252
γ-tocopherol	GWAS	13	-	$1 \times 10{-}5$	0.001	log10-transformed metabolites concentration	9.8%	6,226	24816252
Retinol	GWAS	26	-	$1 \times 10{-}5$	0.001	log10-transformed metabolites concentration	20.6%	1,960	28263315
Ascorbate	GWAS	14	-	$1 \times 10{-}5$	0.001	log10-transformed metabolites concentration	21.7%	2,085	24816252

GISCOME outcome estimates were adjusted in the original GWAS for age, sex, ancestry, and baseline stroke severity measured by the National Institutes of Health Stroke Scale [13]. The primary outcome contrast was mRS 0-2 versus mRS 3-6. As only de-identified summary statistics were analyzed, no additional institutional review was required; ethics approval and informed consent had been obtained in the contributing studies.

The availability of genetic instruments varied substantially across phenotypes. Absolute retinol and β-carotene were represented by two SNPs each, whereas metabolite retinol was represented by 25 SNPs after harmonization. Absolute lycopene was represented by four SNPs and absolute

ascorbate by nine. This variation affected both statistical precision and the range of sensitivity analyses available. In particular, an estimate from two variants cannot be meaningfully stress-tested using methods that require multiple independent instruments.

Harmonized effect alleles were aligned so that odds ratios represented the association of a genetically predicted higher antioxidant level with odds of poor functional outcome. IVW was the primary analysis because it efficiently combines variant-specific Wald ratios when instruments are valid [23]. For exposures with three or more instruments, weighted-median and MR-Egger estimates were used as complementary sensitivity analyses [21,22]. Cochran's Q statistic assessed heterogeneity. Horizontal pleiotropy was explored using the MR-Egger intercept and the MR-PRESSO global test where the instrument number permitted [24]. PhenoScanner V2 was used during instrument screening for associations with potential confounders [25]. Analyses were conducted in R using MendelianRandomization and MR-PRESSO packages. Two-sided P values are reported without a study-wide multiplicity correction; findings are therefore interpreted as exploratory.

3. Results

For absolute ascorbate, the IVW estimate was 1.256 (95% CI 0.776-2.003; P=0.353). The corresponding estimate for lycopene was 0.914 (95% CI 0.672-1.243; P=0.567). For β-carotene, the IVW estimate was 1.053 (95% CI 0.627-1.771; P=0.843). None of these confidence intervals excluded the null. The retinol finding had a much smaller point estimate but a wide confidence interval, consistent with limited precision rather than a definitive treatment-relevant effect.

The main IVW estimates are presented in Figure 1 and Table 2. Among absolute antioxidant phenotypes, ascorbate, β-carotene, and lycopene were not associated with poor functional outcome. Absolute retinol showed a nominal association with lower odds of poor outcome (OR 0.094, 95% CI 0.012-0.710; P=0.022). This result was estimated from two SNPs, so weighted-median and MR-Egger analyses were not available.

The metabolite analyses likewise did not yield a consistent association pattern. The IVW odds ratio was 0.957 (95% CI 0.211-4.348; P=0.955) for α-tocopherol and 1.171 (95% CI 0.561-2.442; P=0.675) for γ-tocopherol. Metabolite ascorbate and retinol had IVW odds ratios of 0.841 (95% CI 0.632-1.119; P=0.235) and 1.070 (95% CI 0.967-1.183; P=0.190), respectively. The direction for metabolite retinol was not consistent with the absolute-retinol result, which further supports cautious interpretation of the nominal signal.

For relative metabolite phenotypes, no association was observed for α-tocopherol, γ-tocopherol, ascorbate, or retinol. Their IVW confidence intervals crossed the null and were generally imprecise, especially for α-tocopherol. The negative findings should therefore be interpreted as absence of convincing genetic evidence in the available datasets rather than proof that an effect is impossible.

Table 2. Associations between genetically predicted per unit increase in dietary-derived antioxidants and functional outcome after ischemic stroke in Mendelian randomization analyses.

		Inverse-variance weighted		Weighted median		MR-Egger	
Outcome	Exposure	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Functional Outcome After Ischemic Stroke	Absolute circulating antioxidants						
	Ascorbate (9 SNPs)	1.256(0.776,2.003)	0.353	1.203(0.671,2.159)	0.535	1.121(0.524,2.402)	0.777
	Retinol (2 SNPs)	0.094(0.012,0.710)	0.022	—	—	—	—
	β-Carotene (2 SNPs)	1.053(0.627,1.771)	0.843	—	—	—	—
	Lycopene (4 SNPs)	0.914(0.672,1.243)	0.567	0.812(0.616,1.243)	0.140	0.624(0.432,0.901)	0.128
	Circulating antioxidant metabolites						
	α-tocopherol (10 SNPs)	0.957(0.211,4.348)	0.955	1.523(0.213,10.886)	0.675	0.295(0.009,9.460)	0.510

γ-tocopherol (13 SNPs)	1.171(0.561,2.442)	0.675	1.043(0.373, 2.922)	0.936	0.311(0.055,1.751)	0.212
Ascorbate (12 SNPs)	0.841(0.632,1.119)	0.235	0.870(0.588,1.286)	0.485	0.983(0.595,1.623)	0.946
Retinol (25 SNPs)	1.070(0.967,1.183)	0.190	1.024(0.879,1.194)	0.758	1.064(0.805,1.406)	0.666

The null results should not be simplified to a claim that oxidative stress is irrelevant to recovery. Instead, they suggest that the genetically proxied baseline levels of these particular circulating measures do not show strong and consistent associations with the available global disability phenotype. Oxidative injury may still operate through local tissue processes, rapidly changing metabolites, inflammatory interactions, or subgroups that are not captured by a single circulating concentration. This is a common interpretive boundary for MR of nutritional biomarkers, where a genetic proxy may explain a small portion of exposure variance and does not emulate a clinical intervention.

For exposures with sufficient instruments, Cochran's Q tests did not indicate statistically detectable heterogeneity. MR-Egger intercept tests and MR-PRESSO global tests did not provide evidence of directional horizontal pleiotropy. The detailed heterogeneity and pleiotropy results are summarized in Table 3, while the corresponding MR-Egger sensitivity estimates are presented in Figure 2. Weighted-median and MR-Egger point estimates were broadly directionally compatible with the null IVW findings for most analyzable exposures, although several estimates had wide confidence intervals. Sensitivity analyses cannot establish instrument validity, particularly for phenotypes represented by few variants.

From a clinical perspective, these findings should not be used to recommend against nutrition assessment or correction of established deficiency in stroke survivors. Nutritional risk, dysphagia, sarcopenia, and inadequate intake remain relevant rehabilitation concerns. Rather, the analysis indicates that routine antioxidant supplementation aimed specifically at improving global functional outcome lacks genetic support from the phenotypes examined here. Trials designed for a clinically defined deficiency state, a specific formulation, and a clearly timed rehabilitation setting address a different question and may still be justified where there is a strong biological and clinical rationale.

Table 3. MR sensitivity analysis results of associations between circulating antioxidants and functional outcome after ischemic stroke. Note: I^2 values below zero were truncated to 0. The absolute-retinol estimate is based on two SNPs and was not eligible for MR-Egger, weighted-median, or MR-PRESSO analyses.

Exposure	No. of SNPs	Heterogeneity			Pleiotropy						
		Inverse-variance weighted			MR-Egger			MR-Egger intercept		MR-PRESSO	
		Q	I^2	P	Q	I^2	P	intercept	P	No. outlier	P
Absolute circulating antioxidants											
Ascorbate	9	1.504	0	0.993	1.36	0	0.987	0.010	0.717	0	0.992
Retinol	2	0.437	0	0.509	—	—	—	—	—	—	—
β-Carotene	2	1.453	0.312	0.228	—	—	—	—	—	—	—
Lycopene	4	7.451	0.597	0.059	1.653	0	0.438	0.154	0.138	0	0.209
Circulating antioxidant metabolites											
α-Tocopherol	10	3.115	0	0.96	2.569	0	0.958	0.037	0.481	0	0.956
γ-Tocopherol	13	16.575	0.276	0.166	13.133	0.162	0.285	0.059	0.118	0	0.178
Ascorbate	12	6.579	0	0.832	6.035	0	0.812	-0.021	0.478	0	0.874
Retinol	25	28.761	0.166	0.229	28.759	0.200	0.188	0.001	0.969	0	0.233

Outcome	Exposure	No.SNPs	Heterogeneity test			MR method	OR(95%CI)	*p*-Vaule
			Cochran's Q statistic	I^2	*p*-Value			
Functional Outcome Aafter Ischemic Stroke	Absolute circulating antioxidants							
	Ascorbate	9	1.504	-4.321	0.993	IVW	1.256(0.776,2.003)	0.353
	Retinol	2	0.437	-1.289	0.509	IVW	0.094(0.012,0.710)	0.022
	β-Carotene	2	1.453	0.312	0.228	IVW	1.053(0.627,1.771)	0.843
	Lycopene	4	7.451	0.597	0.059	IVW	0.914(0.672,1.243)	0.567
	Circulating antioxidants metabolites							
	α-Tocopherol	10	3.115	-1.89	0.96	IVW	0.957(0.211,4.348)	0.955
	γ-Tocopherol	13	16.575	0.276	0.166	IVW	1.171(0.561,2.442)	0.675
	Ascorbate	12	6.579	-0.672	0.832	IVW	0.841(0.632,1.119)	0.235
	Retinol	25	28.761	0.166	0.229	IVW	1.070(0.967,1.183)	0.19

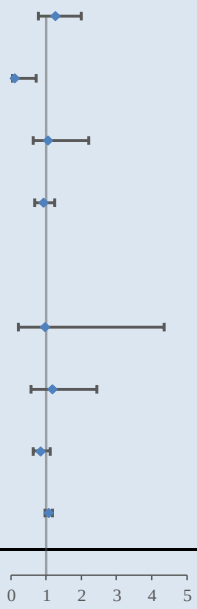


Figure 1. Primary IVW estimates for absolute circulating antioxidants and circulating antioxidant metabolites in relation to poor functional outcome after ischemic stroke.

Absolute circulating antioxidants	No.SNPs	OR [95% CI]	p-Value
Ascorbate	9	1.121 (0.524,2.402)	0.777
Lycopene	4	0.624 (0.432,0.901)	0.128
Circulating antioxidants metabolites			
α-Tocopherol	10	0.295 (0.009,9.460)	0.510
γ-Tocophero	13	0.311 (0.055,1.751)	0.212
Ascorbate	12	0.983 (0.595,1.623)	0.946
Retinol	25	1.064 (0.805,1.406)	0.666

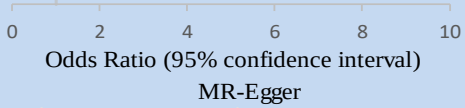


Figure 2. MR-Egger sensitivity estimates for absolute circulating antioxidants and circulating antioxidant metabolites in relation to poor functional outcome after ischemic stroke.

4. Discussion

In this two-sample MR analysis, genetically predicted circulating concentrations of most diet-

derived antioxidants were not associated with functional outcome after ischemic stroke. The only nominally significant result was for absolute retinol. Because that estimate was based on two variants and could not be evaluated with MR-Egger, weighted-median, or MR-PRESSO methods, it should be regarded as hypothesis-generating rather than as evidence that retinol supplementation improves recovery.

The discrepancy between absolute and metabolite retinol also illustrates why phenotype definition must be considered before translation. The absolute-retinol GWAS is driven by variants in key transport genes, whereas relative metabolite levels may reflect a broader metabolomic context. Either phenotype can capture biological information, but neither alone establishes a direct nutritional treatment target. Future work should use contemporary, larger metabolite GWASs, examine whether the same causal variant drives the exposure and outcome signal, and evaluate clinically specific outcomes such as activities of daily living, cognition, fatigue, and motor recovery.

The results are clinically relevant because post-stroke nutrition is commonly discussed in rehabilitation, but micronutrient supplementation should not be inferred from biological plausibility alone. Oxidative pathways are involved in ischemic injury [2-4], yet a lifelong genetically proxied circulating biomarker is not equivalent to a short-term nutritional intervention in the acute or subacute recovery phase. Nutrient effects may depend on baseline deficiency, dose, formulation, timing, interactions with medicines, and the ability of a compound or its metabolites to reach relevant tissue. This distinction may explain why experimental antioxidant findings and observational associations do not necessarily translate into a clear MR signal for global functional outcome.

Retinol is transported in blood primarily through the RBP4 and transthyretin pathway, and the two instruments in the absolute-retinol GWAS were located near RBP4 and TTR [16]. Retinoid signaling may be relevant to neural differentiation, synaptic remodeling, oxidative stress responses, and cell survival. Observational studies have also linked vitamin A-related measures with post-stroke outcome [26,27]. Nevertheless, the present genetic estimate does not distinguish retinol itself from genetically correlated aspects of its transport, lipid metabolism, or broader physiology. The very wide confidence interval further limits precision. Replication with a larger retinol GWAS, independent post-stroke outcome data, colocalization, and rigorous pleiotropy assessment is required before any clinical interpretation.

The null findings for vitamin C, vitamin E-related phenotypes, β-carotene, and lycopene align with the mixed clinical evidence for antioxidant supplementation after stroke. A small case-control study did not demonstrate improved stroke recovery with vitamin C supplementation [7], and a systematic review of vitamin E trials did not establish a consistent benefit for stroke prevention [6]. These sources cannot answer the present etiologic question directly, but they reinforce the need for restraint when moving from antioxidant biology to rehabilitation recommendations.

The present design also differs from studies of incident stroke. Genetic determinants of antioxidant concentration may influence vascular risk, acute lesion biology, or recovery through different pathways. Functional outcome after established stroke is influenced by initial severity, lesion location, reperfusion, complications, rehabilitation access, mood, cognition, and social context. A single nutritional biomarker is therefore unlikely to explain a large proportion of between-patient functional variation.

This study used summary statistics from independent exposure and outcome GWASs, a clinically meaningful functional outcome, and several complementary MR sensitivity approaches. The outcome GWAS adjusted for major prognostic factors, including baseline stroke severity. The analysis also evaluated both absolute concentrations and metabolite measures, recognizing that these phenotypes are not interchangeable.

Several limitations warrant emphasis. First, genetic instruments for several antioxidants were few and some discovery GWASs were small, limiting power and the ability to assess pleiotropy. Second,

the metabolite instrument threshold was less stringent than the conventional genome-wide threshold; results should be considered exploratory. Third, MR reflects genetically predicted lifetime differences in measured circulating levels, not the effect of changing dietary intake or prescribing a supplement after stroke. Fourth, GISCOME assessed global disability at approximately 3 months and does not capture specific rehabilitation outcomes such as gait, upper-limb function, cognition, or quality of life. Fifth, the underlying datasets were primarily of European ancestry, which limits generalizability. Finally, no study-wide multiplicity correction was applied across the antioxidant phenotypes; the retinol result is consequently not confirmatory.

Future studies should separate descriptive nutritional associations from causal claims. A pragmatic next step would be to combine a well-powered prospective rehabilitation cohort with repeated dietary assessment, biochemical measurements, and standardized functional outcomes, while treating the present MR findings as one component of evidence. Such a design could test whether measured deficiency, dietary pattern, inflammation, and rehabilitation dose interact after stroke. Genetic analyses could then be used to prioritize robust biomarker signals for replication rather than to substitute for clinical trials.

The present paper is therefore best viewed as a focused genetic-evidence study rather than a clinical nutrition guideline. Its main contribution is to define which antioxidant hypotheses are not currently supported by the available summary data and to identify absolute retinol as a signal that merits methodologically stronger replication.

5. Conclusions

This MR analysis found no convincing evidence that genetically predicted circulating ascorbate, tocopherols, β-carotene, lycopene, or retinol metabolites influence poor functional outcome after ischemic stroke. The nominal inverse association for absolute retinol was based on two genetic instruments and requires independent replication. Current results do not justify antioxidant supplementation as a strategy to improve post-stroke functional recovery.

Data Availability Statement

All data used in this study were publicly available GWAS summary statistics from the cited source studies and the GISCOME network. The analyses were based on publicly available GWAS summary statistics; no individual-level data were accessed.

Ethics Statement

This study analyzed publicly available, de-identified summary statistics. Ethics approval and informed consent were obtained by the investigators of the contributing GWASs; no additional ethical approval was required for this secondary analysis.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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