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Review Article

Association of GATA4 polymorphisms with the risk of hypospadias and congenital heart defects in Indian children: A Review

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Abstract

Background: Congenital heart disease (CHD) and hypospadias are common developmental anomalies with both affecting approximately 1% of neonates. Emerging data suggest these conditions often co-occur, hinting at shared genetic pathways. This review evaluates the role of GATA4, a transcription factor implicated in both cardiac and urogenital development, and its polymorphisms in the joint risk of CHD and hypospadias, with a focus on evidence relevant to South Asian and Indian populations.
Materials and Methods: We conducted a comprehensive literature search (PubMed/Google Scholar) for studies on GATA4 variants, hypospadias, and CHD, including functional assays and epidemiological association studies.
Results: Several GATA4 polymorphisms—especially rs12458, rs1139244, and c.620C>T—have been associated with either hypospadias or CHD in diverse populations.
Discussion and Conclusion: A single Chinese cohort reported rs12458's association with hypospadias (OR 1.42), while rs1139244 was linked to CHD in Chinese children (OR 1.33), and c.620C>T was noted in South Indian CHD cases. Functional assays confirm that these variants modulate GATA4 expression or activity in vitro. GATA4 polymorphisms potentially bridge cardiac and urogenital developmental defects. Future case-control studies in Indian populations could elucidate these associations and enable targeted screening strategies.

Keywords: Congenital heart disease, Developmental anomalies, Hypospadias, GATA4 polymorphism, South Asian population

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1. Introduction

Congenital anomalies are a leading global cause of neonatal morbidity and mortality, contributing significantly to infant hospitalizations, surgical interventions, and long-term health burdens. Among these, congenital heart defects (CHDs) and hypospadias are among the most commonly reported structural malformations. CHDs affect approximately 1 in 100 live births, with a global prevalence of around 1%. In the U.S. alone, nearly 40,000 infants are born each year with some form of congenital heart anomaly.[1] The burden is particularly high in low- and middle-income countries, where early diagnosis and surgical correction are limited by infrastructure.[2] Hypospadias, a malformation in which the urethral opening is located along the underside of the penis, occurs in 0.3% to 0.8% of male births, and its incidence appears to be rising in several regions.[3,4]

Interestingly, epidemiological studies have shown a co-occurrence of CHD and hypospadias in up to 1.8% of cases, higher than the baseline prevalence of either condition alone.[5] This non-random association suggests shared developmental pathways or common genetic etiologies, making the study of such overlapping phenotypes clinically and biologically relevant. Developmentally, both the heart and external genitalia derive from mesodermal lineages and are sensitive to disruptions in transcriptional regulation during embryogenesis. This has led researchers to investigate key transcription factors involved in cardiac and urogenital development, particularly those with pleiotropic roles across tissues.

One such gene is GATA binding protein 4 (GATA4), a member of the GATA family of zinc-finger transcription factors. GATA4 binds to GATA motifs in the promoter

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regions of numerous target genes and is vital for cardiac morphogenesis, regulating processes such as endocardial cushion formation, myocardial proliferation, septation, and outflow tract development.[6,7] Murine knockout models of GATA4 result in embryonic lethality due to severe heart malformations, highlighting its indispensable role in early cardiogenesis.[8] Beyond its role in the heart, GATA4 is also expressed in developing gonads and the genital tubercle, where it is involved in Leydig cell differentiation, urogenital ridge development, and androgen biosynthesis, all crucial to penile and urethral formation.[9,10] This dual expression pattern raises the hypothesis that GATA4 dysregulation may be a molecular link between CHD and hypospadias.

1.1. Recent studies have identified specific GATA4 polymorphisms associated with either condition

rs12458, located in the 3′ untranslated region (3′ UTR), may affect microRNA binding and post-transcriptional regulation of GATA4 expression.[11] rs1139244, a noncoding regulatory variant, has been associated with altered transcriptional activity in cardiac cells.[12] c.620C>T, a coding variant found predominantly in South Indian CHD cohorts, leads to amino acid substitutions that may alter DNA-binding affinity or disrupt co-factor interactions.[13] Although these variants have been independently linked to either CHD or hypospadias in Chinese and Indian populations, a systematic investigation into their combined effect in individuals with both anomalies is lacking. No Indian study has yet evaluated GATA4 polymorphisms in the context of coexisting CHD and hypospadias, despite the availability of region-specific data showing allele variability in South Indian subpopulations.[14] Given the accumulating evidence of genotype–phenotype correlations and the shared developmental origins of cardiac and urogenital structures, a comprehensive investigation is both timely and warranted. Understanding the role of GATA4 in dual phenotypes may ultimately contribute to early genetic screening, better clinical surveillance and potentially novel therapeutic approaches for children affected by these congenital anomalies. This review examines current evidence, highlights genetic and functional studies, and proposes a research framework to study this association in South Indian children. Highlighting the research gap in Indian cohorts, particularly in the South Indian context and proposes a roadmap for future investigations, including molecular, epidemiological, and translational strategies.

This was aimed to explore the association between GATA4 gene polymorphisms and the co-occurrence of hypospadias and congenital heart defects (CHD) in Indian children, with emphasis on genotype–phenotype correlations and functional implications.This review had the objectives to synthesizes existing literature on GATA4 polymorphisms and their functional consequences, to explore the molecular mechanisms by which these variants may disrupt cardiac and urogenital development.

2. Materials and Methods

2.1. Literature review and methods

A comprehensive systematic literature search was conducted using electronic databases including PubMed, Google Scholar, and Scopus for peer-reviewed studies published up to June 2025. The search employed the following keywords and MeSH terms: GATA4 polymorphism, hypospadias, congenital heart defects (CHD), rs12458, rs1139244, c.620C>T, GATA4 mutation, TBX5, and functional promoter assays. Boolean operators were employed to narrow and refine the search results.

The aim was to retrieve articles reporting original data on the association of GATA4 polymorphisms with CHD or hypospadias, functional studies assessing the molecular consequences of GATA4 variants, population-specific genetic investigations focused on South Asian, especially Indian, cohorts. Additionally, reference lists of key articles and reviews were manually screened to identify any relevant studies that might have been missed in the initial search. Recent reviews and meta-analyses were examined to place individual findings in broader context.[15,16]

2.2. Inclusion and exclusion criteria

2.2.1. To ensure scientific rigor, the following inclusion criteria were applied

Original research involving human participants, including case–control, cohort, or population-based studies;Reports containing genotype frequencies, odds ratios (ORs), confidence intervals (CIs), and p-values;Studies conducting functional analyses, including luciferase assays, mRNA expression profiling, or animal models;

2.2.2. Exclusion criteria included

Case reports, reviews without primary data, and conference abstracts lacking methodological details; Animal-only studies, unless they provided mechanistic insight into human-relevant GATA4 function;Articles without sufficient genotyping or statistical outcome data (e.g., missing ORs or allele frequencies).This selection framework aligns with PRISMA guidelines for genetic association studies.[17]

2.3. Study selection and key findings

The search strategy initially yielded 78 unique articles. After removing duplicates and applying inclusion criteria through title/abstract and full-text screening, a total of fifteen articles were selected for detailed analysis. These comprised around five studies investigated the association between GATA4 polymorphisms and congenital heart disease (CHD).Several authors have investigated GATA4 variants in hypospadias, with four studies reporting significant findings.Six functional investigations, including luciferase reporter assays, in vitro mutagenesis, and animal models.

2.4. Notable studies included

A large case–control study in China identifying rs12458 as significantly associated with hypospadias (OR: 1.42; 95% CI: 1.17–2.35; p = 0.036).[18] An association between rs1139244 and CHD in 450 Chinese cases and 500 controls (OR: 1.33; p = 0.025), highlighting the regulatory potential of this SNP.[19] In South India, authors identified a significant overrepresentation of the c.620C>T variant in CHD patients compared to matched controls, suggesting a regional allele effect ($p < 0.05$).[20] A landmark paper by Garg et al. (2003) provided functional evidence that GATA4 mutations impair interaction with TBX5, disrupting cardiac transcriptional regulation.[21] Additional studies reviewed investigated noncoding variants and microRNA binding effects,[11,22] and also functionally characterized GATA4 mutations affecting promoter activation.[23]

2.5. Data Extraction and Synthesis

Data were systematically extracted from all included studies into a predefined table, with the following fields:

1. Study location and population;
2. Sample size (cases and controls);
3. SNPs analyzed (e.g., rs12458, rs1139244, c.620C>T);
4. Genotype and allele frequencies;
5. Odds ratios (OR), 95% confidence intervals (CI), and p-values;
6. Methodological notes (e.g., adjustment for confounders, genotyping methods).
7. Functional studies, extraction focused on:
8. Type of assay (e.g., luciferase reporter, EMSA, qPCR);
9. Cell lines used (e.g., cardiomyocytes, epithelial cells);
10. Variant impact (up/downregulation, loss-of-function, miRNA binding changes);
11. Animal model phenotypes, where applicable.

All extracted data were cross-verified and summarized to identify consistent patterns of association and mechanistic insights. Findings were grouped by phenotype (CHD vs. hypospadias) and variant type (coding vs. noncoding), enabling structured comparison.The synthesis also evaluated methodological robustness, identifying studies with adequate power, ethnic matching, and functional validation as higher quality. These were prioritized in the interpretation phase.

3. Results

3.1. GATA4 polymorphisms and risk of hypospadias

Several studies have identified associations between single nucleotide polymorphisms (SNPs) in the GATA4 gene and increased risk of hypospadias. In a pivotal study by Chen et al., a case-control analysis involving 500 Chinese children with hypospadias and 600 healthy controls revealed that the T allele of rs12458 was significantly more prevalent among cases (30% vs. 22%).[18] The odds ratio (OR) was calculated at 1.42 (95% CI: 1.17–2.35; p = 0.036), indicating a moderate but statistically significant increase in risk associated with this variant.

In the same study, functional luciferase assays demonstrated that constructs carrying the T allele exhibited lower transcriptional activity compared to those with the wild-type allele. This indicates that the rs12458 T variant may lead to reduced GATA4 expression, potentially disrupting normal urethral development. These mechanistic findings further support a causal role for noncoding regulatory variants in the pathogenesis of hypospadias. Other variants in GATA4 have also been suggested, although less frequently, with further studies needed to validate their significance in diverse ethnic populations.

3.2. GATA4 polymorphisms and risk of congenital heart defects (CHD)

The role of GATA4 variants in the etiology of congenital heart defects is well-documented. In a study by Kalayinia S et al., involving CHD patients and controls, the G allele of rs1139244 was significantly associated with increased CHD risk.[24] This SNP resides in a potential regulatory region, suggesting a possible impact on gene transcription or RNA stability.

In India, Mattapally et al. evaluated the c.620C>T polymorphism in a South Indian cohort and found it to be significantly more frequent among CHD patients ($p < 0.05$).[25] This variant leads to a missense mutation altering the amino acid sequence of the GATA4 protein, possibly affecting its DNA-binding affinity or interaction with cofactors such as TBX5.

Despite strong individual associations between GATA4 polymorphisms and CHD or hypospadias, no study to date has systematically explored the co-occurrence of these two anomalies in the same individuals.

3.3. Functional analyses of gata4 variants

Functional studies using in vitro models have helped elucidate how different GATA4 variants contribute to developmental abnormalities. Chen J et al. demonstrated that the H436Y missense mutation, commonly found in CHD patients, leads to a significant reduction in transcriptional activation of cardiac-specific promoters.[18] This suggests a loss-of-function effect, likely disturbing cardiogenesis.

Pulignani et al. identified several 3′ untranslated region (3′ UTR) variants that altered microRNA (miRNA) binding, consequently modulating GATA4 post-transcriptional expression.[11] Given that miRNA-mediated repression plays a critical role in tissue-specific gene regulation, these findings highlight a noncoding mechanism influencing disease phenotype.

Garg et al. emphasized that GATA4 mutations can impair its physical interaction with TBX5, a key partner in the cardiac transcription factor network.[5] The synergy

between GATA4 and TBX5 is crucial for the activation of several genes involved in cardiac septation and morphogenesis. Heterogeneity in gene expression responses among cells and individuals involves epigenetic mechanisms. Advancing technology allowing genome-scale interrogation of epigenetic marks provides a rapidly expanding view of the complexity and diversity of the epigenome.[26]

3.3. Overlapping molecular and developmental mechanisms

Animal model studies provide compelling evidence that heterozygous GATA4 mutations result in overlapping phenotypes involving the heart and urogenital system. Mice with GATA4 haploinsufficiency exhibit atrial and ventricular septal defects, as well as atrioventricular cushion malformations.[21,27] This reflects the gene's critical role during mesodermal differentiation.

Moreover, embryonic expression patterns show that GATA4 is co-expressed in the cardiogenic mesoderm and the urogenital ridge, both of which develop during similar stages of embryogenesis. Variants like rs12458, although noncoding, may have regulatory effects across multiple organ systems. This dual expression pattern suggests a plausible shared developmental vulnerability, making GATA4 a compelling candidate gene in syndromes involving both cardiac and genital anomalies. The results have been summarized in **Table 1**.

Table 1: Summary of GATA4 polymorphisms, functional impact, and developmental associations with hypospadias and congenital heart defects

Category	Variant / Study	Population / Sample	Key Findings	Implications
Hypospadias Risk	rs12458 (T allele) – Chen et al.	500 hypospadias cases, 600 controls (Chinese)	T allele more prevalent in cases (30% vs. 22%); OR = 1.42 (95% CI: 1.17–2.35; p = 0.036)	Increased risk of hypospadias; reduced transcriptional activity in luciferase assay
CHD Risk	rs1139244 (G allele) – Kalayinia et al.	CHD cases and matched controls	Associated with increased CHD risk; located in regulatory region	May affect gene transcription or RNA stability
	c.620C>T – Mattapally et al.	South Indian CHD cohort	Missense variant significantly more frequent in CHD patients ($p < 0.05$)	Alters amino acid sequence; may impact DNA binding or TBX5 interaction
Functional Analysis	H436Y – Chen J et al.	CHD patients	Reduced activation of cardiac-specific promoters	Suggests loss-of-function affecting cardiogenesis
	3′ UTR variants – Pulignani et al.	In vitro models	Altered miRNA binding; affects post-transcriptional regulation	Indicates noncoding mechanism influencing expression
	TBX5 interaction – Garg et al.	Experimental studies	GATA4 mutations impair interaction with TBX5	Affects cardiac septation and morphogenesis
Overlapping Developmental Mechanisms	GATA4 haploinsufficiency – Animal models	Mice models	Cardiac (septal) and urogenital defects observed	Supports dual developmental role of GATA4
	Embryonic co-expression patterns	Developmental studies	GATA4 co-expressed in heart and urogenital ridge	Suggests shared embryological vulnerability

This table presents key GATA4 gene variants associated with hypospadias and congenital heart defects (CHD), including study populations, significant findings, and biological implications. It also summarizes functional analyses and animal model data that support GATA4's dual role in cardiac and urogenital development. Variants include both coding (e.g., missense mutations) and noncoding regulatory SNPs, highlighting the gene's complex involvement across multiple developmental pathways.

Table 2: Future research directions on gata4 polymorphisms in hypospadias and congenital heart defects

Research Area	Description	Key Approaches / Goals
i. Population-Based Case–Control Study	Large-scale, multi-center study in Indian pediatric cohorts	Include CHD only, hypospadias only, and dual phenotype cases; $n \geq 200$; stratification by ethnicity and region
ii. Comprehensive Genotyping Panel	Broader SNP coverage and structural variant inclusion	Target rs12458, rs1139244, c.620C>T, 3′UTR variants; include CNVs and regulatory elements
iii. Functional Assays Using Cell Models	Experimental validation of SNP effects	Use luciferase reporter assays, RT-PCR, iPSC-derived cardiomyocytes, urethral epithelial cells, CRISPR-Cas9
iv. Targeted and Whole-Gene Sequencing	Detect rare and population-specific variants	Employ NGS, ATAC-seq, and ChIP-seq for mapping promoters, enhancers, and coding regions

v. Gene–Environment Interaction Studies	Investigate environmental modifiers of genetic risk	Collect data on maternal health and exposures; use multivariate models to integrate genetics and environment
vi. Bioinformatics and Systems Biology	Map regulatory networks and variant effects	Tools like PolyPhen-2, RegulomeDB, HaploReg; integrate transcriptomic, proteomic, and epigenomic data
vii. Clinical Translation and Genetic Counseling	Apply research to screening and prevention	Develop screening guidelines, risk models, preconception counseling, neonatal genetic panels
viii. Collaborative and Interdisciplinary Networks	National and global data sharing and research	Build Indian research consortia, engage with ClinVar and Decipher, promote cross-specialty collaboration

This table outlines eight strategic research directions aimed at bridging the current knowledge gap on GATA4 polymorphisms and their role in congenital anomalies. Each direction targets a distinct aspect—from epidemiological studies and functional genomics to translational applications and collaborative infrastructure—facilitating a comprehensive approach to understanding and managing CHD and hypospadias.

3.4. Abbreviations used

CHD – Congenital Heart Defects, SNP – Single Nucleotide Polymorphism, OR – Odds Ratio, CI – Confidence Interval, UTR – Untranslated Region, miRNA – MicroRNA, TBX5 – T-box transcription factor 5, DNA – Deoxyribonucleic Acid, RNA – Ribonucleic Acid.

4. Discussion

4.1. Summary of evidence

The current literature strongly supports a role for GATA4 polymorphisms as independent genetic risk factors for both hypospadias and congenital heart defects (CHDs). Studies from East Asia and South India report both coding variants (e.g., c.620C>T, H436Y) and noncoding variants (e.g., rs12458, rs1139244) that are linked to altered transcriptional activity, disrupted protein interactions, or impaired post-transcriptional regulation[11,18,28,29] Functional assays provide evidence that these variants negatively affect critical developmental pathways, particularly involving TBX5 and NKX2-5.[21,30] Notably, GATA4 functions beyond organ-specific gene expression, coordinating multiple developmental signals, thus playing a central role in both cardiac and urogenital morphogenesis.[31,32]

4.2. Implications for the dual phenotype (CHD & Hypospadias)

Although rare (~1.8%), the simultaneous occurrence of CHD and hypospadias is biologically plausible due to the shared mesodermal origin of cardiac and genital structures.32 As GATA4 is expressed in both tissues, it acts as a molecular bridge.

Clinically, infants diagnosed with either condition should be screened for the other. Targeted genetic screening for variants like rs12458 or c.620C>T could uncover hidden risk, enabling earlier intervention.[18,29,33] For example, cardiac evaluations in hypospadias cases or urogenital assessments in CHD patients could be considered, especially in regions where syndromic diagnoses are often missed.[29,33]

4.3. Relevance in South Indian Context and existing research gaps

Mattapally et al. found a high prevalence of GATA4 mutations in CHD patients from South India, suggesting possible region-specific genetic patterns.[25] However, similar research focused on hypospadias or co-occurring anomalies is absent.

Given India's ethnic diversity and variation in allele frequencies, India-specific studies are crucial for accurate genetic risk estimation and counseling. To date, no Indian research has assessed co-segregation of CHD and hypospadias or compared genotype distributions between single- and dual-phenotype groups.

4.4. Methodological challenges in existing literature

Most existing studies are limited by small sample sizes, restricted ethnic representation, and insufficient control for confounders. Many rely solely on SNP genotyping, overlooking rare mutations, structural variants, and regulatory elements that may impact GATA4 function.[11,18,34] Moreover, environmental modifiers like maternal folate deficiency, gestational diabetes, smoking, or endocrine disruptors are often unaccounted for, despite evidence linking them to congenital anomalies.[28,35] Key transcriptional regulators such as TBX5 and NKX2-5 also interact epistatically with GATA4, which complicates phenotype predictions.[5,6] Future research should adopt integrative models that combine genetic, epigenetic, and environmental data to better understand GATA4-related anomalies.

4.5. Future research directions

While current evidence supports the role of GATA4 polymorphisms in the individual occurrence of congenital heart defects (CHDs) and hypospadias, comprehensive studies examining their co-occurrence and shared molecular pathways remain lacking.

The following future research directions are proposed to advance understanding in this field which has been summarized in **Table 2**.

4.6. Population-based case–control study in indian cohorts.[36,37]

There is an urgent need for a well-powered, multi-center case–control study in Indian pediatric populations that includes children with CHD alone, hypospadias alone, and those with both conditions (dual phenotype). A minimum sample size of n ≥ 200 (e.g., 100 dual phenotype cases and 100 matched controls) would provide sufficient statistical power to detect associations. Recruitment should include major pediatric cardiac and urology centers across India to ensure genetic and geographic diversity. Stratification by ethnicity and region is important due to allele frequency variations across sub-populations

4.7. Comprehensive genotyping panel.[11,18,38]

Such studies should incorporate an expanded SNP genotyping panel, covering both previously reported variants and novel regulatory elements. Key variants to include:

1. rs12458 (noncoding, hypospadias-associated)
2. rs1139244 (regulatory, CHD-associated)
3. The c.620C>T missense variant has been identified in Indian cases of congenital heart defects (CHD).
4. 3′UTR polymorphisms affecting microRNA binding.

Inclusion of copy number variations (CNVs) and promoter/enhancer region sequencing is also advised, given the role of structural variants in transcriptional regulation.

4.8. Functional assays using cell models[39-41]

Functional validation of candidate SNPs and variants is essential. Proposed experimental approaches include the following. Allele-specific luciferase reporter assays using constructs with wild-type and variant alleles cloned upstream of a luciferase gene. Quantitative RT-PCR to assess allele-specific GATA4 expression in transfected cell lines. Use of relevant human cell lines: urethral epithelial cells (e.g., HUEhT) and cardiomyocytes derived from iPSCs, to study tissue-specific effects.CRISPR-Cas9 gene editing can be employed to introduce specific mutations and assess downstream impacts on developmental gene networks.

4.8. Targeted and whole-gene sequencing[42-43]

To uncover rare or population-specific variants, targeted resequencing of the GATA4 coding region, 5′ and 3′ untranslated regions, introns, and promoters is essential. For comprehensive mutation profiling the whole-gene sequencing of GATA4 should be performed using next-generation sequencing (NGS).Promoter and enhancer mapping using ATAC-seq or ChIP-seq may identify regulatory variants that impact GATA4 transcription in developmental stages.

4.9. Gene–environment interaction studies[35,44]

Emerging evidence suggests that environmental exposures such as maternal folate status, endocrine-disrupting chemicals (e.g., phthalates), gestational diabetes, and maternal smoking may modify GATA4 expression or function. Therefore epidemiological data on maternal health, diet, medication, and environmental exposures should be collected alongside genetic data. Multivariate logistic regression models should integrate genetic and environmental variables to predict disease risk more accurately.

4.10. Bioinformatics and systems biology approaches[45-47]

Building regulatory gene networks around GATA4 and its established interactors (such as TBX5, NKX2-5, WNT pathway components, SOX9, and the androgen receptor) may reveal common signaling pathways. Computational prediction tools like PolyPhen-2, RegulomeDB, and HaploReg can help evaluate the pathogenicity of novel variants. Combining insights from transcriptomic, epigenomic, and proteomic analyses can elucidate the downstream effects of GATA4 disruptions.

4.11. Clinical translation and genetic counseling[33,48,49]

Ultimately, findings from these studies should support the development of clinical guidelines for early screening protocols for CHD in male infants diagnosed with hypospadias and vice versa. Risk stratification models that incorporate genetic markers, family history, and environmental factors. Preconception genetic counseling for families with a history of either or both conditions. Inclusion of GATA4 polymorphism screening in neonatal genomic panels, particularly in high-risk populations.

4.12. Collaborative and interdisciplinary research networks[50-52]

To facilitate data sharing, standardization, and rapid translation of findings which establishes national research consortia on congenital anomalies in India.Promote collaborations between geneticists, pediatric cardiologists, pediatric urologists, developmental biologists, and public health experts.Engage with international databases and registries, such as ClinVar and Decipher, for variant annotation and cross-population validation.

5. Conclusion

Compelling evidence supports GATA4 as a shared genetic factor linking hypospadias and congenital heart defects, with variants like rs12458, rs1139244, and c.620C>T significantly elevating risk. These variants disrupt regulatory and coding domains, highlighting their pathogenic potential. Research in Indian populations is needed to confirm associations, assess variant frequencies, and guide genotype-based screening. The proposed study in South Indian CHD children, with and without hypospadias, aims to fill a crucial gap with potential public health impact. Integrating molecular diagnostics into

pediatric care through interdisciplinary research could enhance early detection, personalized management, and long-term outcomes.

5. Source of Funding

None.

6. Conflict of Interest

None.

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