Observational Study

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Detection of the genetic association of circulating *Helicobacter pylori* antibodies with atrial fibrillation

Xizhi Wang, MS[a], Tianxiang Fang, MS[b], Wenjun Shen, MD[a,*]

Abstract

Helicobacter pylori (*H pylori*) infection and *H pylori* antibodies have been reported to be associated with an increased risk of atrial fibrillation (AF) in several observational studies. However, whether this relationship is causal and which *H pylori* antibodies serve as the determinant of AF remains largely unclear. Recently published Genome-wide association studies on 7 different antibodies of *H pylori*-specific proteins and AF (2 correction methods) were included in this study. A two-sample Mendelian randomization study was employed to investigate the causal effects of circulating *H pylori* antibodies on the risk of AF. Genetically predicted serum *H pylori* Catalase antibody level was associated with an increased risk of AF (Firth correction) (odds ratio = 1.137, 95% confidence interval: 1.008–1.282, $P = .037$) and AF (saddlepoint approximation correction) (odds ratio = 1.139, 95% confidence interval: 1.010–1.284, $P = .034$). No significant causal correlations were found between other *H pylori* antibodies and AF. This Mendelian randomization study demonstrates that *H pylori* Catalase antibody is the only causal determinant associated with the risk of AF in terms of *H pylori*-related antibodies.

Abbreviations: AF = atrial fibrillation, CagA = cytotoxin-associated gene-A, GroEL = chaperonin GroEL, GWAS = genome-wide association study, IgG = immunoglobulin G, IV = instrumental variable, MR = Mendelian randomization, OMP = outer membrane protein, RSS = residual sum of aquares, SE = standard error, SNP = single-nucleotide polymorphism, SPA = saddlepoint approximation, UreA = urease subunit-A, VacA = vacuolating cytotoxin-A.

Keywords: atrial fibrillation, causality, genome-wide association study, *Helicobacter pylori*, Mendelian randomization

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is characterized by irregular and often abnormal atrial cardiomyocytes' fast contractions, resulting in various complications, such as thromboembolic stroke, heart failure, cognitive impairment, and even sudden cardiac arrest.[1] With the aging population and lifestyle changes, the prevalence of AF is rapidly growing and becoming an urgent public health issue.[2] Despite substantial efforts to understand the etiology of AF, the underlying causative mechanisms of AF in patients have yet to be fully understood, and effective diagnostic instruments and therapies for AF are still challenging.[3] Therefore, elucidating the potential driving risk factors of AF is an important objective in reducing the incidence of AF.

Helicobacter pylori (*H pylori*) is a gram-negative microaerobic bacteria and there are approximately half of the world's population has been infected by *H pylori* infection.[4] Antibodies to *H pylori* were found in patients with *H pylori* infection, such as anti-*H pylori* immunoglobulin G (IgG), cytotoxin-associated gene-A (CagA), Catalase, chaperonin GroEL (GroEL), outer membrane protein (OMP), urease subunit-A (UreA), and vacuolating cytotoxin-A (VacA) antibodies.[5] Existing evidence suggests that microbiota dysbiosis is associated with a higher risk of AF.[6–8] *H pylori* infection has been considered a chronic inflammation status and may play a role in the development of cardiovascular disease.[9] As a pathogenic bacteria, *H pylori* has also been proposed to be associated with a higher risk of AF in observational studies, but the results remain disputable.[10–12] One previous study has documented a general association between *H pylori* seropositivity and AF.[10] Another research has yielded contradictory results and failed to find any significant correlation between *H pylori* infection and AF.[13] Further larger research is

XW and TF contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are publicly available.

Details regarding ethical approval and informed consents can be found in the original articles where the summary statistics of the data come from.

Supplemental Digital Content is available for this article.

[a] *Department of Cardiology, Lihuili Hospital Affiliated to Ningbo University, Ningbo, China,* [b] *Health Science Center, Ningbo University, Ningbo, China.*

** Correspondence: Wenjun Shen, Department of Cardiology, Lihuili Hospital Affiliated to Ningbo University, 57 Xingning Road, Ningbo 315000, China (e-mail: shenwj2024@163.com).*

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warranted. Moreover, distinguishing causality from spurious association in observational studies is difficult. Further studies are warranted to clarify the causative relationship between *H pylori* and AF.

Mendelian randomization (MR) is an approach for making causal inferences.[14] Using genetic variants as instrumental variables (IVs), MR effectively overcomes the bias caused by confounding or reverse causality.[15,16] Given advantages, a large number of studies in recent years have utilized this method to conduct research. In this study, we aimed to investigate the causality between circulating *H pylori* antibodies and AF risk.

2. Methods

2.1. Study design

A two-sample MR study was conducted to evaluate the causal effect of anti-*H pylori* antibody levels on the risk of AF. The MR design was expected to fulfill 3 core assumptions.[17] First, the genetic IVs should be strongly concerned with anti-*H pylori* antibodies. Second, IVs should not be related to potential confounders. Third, IVs can only induce AF through *H pylori* antibodies; in other words, IVs should not be directly associated with AF. Figure 1 presents the flowsheet of our study.

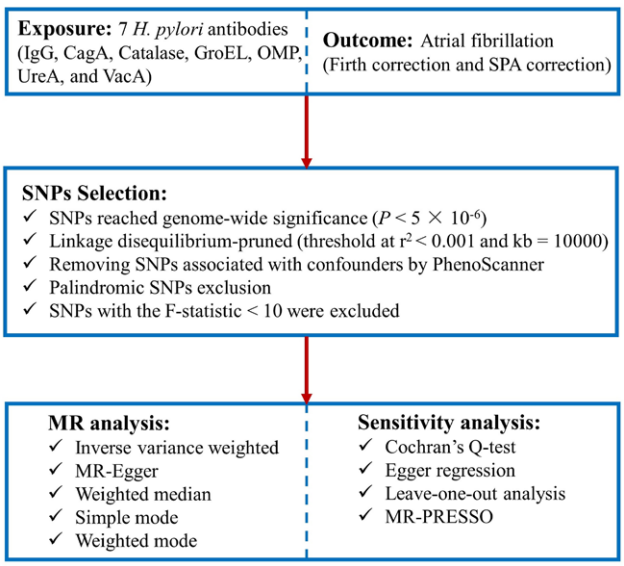

Figure 1. Flow chart of our MR study.

2.2. Data source

In this MR study, the data sources for exposure and outcome in this study are summary data from genome-wide association study (GWAS) studies conducted in European populations. Downloadable GWAS summary statistics for 7 circulating *H pylori* antibody levels (anti-*H pylori* IgG, CagA, Catalase, GroEL, OMP, UreA, and VacA) were determined from public data compiled in the EBI database (https://gwas.mrcieu.ac.uk/datasets/). The summary statistics data for AF (Firth correction and saddlepoint approximation [SPA] correction) were obtained from the recently published GWAS including a total of 407,746 individuals.[18] The detailed information is shown in Table 1.

2.3. Selection and validation of IVs

Single-nucleotide polymorphisms (SNPs) from GWAS were applied as IVs. In line with previous MR studies, to obtain a sufficient number of IVs and increase statistical power, we set the *P* value threshold for IVs to 5×10^{-6} in this MR study.[19] To check for the independence of selected SNPs, we performed linkage disequilibrium filtering on SNPs with an appropriate threshold ($r^2 < 0.001$ within 10,000 kb). In addition, we looked up the selected SNPs on PhenoScanner to evaluate whether these SNPs were associated with other traits and made an additional exclusion of SNPs associated with confounding traits at the genome-wide significance level.[20] Subsequently, palindromic SNPs were removed to avoid accidental bias when harmonizing *H pylori* antibodies and the AF GWAS dataset. Finally, the *F*-statistic for each SNP was calculated ($F = \text{beta}^2/\text{se}^2$) to evaluate the strength of IVs.[21] To minimize potential weak instrument bias, SNPs with *F*-statistics lower than 10 were removed.

2.4. Statistical analysis

Causal estimates were evaluated using the TwoSampleMR package (V.0.5.6) in the software R using inverse variance weighted as the default method, which was further verified with MR-Egger and weighted median methods.[22] The Cochran *Q* test was applied to assess the heterogeneity.[23] In addition, the MR-PRESSO test, MR-Egger intercept test, and leave-one-out analysis were performed as a sensitivity analysis to estimate the reliability of the effect estimates.[24,25] Statistical significance was defined as a *P* value less than .05.

3. Results

There were 10, 12, 7, 4, 6, 9, and 10 IVs for antibody levels of anti-*H pylori* IgG, CagA, Catalase, GroEL, OMP, UreA, and

Table 1

Details of the GWAS data used for Mendelian randomization analyses.

Phenotype	Data source	Ethnicity	Sample size	Year	GWAS ID
Anti-*Helicobacter pylori* IgG	Chong A et al	European	4683	2021	ieu-b-4905
CagA	Butler-Laporte G et al	European	985	2020	ebi-a-GCST90006911
Catalase	Butler-Laporte G et al	European	1558	2020	ebi-a-GCST90006912
GroEL	Butler-Laporte G et al	European	2716	2020	ebi-a-GCST90006913
OMP	Butler-Laporte G et al	European	2640	2020	ebi-a-GCST90006914
UreA	Butler-Laporte G et al	European	2251	2020	ebi-a-GCST90006915
VacA	Butler-Laporte G et al	European	1571	2020	ebi-a-GCST90006916
AF (Firth correction)	Mbatchou J et al	European	407,746	2021	ebi-a-GCST90013902
AF (SPA correction)	Mbatchou J et al	European	407,746	2021	ebi-a-GCST90013952

AF = atrial fibrillation, CagA = cytotoxin-associated gene-A, GroEL = chaperonin GroEL, GWAS = genome-wide association study, IgG = immunoglobulin G, OMP = outer membrane protein, SPA = saddlepoint approximation, UreA = urease subunit-A, VacA = vacuolating cytotoxin-A.

VacA, respectively. The detailed information about SNPs for these 7 exposures included as IVs in our analysis is presented in Table S1, Supplemental Digital Content, https://links.lww.com/MD/O966. Circulating antibody levels of IgG, CagA, Catalase, GroEL, OMP, UreA, VacA, and AF (Firth correction and SPA correction) were estimated by the inverse variance weighted method, and the results are presented in Figure 2 and Table S2, Supplemental Digital Content, https://links.lww.com/MD/O966. Genetically determined Catalase antibody levels were significantly associated with an increased risk of AF (Firth correction) (odds ratio = 1.137, 95% confidence interval: 1.008–1.282, $P = .037$) and AF (SPA correction) (odds ratio = 1.139, 95% confidence interval: 1.010–1.284, $P = .034$). Namely, similar results were obtained using 2 summary statistics data of AF corrected by different statistical methods. For anti-*H pylori* IgG, CagA, GroEL, OMP, UreA, and VacA, there were no significant causal associations between them and AF (either Firth correction or SPA correction). Scatter plots of the potential effects of 7 anti-*H pylori* antibodies levels-associated SNPs on AF (Firth correction and SPA correction) are shown in Figure 3 and Figures S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/O967.

As listed in Table S3, Supplemental Digital Content, https://links.lww.com/MD/O966, there was no evidence of heterogeneity in the biomarkers of *H pylori* infection except for GroEL. Moreover, the MR-Egger regression and the appearance of the funnel plots showed that the exposure was less likely to affect the outcome through confounders (all *P*-values for MR-Egger intercept > .05) (Figures S3 and S4, Supplemental Digital Content, https://links.lww.com/MD/O967, Table S4, Supplemental Digital Content, https://links.lww.com/MD/O966). Specifically, for the positive results Catalase, Cochran *Q* test indicates no significant heterogeneity ($P > .05$) (Table 2). Neither the MR-Egger intercept test nor the MR-PRESSO global test identified any horizontal pleiotropy ($P > .05$) (Table 3). Visually, the leave-one-out analysis proved that no single SNP was driving the causal effect of Catalase on AF (Fig. 4). Moreover, the leave-one-out analysis indicated the reliability of the other 6 causal association pairs, as removing any of the SNPs did not lead to a significant alteration (Figures S5 and S6, Supplemental Digital Content, https://links.lww.com/MD/O967).

4. Discussion

In this study, we used an MR method to explore the directional causal relationship between 7 different antibodies of *H pylori*-specific proteins and AF based on large-scale GWAS summary statistics. After conducting a series of MR analysis procedures, we found that circulating Catalase antibody levels were significantly associated with an increased risk of AF. There is no evidence to support the causal association of anti-*H pylori* IgG, CagA, GroEL, OMP, UreA, and VacA with AF. Besides, the results of the sensitivity analysis detected no heterogeneity (except GroEL), horizontal pleiotropy, or potentially influential IVs, suggesting the causal inferences of our MR study were robust. To the best of our knowledge, this study was the first to

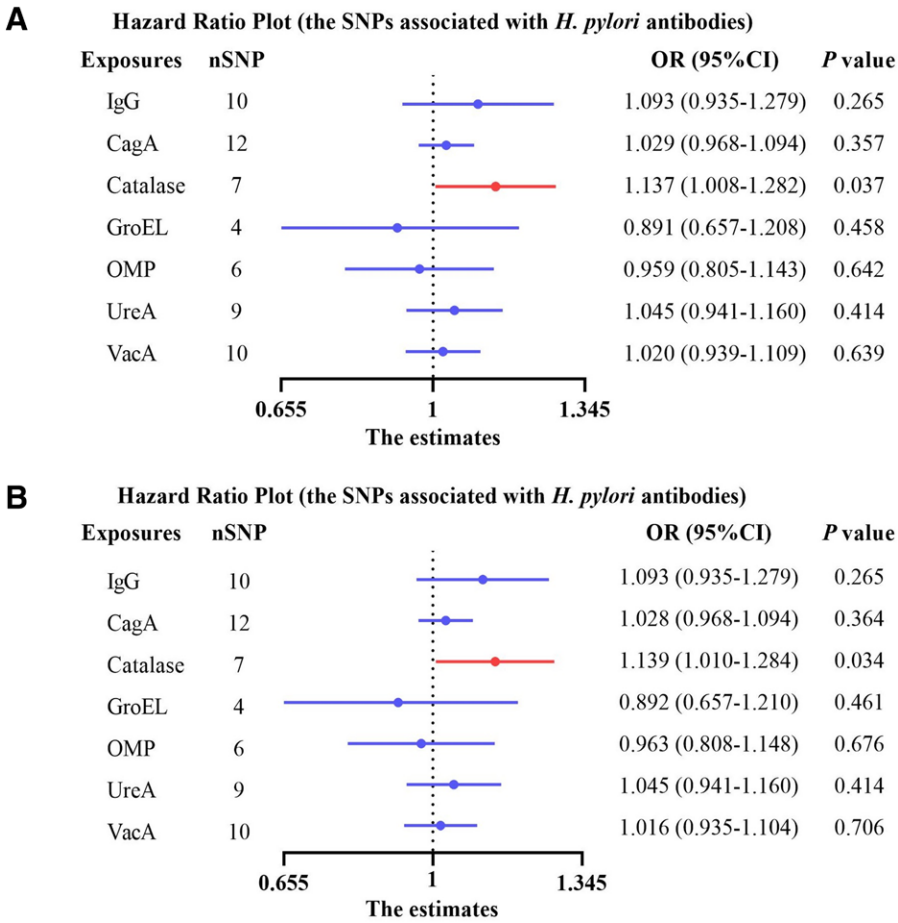

Figure 2. Forest plot for effects of circulating levels of 7 *Helicobacter pylori* antibodies on the risk of atrial fibrillation based on the IVW. (A) *H pylori* antibodies on AF (Firth correction), (B) *H pylori* antibodies on AF (SPA correction). AF = atrial fibrillation, CI = confidence interval, IVW = inverse variance weighted, OR = odds ratio, SPA = saddlepoint approximation.

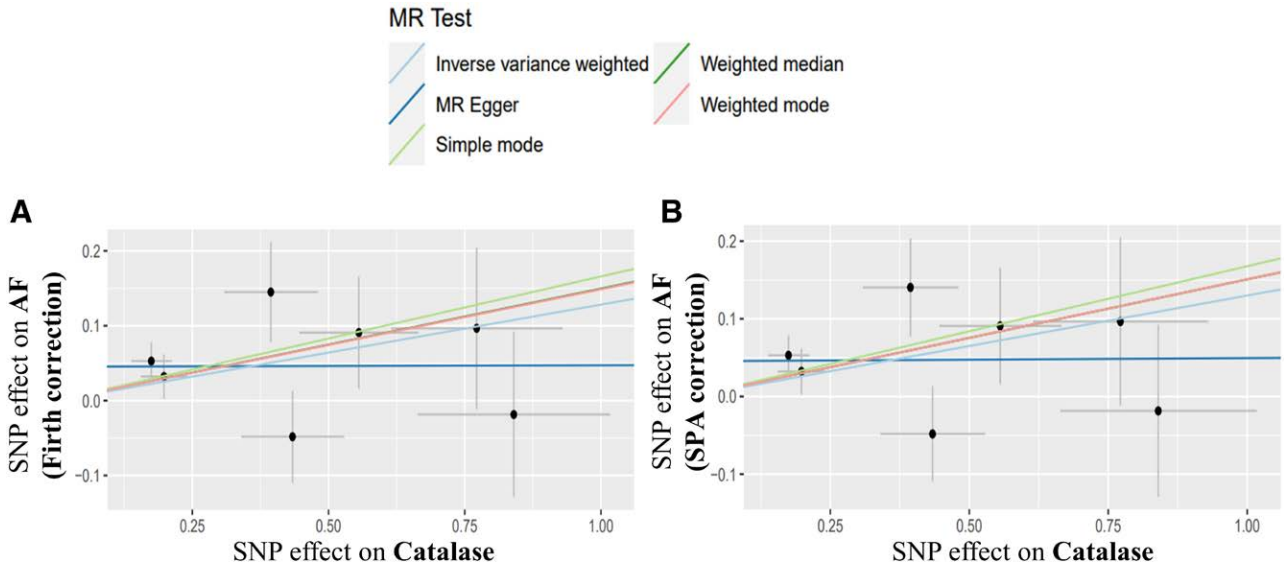

Figure 3. Scatter plots of the positive results for effects of Catalase on the risk of atrial fibrillation. (A) Catalase on AF (Firth correction). (B) Catalase on AF (SPA correction). AF = atrial fibrillation, SPA = saddlepoint approximation.

Table 2

Results of heterogeneity by Cochran *Q* test.

			Cochran *Q* test		
Exposure	**Outcome**	**Method**	***Q***	***Q*_df**	***P*-value**
Catalase	AF (Firth correction)	MR-Egger	5.859	5	.320
		IVW	7.964	6	.240
Catalase	AF (SPA correction)	MR-Egger	5.934	5	.313
		IVW	8.023	6	.263

AF = atrial fibrillation, IVW = inverse variance weighted, MR = Mendelian randomization, SPA = saddlepoint approximation.

Table 3

Results of horizontal pleiotropy by MR-Egger intercept test and MR-PRESSO global test.

		MR-Egger intercept test			MR-PRESSO global test	
Exposure	**Outcome**	**Intercept**	**SE**	***P*-value**	**RSS obs**	***P*-value**
Catalase	AF (Firth correction)	0.045	0.034	.238	10.735	.299
Catalase	AF (SPA correction)	0.045	0.034	.242	10.842	.275

AF = atrial fibrillation, MR = Mendelian randomization, RSS = residual sum of squares, SE = standard error, SPA = saddlepoint approximation.

provide evidence of causal links between circulating *H pylori* antibodies and AF risk.

As we all know, *H pylori* infection is an important causative factor for chronic gastritis, peptic ulcer, and gastric cancer. Recent studies have found that *H pylori* infection might be associated with a variety of extragastric diseases including cardiovascular diseases.[26] Despite advances in our understanding of AF, there is still much to be learned about the complex processes that underlie AF and it is crucial to determine effective strategies for treating AF. At present, the connection between *H pylori* infection and AF is contradictory and remains debatable.[13,27] Although some studies have reported an association of *H pylori* infection with increased AF risk, it is difficult to distinguish causal association from spurious association in observational studies.[11,28] Hereby, taking advantage of the GWAS datasets on *H pylori* antibodies and MR analysis, we conducted a two-sample MR to investigate the causal relationship between *H pylori* antibodies and AF risk. To gain more credible results, we included 2 AF summary statistics which were obtained using different methods of statistical correction as our outcome parameters. Lastly, we found that patients with Catalase-positive *H pylori* infection had a higher risk of AF.

AF, the most common sustained arrhythmia, is driven by a complex interplay of electrical, structural, metabolic, and inflammatory abnormalities. Although existing data do not directly clarify the connection between Catalase antibodies and AF, these antibodies may indirectly contribute to the initiation and progression of AF by modulating multiple pathophysiological pathways. Catalase, a crucial intracellular antioxidant enzyme, decomposes hydrogen peroxide (H_2O_2) into water and oxygen, thereby reducing reactive oxygen species accumulation.[29] Catalase antibodies may interfere with its function through direct enzyme activity inhibition by binding to active or allosteric sites, inhibiting catalytic activity and causing H_2O_2 accumulation and oxidative stress. Moreover, these antibodies may form immune complexes that induce the ubiquitination and degradation of Catalase, thereby diminishing its intracellular levels. Catalase antibodies also affect subcellular localization by disrupting Catalase's intracellular distribution, preventing effective H_2O_2 clearance in specific regions (e.g., mitochondria or sarcoplasmic reticulum), leading to localized oxidative stress.[30] In the context of AF, oxidative stress is known to contribute to atrial remodeling and inflammation.[31] Notably, oxidative stress resulting from Catalase antibody-induced dysfunction amplifies inflammatory and fibrotic signaling pathways (e.g., transforming growth factor-β1 and nuclear factor-κB). This exacerbates atrial tissue damage, promotes electrical instability, and perpetuates a pro-arrhythmic environment, all of which are closely associated with AF. In addition, Catalase activity can affect various cell signaling pathways involved in AF pathophysiology. For example, oxidative stress activates pathways such as the renin–angiotensin–aldosterone system and the angiotensin II type 1 receptor pathway, which drive inflammation, fibrosis, and electrical heterogeneity in atrial tissue, ultimately increasing AF risk.[32] Furthermore, the immune system plays a significant role in AF, with immune cells and their mediators contributing to atrial fibrosis and electrical remodeling. Research has reported that Catalase may

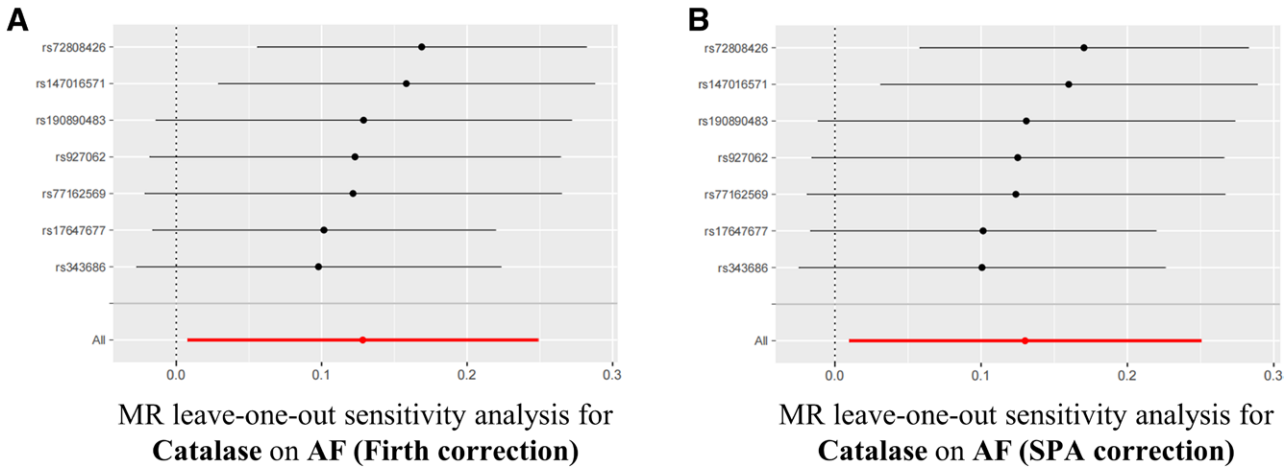

Figure 4. Leave-one-out analysis of the causal association between circulating Catalase levels and atrial fibrillation risk. (A) Catalase on AF (Firth correction). (B) Catalase on AF (SPA correction). AF = atrial fibrillation, SPA = saddlepoint approximation.

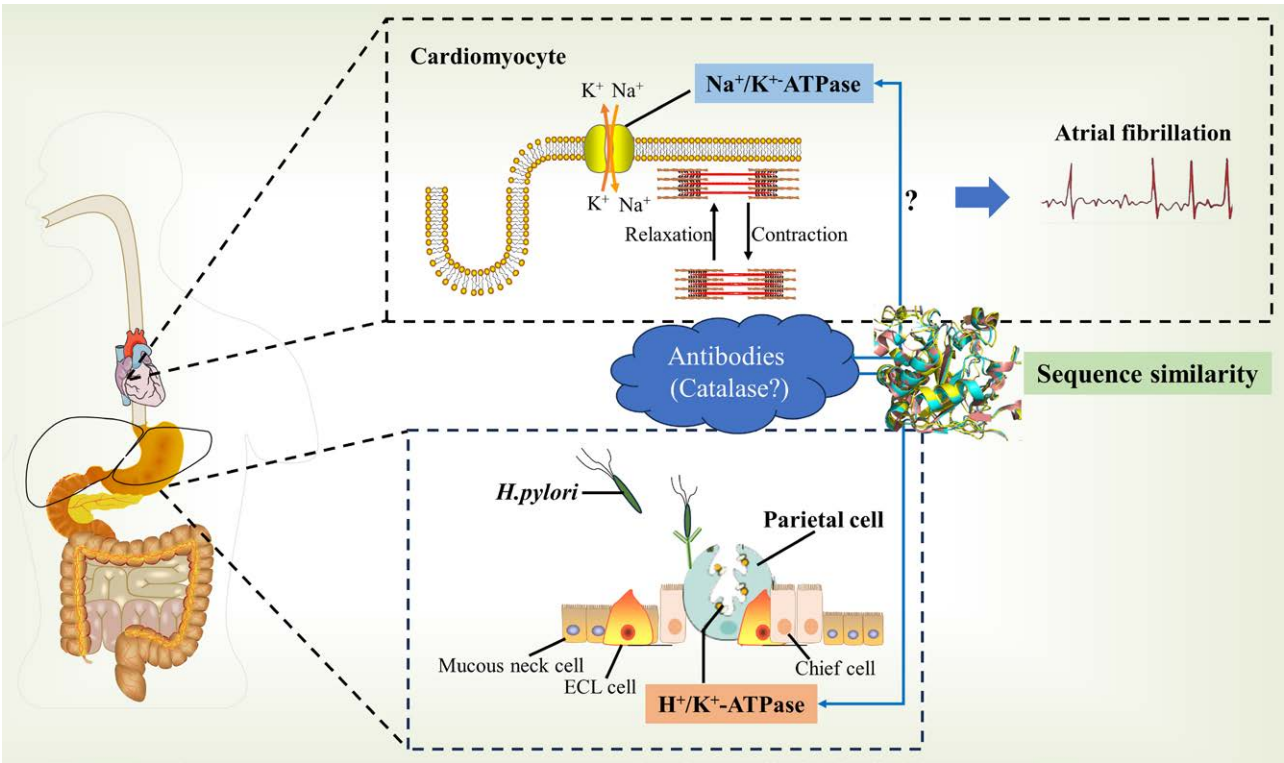

Figure 5. Possible pathogenetic mechanisms of Catalase on AF. The gastric proton pump, H^+/K^+-ATPase, on parietal cells is the major target of patients with *Helicobacter pylori* infection. Gastric H^+/K^+-ATPase and cardiac Na^+/K^+-ATPase show a high degree of sequence similarity. Catalase-positive antibodies to H^+/K^+-ATPase may also be antibodies to Na^+/K^+-ATPase, thus the imbalance of ion homeostasis finally triggers AF. AF = atrial fibrillation.

influence immune responses by modulating the redox balance within immune cells, potentially altering their activity and the subsequent inflammatory processes that could contribute to AF.[33] Catalase antibodies may promote AF through disrupting calcium ion regulation. Specifically, oxidative substances (i.e., H_2O_2) accumulation leads to abnormal sarcoplasmic reticulum calcium release, triggering arrhythmias via calcium overload and delayed afterdepolarizations.[34] These calcium-mediated disturbances in cellular excitability can directly trigger arrhythmias, further exacerbating AF progression. In summary, Catalase antibodies likely influence AF through multiple interconnected mechanisms, including enzyme activity inhibition, oxidative stress exacerbation, disruption of cell signaling pathways and calcium ion regulation, and promotion of inflammation and fibrosis.

Consistent with a previously published article, Catalase was located on the bacterial surface during autolysis of *H pylori*.[35] Adhesion of *H pylori* to human gastric epithelial cells is vital for bacterial colonization. Additionally, it has been recognized that bacterial attachment to the host cells' surface is an initial step for *H pylori* invasion and may contribute to chronic infection.[36] Some patients with *H pylori* infection have autoantibodies to the H^+/K^+-ATPase of gastric parietal cells.[37] Remarkably, H^+/K^+-ATPase, the proton pump of gastric cells, and $Na^+/$

K^+-ATPase, the pump of cardiac cells, show the highest degree of sequence similarity among all other members of the P-type ATPases family.[38] It is tempting to hypothesize that antibodies to H^+/K^+-ATPase may also be antibodies to Na^+/K^+-ATPase, thus causing an atrial insult. The role of these pumps is maintaining ionic homeostasis by hydrolyzing ATP and loss of this balance may trigger AF by determining depolarization delay and inducing premature atrial contractions. Here, we describe the current knowledge regarding the possible pathogenesis of AF caused by Catalase (Fig. 5). Indeed, there is currently limited evidence on the role of *H pylori* infection concerning pathophysiological mechanisms in human patients with AF, prompting further research in this area in the future.

It is worth noting that a newly published research identified Catalase as the *H pylori* protein that binds to lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) to initiate the invading process.[39] Based on their current findings, Zeng et al concluded that the identified LOX-1–Catalase interaction may serve as a potential drug target for alleviating *H pylori* infection.[39] Notably, our research reveals the causal relationship between Catalase-positive *H pylori* infection and AF risk. Accordingly, 1 hypothesis that warrants future exploration is that targeting Catalase may be an intervention strategy to reduce the risk in patients with AF. Further pathomechanistic and interventional studies are required.

Our study has some limitations. First of all, the *P* value threshold for IVs selection was 5×10^{-6}, which may induce weak instrument bias to the overall estimates. Second, the sample size of the *H pylori* infection GWAS data was small due to limited data provenance, and studies with larger sample sizes are needed. Third, since this MR analysis mainly focused on populations of European descent, whether it is a common phenomenon in other ethnic groups should be further evaluated.

5. Conclusion

In conclusion, our study demonstrates that genetically predicted Catalase-positive *H pylori* infection is causally associated with an elevated risk of AF. It was plausible that targeting Catalase and thus alleviating *H pylori* infection might decrease the incidence of AF. However, additional studies are still needed to further confirm our results and there is still a long way to go before we understand the precise mechanisms and methods of translational medicine.

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Author contributions

Conceptualization: Xizhi Wang, Wenjun Shen.
Data curation: Tianxiang Fang.
Formal analysis: Tianxiang Fang.
Funding acquisition: Wenjun Shen.
Methodology: Xizhi Wang, Tianxiang Fang.
Software: Tianxiang Fang.
Supervision: Wenjun Shen.
Validation: Wenjun Shen.
Writing – original draft: Xizhi Wang.
Writing – review & editing: Xizhi Wang, Tianxiang Fang, Wenjun Shen.

References

[1] Brundel BJJM, Ai X, Hills MT, Kuipers MF, Lip GYH, de Groot NMS. Atrial fibrillation. Nat Rev Dis Primers. 2022;8:21.
[2] Dai H, Zhang Q, Much AA, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes. 2021;7:574–82.
[3] Zhang H, Dhalla NS. The role of pro-inflammatory cytokines in the pathogenesis of cardiovascular disease. Int J Mol Sci. 2024;25:1082.
[4] Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and *Helicobacter pylori* treatment. N Engl J Med. 2020;382:427–36.
[5] Butler-Laporte G, Kreuzer D, Nakanishi T, Harroud A, Forgetta V, Richards JB. Genetic determinants of antibody-mediated immune responses to infectious diseases agents: a genome-wide and HLA association study. Open Forum Infect Dis. 2020;7:ofaa450.
[6] Dai H, Hou T, Wang Q, et al. Roles of gut microbiota in atrial fibrillation: insights from Mendelian randomization analysis and genetic data from over 430,000 cohort study participants. Cardiovasc Diabetol. 2023;22:306.
[7] Gawałko M, Agbaedeng TA, Saljic A, et al. Gut microbiota, dysbiosis and atrial fibrillation. Arrhythmogenic mechanisms and potential clinical implications. Cardiovasc Res. 2022;118:2415–27.
[8] Fang C, Zuo K, Liu Z, et al. Disordered gut microbiota promotes atrial fibrillation by aggravated conduction disturbance and unbalanced linoleic acid/SIRT1 signaling. Biochem Pharmacol. 2023;213:115599.
[9] Cai X, Zheng S, Zhang Y, Huang Y. *Helicobacter pylori*, non-alcoholic liver disease and atrial fibrillation: is there a link? Liver Int. 2020;40:2037–8.
[10] Bunch TJ, Day JD, Anderson JL, et al. Frequency of *Helicobacter pylori* seropositivity and C-reactive protein increase in atrial fibrillation in patients undergoing coronary angiography. Am J Cardiol. 2008;101:848–51.
[11] Wang DZ, Chen W, Yang S, et al. *Helicobacter pylori* infection in Chinese patients with atrial fibrillation. Clin Interv Aging. 2015;10:813–9.
[12] Badran HM, Mahfouz ME. Cytotoxin-associated gene-A bearing strains of *Helicobacter pylori* and atrial fibrillation due to ischemic origin: is there a link? Eur J Cardiovasc Prev Rehabil. 2007;14:518–20.
[13] Tetta C, Moula AI, Matteucci F, et al. Association between atrial fibrillation and *Helicobacter pylori*. Clin Res Cardiol. 2019;108:730–40.
[14] Richmond RC, Davey Smith G. Mendelian randomization: concepts and scope. Cold Spring Harb Perspect Med. 2022;12:a040501.
[15] Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol. 2016;27:3253–65.
[16] Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601.
[17] Larsson SC, Butterworth AS, Burgess S. Mendelian randomization for cardiovascular diseases: principles and applications. Eur Heart J. 2023;44:4913–24.
[18] Mbatchou J, Barnard L, Backman J, et al. Computationally efficient whole-genome regression for quantitative and binary traits. Nat Genet. 2021;53:1097–103.
[19] Guo X, Tang P, Zhang X, Li R. Causal associations of circulating *Helicobacter pylori* antibodies with stroke and the mediating role of inflammation. Inflamm Res. 2023;72:1193–202.
[20] Staley JR, Blackshaw J, Kamat MA, et al. PhenoScanner: a database of human genotype–phenotype associations. Bioinformatics. 2016;32:3207–9.
[21] Yu C, Xu J, Xu S, et al. Exploring genetic associations of Crohn's disease and ulcerative colitis with extraintestinal cancers in European and East Asian populations. Front Immunol. 2024;15:1339207.
[22] Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol. 2017;46:1985–98.
[23] Cohen JF, Chalumeau M, Cohen R, Korevaar DA, Khoshnood B, Bossuyt PMM. Cochran *Q* test was useful to assess heterogeneity in likelihood ratios in studies of diagnostic accuracy. J Clin Epidemiol. 2015;68:299–306.
[24] Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50:693–8.
[25] Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32:377–89.
[26] Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. *Helicobacter pylori* and extragastric diseases: a review. World J Gastroenterol. 2018;24:3204–21.

[27] Farah R, Hanna T, Levin G. Is there a link between atrial fibrillation and *Helicobacter pylori* infections? Minerva Gastroenterol. 2023;70:177–80.
[28] Montenero AS, Mollichelli N, Zumbo F, et al. *Helicobacter pylori* and atrial fibrillation: a possible pathogenic link. Heart. 2005;91: 960–1.
[29] Goyal MM, Basak A. Human catalase: looking for complete identity. Protein Cell. 2010;1:888–97.
[30] Sies H. Role of metabolic H2O2 generation: redox signaling and oxidative stress. J Biol Chem. 2014;289:8735–41.
[31] Kallergis EM, Goudis CA, Vardas PE. Atrial fibrillation: a progressive atrial myopathy or a distinct disease? Int J Cardiol. 2014;171: 126–33.
[32] Hou A, Shi D, Huang H, Liu Y, Zhang Y. Inflammation pathways as therapeutic targets in angiotensin II induced atrial fibrillation. Front Pharmacol. 2025;16:1515864.
[33] Martins ILF, Almeida FVDS, Souza KP, Brito FCF, Rodrigues GD, Scaramello CBV. Reviewing atrial fibrillation pathophysiology from a network medicine perspective: the relevance of structural remodeling, inflammation, and the immune system. Life (Basel). 2023;13:1364.
[34] Nattel S, Heijman J, Zhou L, Dobrev D. Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. Circ Res. 2020;127:51–72.
[35] Phadnis SH, Parlow MH, Levy M, et al. Surface localization of *Helicobacter pylori* urease and a heat shock protein homolog requires bacterial autolysis. Infect Immun. 1996;64:905–12.
[36] Huang Y, Wang QL, Cheng DD, Xu WT, Lu NH. Adhesion and invasion of gastric mucosa epithelial cells by *Helicobacter pylori*. Front Cell Infect Microbiol. 2016;6:159.
[37] Neumann WL, Coss E, Rugge M, Genta RM. Autoimmune atrophic gastritis—pathogenesis, pathology and management. Nat Rev Gastroenterol Hepatol. 2013;10:529–41.
[38] Faraj SE, Valsecchi WM, Cerf NT, Fedosova NU, Rossi RC, Montes MR. The interaction of Na(+), K(+), and phosphate with the gastric H,K-ATPase. Kinetics of E1-E2 conformational changes assessed by eosin fluorescence measurements. Biochim Biophys Acta Biomembr. 2021;1863:183477.
[39] Zeng J, Xie C, Huang Z, et al. LOX-1 acts as an N(6)-methyladenosine-regulated receptor for *Helicobacter pylori* by binding to the bacterial catalase. Nat Commun. 2024;15:669.