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Assessing the Causal Impact of Social Isolation on Angina Risk: Evidence from a Two-Sample Mendelian Randomization Study

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Introduction: Previous observational studies have indicated an association between social isolation and an increased risk of cardiovascular diseases such as angina, but various factors may confound these studies. This study employs Mendelian randomization to investigate the causal relationship between social isolation and angina, minimizing potential confounding effects.

Methods: We conducted a two-sample Mendelian randomization analysis using genetic variants as instrumental variables for social isolation. Genetic data for social isolation was sourced from a large-scale genome-wide association study (GWAS), while outcome data for angina came from an independent GWAS dataset.

Results: Our findings suggest that a higher genetic predisposition to social isolation and loneliness is significantly associated with an increased risk of developing angina (Odds Ratio [OR] = 1.07, 95% confidence interval [*CI*]: 1.03–1.11, $P< 0.01$). The analysis did not provide strong evidence of horizontal pleiotropy affecting the results. This supports the hypothesis that social isolation may causally contribute to the risk of angina.

Conclusion: Our study demonstrates the hypothesis that social isolation causally influences the risk of angina and emphasizes the importance of interventions targeting social isolation and loneliness as social factors in the prevention and management of cardiovascular diseases.

Keywords: angina, genome-wide association study, Mendelian randomization

Introduction

The World Health Organization (WHO) has recognized loneliness and social isolation as significant public health concerns in our aging society, prioritizing them in the Decade of Healthy Aging initiative.[1] For instance, 20–34% of older people in China, Europe, Latin America, and the United States of America are lonely.[1] Social isolation and loneliness are severe yet underappreciated public health risks that affect a considerable part of the population. Around 25% of Americans aged 65 and older who live in community settings are regarded as socially isolated, and a substantial number of adults in the United States express feelings of loneliness.[2] Some researchers found that despite the availability of Percutaneous Coronary Intervention (PCI) procedures, many patients continue to experience angina after PCI.[3] Patients with angina may experience impaired quality of life due to symptoms, activity limitations, and anxiety.[4]

Scholarly research has identified three main ways interpersonal relationships can impact health: behavioral, psychological, and physiological mechanisms.[5,6] Unhealthy behaviors such as physical inactivity and tobacco consumption have been linked to feelings of loneliness and social isolation.[7] Loneliness is associated with lower self-esteem and less effective coping strategies,[8] while social isolation has been shown to decrease self-confidence.[9] Both loneliness and social isolation have been linked to weakened immune function and higher blood pressure.[10,11] This evidence suggests

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that loneliness and social isolation can be significant risk factors for various diseases, including cardiovascular diseases. Addressing these issues could improve public health and overall well-being considerably.

Mendelian randomization is a new approach to exploring causal relationships. MR utilizes genetic variations to construct instrumental variables for exposure, estimating the causal relationship between exposure and disease outcomes.[12] Our study employed a Mendelian randomization (MR) design to explore the causality between loneliness, isolation, and the risk of angina pectoris caused by genetic factors.

Materials and Methods

Study Design

We utilized a two-sample Mendelian Randomization (MR) methodology to explore the potential causal association between loneliness, social isolation, and the incidence of angina. A schematic representation of the study is illustrated in Figure 1. The MR methodology is predicated on three essential assumptions:[13] (a) there is a significant correlation between genetic variants (instrumental variables, IVs) and the exposure of interest. (b) The IVs do not exhibit any association with confounding variables that may influence isolation, loneliness, and angina, thereby ensuring that they remain unaffected by potential factors relating to exposure and outcomes. (c) The IVs influence angina exclusively through their linkage with isolation and loneliness.

The datasets employed in our investigation encompassed subjects of European descent, aiming to mitigate selection bias and enhance the rigor of the analytical framework. However, this research is based on publicly available abstract-level data obtained from comprehensive genome-wide association studies (GWAS) and relevant consortia. Therefore, no further ethical approval or participant consent was required for this analysis.

Data Source

Data on isolation and loneliness were sourced from the UK Biobank (UKB), where a genome-wide association study (GWAS) on loneliness and regular participation in social activities was conducted (Table 1).[14] Genetic associations with isolation and loneliness were extracted from the UK Biobank with the GWAS ID "ukb-b-8476", which included 82,436 cases and 455,364 controls. The outcome of interest was angina, with summary statistics obtained from the Integrative Epidemiology Unit (IEU) Open GWAS database (Table 2).[15] The angina outcome statistics were derived from the GWAS catalogue with a study ID "ebi-a-GCST90038609", involving 15,527 cases and 469,071 controls.

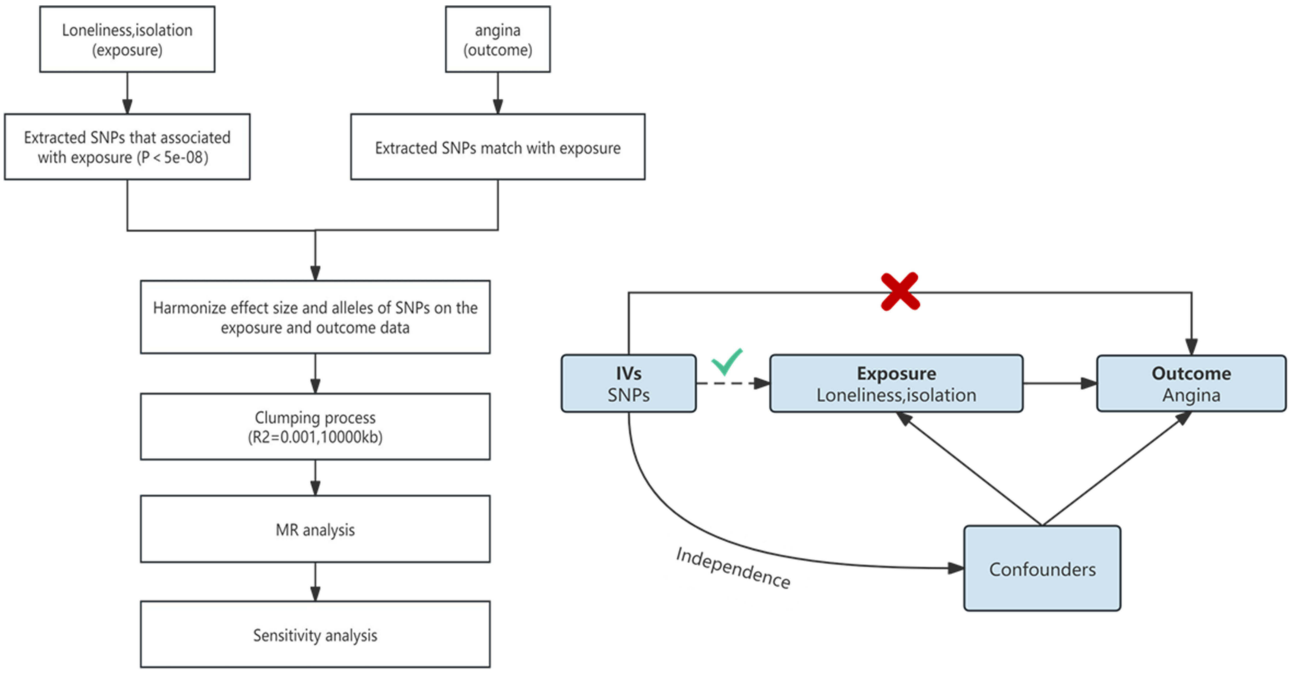

Figure 1 The flowchart of Mendelian randomization analysis. SNPs: single nucleotide polymorphisms.

Table 1 Detailed Information for Instrumental Variables

Chr	SNP	Effect allele	Other allele	β	Loneliness, Isolation		EAF	β	Angina		EAF	F-statistic
					SE	P-value			SE	P-value		
20	rs1022688	A	G	4.853E-03	8.563E-04	1.50E-08	0.330	2.240E-04	3.768E-04	0.540	0.332	32.119
6	rs10456089	A	G	−9.894E-03	1.557E-03	2.10E-10	0.079	−4.754E-04	6.973E-04	0.490	0.076	40.387
7	rs10950394	T	C	4.547E-03	8.129E-04	2.20E-08	0.419	1.165E-03	3.581E-04	0.001	0.429	31.286
9	rs13291079	C	T	−5.458E-03	8.160E-04	2.20E-11	0.423	−4.220E-04	3.610E-04	0.220	0.416	44.745
1	rs159960	G	A	−4.454E-03	8.113E-04	4.00E-08	0.556	1.101E-04	3.603E-04	0.760	0.547	30.135
9	rs2149351	G	T	−5.224E-03	9.397E-04	2.70E-08	0.757	−8.202E-04	4.163E-04	0.042	0.761	30.906
5	rs30266	A	G	4.966E-03	8.563E-04	6.70E-09	0.328	−5.500E-05	3.798E-04	0.860	0.323	33.632
18	rs599550	A	G	8.513E-03	1.123E-03	3.50E-14	0.848	5.490E-04	4.997E-04	0.250	0.852	57.453
17	rs62085660	G	C	−5.350E-03	9.190E-04	5.80E-09	0.742	−4.636E-04	4.025E-04	0.210	0.731	33.890
2	rs6430286	A	G	−4.641E-03	8.156E-04	1.30E-08	0.425	−1.879E-04	3.594E-04	0.600	0.422	32.382
5	rs67988891	G	C	−5.578E-03	8.638E-04	1.10E-10	0.319	1.379E-04	3.805E-04	0.730	0.320	41.695
11	rs7107356	G	A	4.436E-03	8.026E-04	3.30E-08	0.507	2.216E-04	3.532E-04	0.500	0.505	30.545
2	rs74338595	C	T	−5.190E-03	8.855E-04	4.60E-09	0.291	−6.031E-04	3.929E-04	0.120	0.286	34.354
3	rs7626596	A	G	−4.739E-03	8.111E-04	5.20E-09	0.567	−5.165E-04	3.583E-04	0.140	0.567	34.131
9	rs773020	A	G	7.708E-03	1.341E-03	9.00E-09	0.900	5.120E-05	6.002E-04	0.930	0.904	33.040
6	rs7770860	C	T	4.806E-03	8.316E-04	7.50E-09	0.373	6.807E-04	3.682E-04	0.056	0.367	33.402

Note: F-statistic calculated as: $F = R^2 (n-k-1) / k (1-R^2)$.

Abbreviations: Chr, chromosome; SNP, single nucleotide polymorphism; β, regression coefficient; SE, standard error of beta; EAF, allele frequency of effect allele.

Table 2 Characteristics of the Genome-Wide Association Studies

	GWAS ID	Trait	Sample Size	Population
Exposure	ukb-b-8476	Loneliness, Isolation	455,364	European
Outcome	ebi-a-GCST90038609	Angina	469,071	European

Abbreviations: GWAS, genome-wide association study; EBI, European Bioinformatics Institute.

Selection of Instrumental Variables

Single Nucleotide Polymorphisms (SNPs) were selected based on a stringent threshold of $P < 5e\text{-}8$. Since other ancestry groups were not available for our traits of interest, the study exclusively included individuals of European ancestry to minimize demographic bias. We tested for linkage disequilibrium (LD) among the selected SNPs and filtered them using a clumping process with a window size of 5000kb and an r^2 threshold of <0.001. We then assessed LD links to identify any SNPs with potential pleiotropy concerning other traits related to angina, excluding those associated with heart and cardiovascular diseases.[16]

The instrumental variables (IVs) incorporated in the Mendelian randomization (MR) analysis must demonstrate a statistically significant correlation with the exposure variable. The F-statistic is frequently employed to evaluate the strength of the IVs. The F-statistic can be derived utilizing the following formula: $\mathbf{F = R^2(n - k - 1) / k(1 - R^2)}$, where $\mathbf{R^2}$ represents the proportion of variance in the exposure that is accounted for by the genetic instrument, **n** denotes the sample size, and **k** indicates the number of IVs considered. Should the computed F-statistic be less than 10, it signifies a weak association between the IVs and the exposure, necessitating excluding such IVs from the analysis.

Statistical Analysis

All statistical analyses were performed using the open-source packages Two Sample MR (version 0.5.9) and MR-PRESSO (version 1.0) in R (version 4.3.2, https://www.rproject.org/.).[17]

We utilized the inverse-variance weighted (IVW) method as the primary approach to assess the causal effects of loneliness and isolation on the risk of angina. To ensure the robustness of our findings, we complemented the IVW

analysis with additional methods, including the MR-Egger regression, the weighted median, and the weighted mode methods.[18]

A series of sensitivity analyses were conducted to validate the results further. These included the MR-Egger test for detecting pleiotropy, Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) for outlier detection, and Cochran's Q test for assessing heterogeneity. Additionally, a leave-one-out analysis was employed to evaluate the influence of each SNP.

Results

Our Mendelian Randomization (MR) analysis ensured a robust instrumental variable (IV) analysis with an F-statistic greater than 10, indicating no weak instruments were included. We identified 16 independent and genome-wide significant single nucleotide polymorphisms (SNPs) as instrumental variables. We were chosen inverse variance weighted (OR: 1.07, *95% Cl*: 1.03–1.11, *P*<0.01) and weighted median (OR: 1.06, *95% Cl*: 1.01–1.11, *P*=0.03) as the main methods for MR analysis because of their higher statistical efficacy (Figure 2).

Table 3 represented the causal relationships of loneliness and isolation on angina estimated by univariable MR. We observed a strong causal relationship between the exposure loneliness and isolation and the outcome angina (OR: 1.07, *95% Cl*: 1.03–1.11, *P*<0.01). The inverse variance weighting (IVW) method was supported the presence of significant causal effects of loneliness and isolation on the risk of angina occurrence (P<0.05) (Figure 3).

Consistent with the IVW method, the weighted mode yielded an OR of 1.06 (*95% Cl*: 1.01–1.11; *P*<0.05), and the weighted median method reported an OR of 1.06 (*95% Cl*: 1.01–1.11; *P*<0.05), reinforcing the observed association. Scatter plots further supported the estimated impact of IVs on the relationship between loneliness, isolation, and angina, as depicted in Figure 4.

In the context of sensitivity analyses, we assessed heterogeneity and observed an absence of significant heterogeneity, thereby enhancing the robustness of our findings (Figure 5). The uniformity across various Mendelian Randomization (MR) methodologies and the lack of heterogeneity imply that our results are resilient, positing a substantive causal relationship between loneliness and isolation and susceptibility to angina.

Discussion

The use of MR, by employing genetic variants as instrumental variables, has effectively mitigated the influence of potential confounding factors and the issue of reverse causality typically present in conventional epidemiological research. First, our study provides novel evidence supporting a causal relationship between loneliness, isolation, and angina using a two-sample MR. Second, the study indicates that loneliness and isolation may be a risk factor for the occurrence of angina, and there is a positive correlation between the two. With increasing levels of loneliness and isolation, the incidence of angina tends to rise.

The exposure data genetic variation predisposes to loneliness and isolation, derived from the self-reported answers to several questions. These three relevant questions are used to assess loneliness and social isolation. The questions are as

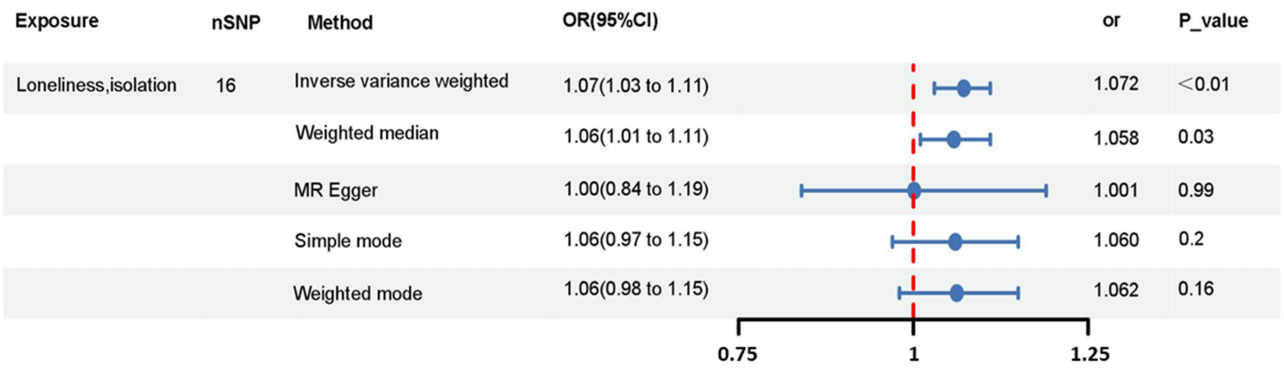

Figure 2 Odds ratios and 95% confidence intervals for the effect of exposure on angina estimated by univariate MR. P<0.05 was considered statistically significant.

Table 3 Causal Relationships of Loneliness, Isolation on Angina Estimated by Univariable MR

Exposure	nSNP	Method	P-value	OR (95% CI)
Loneliness, Isolation	16	Inverse variance weighted	<0.01	1.072 (1.03–1.11)
		Weighted median	0.03	1.058 (1.01–1.11)
		MR Egger	0.99	1.001 (0.84–1.19)
		Simple mode	0.2	1.060 (0.97–1.15)
		Weighted mode	0.16	1.062 (0.98–1.15)

Note: P-value for intercept test of MR-Egger.
Abbreviation: nSNPs, number of SNPs used in MR.

follows:[14] (1) "Do you often feel lonely?" (2) "Including yourself, how many people are living together in your household?" and "How often do you visit friends or family or have them visit you?" (3) "How often are you able to confide in someone close to you?" Beyond these, the frequency of involvement in social activities is also considered for assessment. Individuals who answered "yes" to question one were classified as cases. Those who "live alone" or "never visit family" were defined as cases, and those who "never or rarely confide in family members" were classified as cases.[14] These validated 3-item UCLA loneliness scales, derived from the original 20-item version, were used to measure loneliness effectively.[19] Loneliness can be described as the subjective feeling of being alone or isolated, characterized by the distress of lacking social networks or companionship, or the perception of unmet emotional and social needs due to a discrepancy between expected and actual social relationships, social isolation, on the other hand, is understood as the objective state of having limited interactions with others or the broader community, reflecting a lack of social relationships.[1,2] These conditions highlight the nuanced distinctions between loneliness's internal experience and social isolation's external circumstances.

The issue of loneliness and social isolation in modern society is rising. Loneliness and social isolation represent enormous challenges that we are currently facing. Many researchers considered that isolation and feelings of loneliness are closely related to cardiovascular events such as angina pectoris.[20] A systematic review and meta-analysis of longitudinal studies indicated that deficiencies in social relationships are associated with an increased risk of developing coronary heart disease (CHD) and stroke, poor social relationships were associated with a 29% increase in the risk of incident CHD.[21]

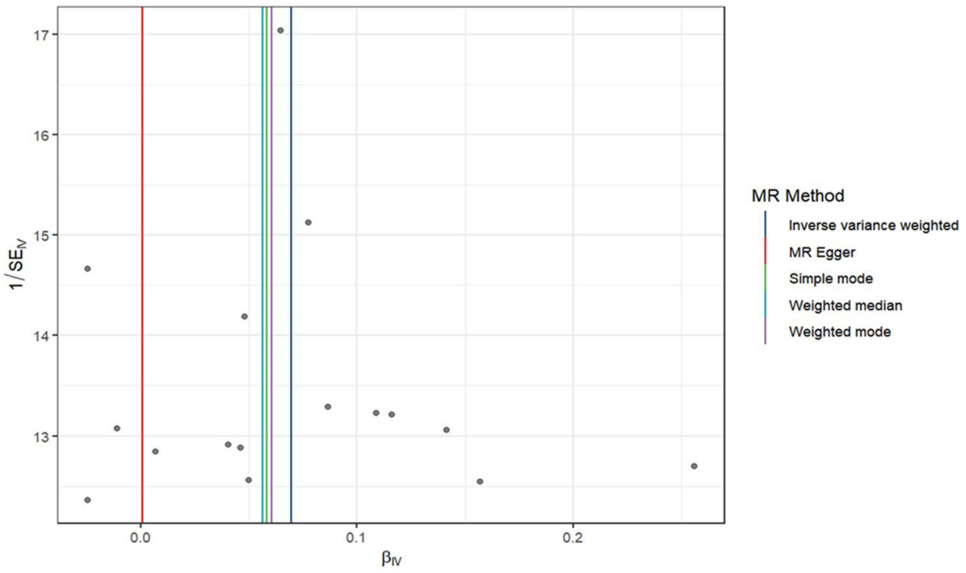

Figure 3 Funnel plots to show the symmetrical distribution of individual variant estimates around the point estimate. The x-axis represents the MR estimate of individual variants; the y-axis represents the inverse of their standard error.

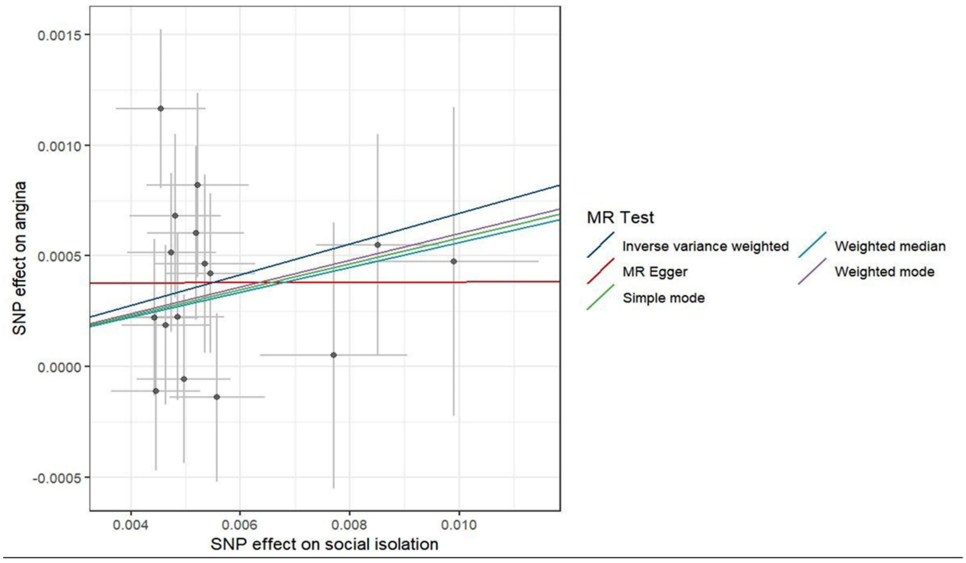

Figure 4 Scatter plots for effect sizes of SNPs for loneliness, isolation exposure and angina; the x-axis represents the effect size of SNPs on exposure; the y-axis represents the effect size of SNPs angina.

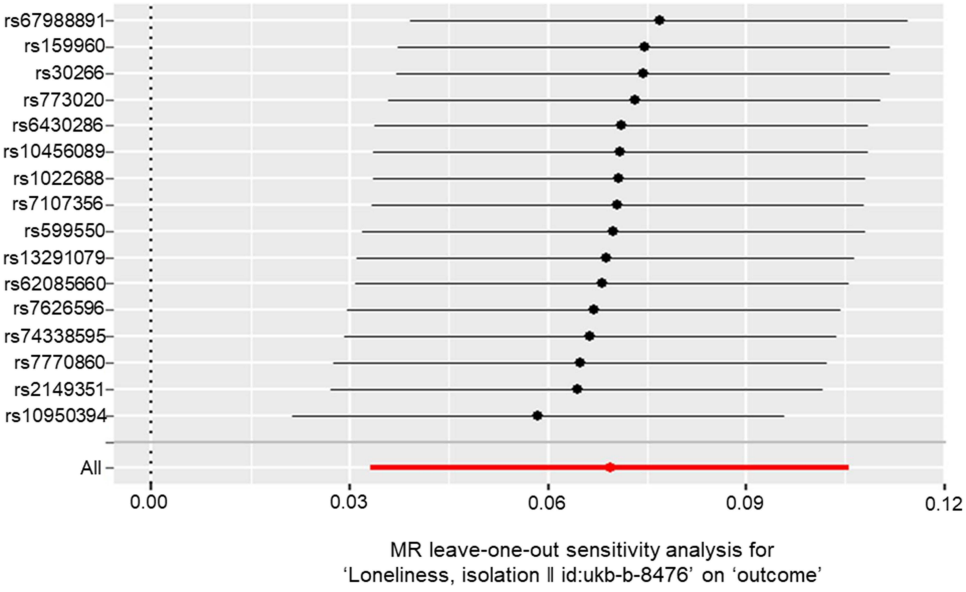

Figure 5 Leave-one-out analyses.

Loneliness and social isolation can lead to chronic inflammation, while social engagement may be a protective factor, reducing this condition.[22] Chronic inflammation is closely linked to the development of coronary heart disease (CHD), the primary cause of angina, which is a common manifestation of CHD. In angina pectoris, inflammatory components are particularly significant in the pathogenesis of atherosclerosis and acute coronary syndrome (ACS).[23] The direct cause of angina is insufficient blood supply to the heart muscle, primarily due to CHD. Sometimes, other types of heart disease or uncontrolled high blood pressure can also trigger angina. Furthermore, inflammation is a crucial driver of coronary artery disease (CAD) and atherosclerosis. Additionally, soluble mediators disrupt the balance between anti-thrombotic and pro-thrombotic forces maintained by endothelial cells, further facilitating the development of coronary artery conditions such as angina pectoris.[24]

Social isolation refers to maintaining minimal social connections or rarely interacting with others, while loneliness is the personal experience of feeling detached and alone.[25] Increasing intervention measures are being proposed to address social isolation and loneliness, including animal therapy, psychotherapy or cognitive behavioral therapy, counselling, exercise, music therapy, social interventions, and technological interventions.[26] Cognitive Behavioral Therapy is believed to improve the health outcomes of coronary heart disease.[27] Social prescription, known as community referral or social prescribing, is gaining increasing attention from individuals as an all-encompassing approach to improving community members' health and well-being.[28]

However, there are currently no studies that specifically intervene in the social isolation and loneliness of patients with cardiovascular diseases such as angina pectoris, and there are no proven effective measures to reduce the frequency of angina attacks by intervening in social isolation and loneliness. Yanjun Song's study suggests that social isolation is not universally associated with negative emotions, highlighting the importance of prioritizing psychological interventions alongside addressing objective isolation.[29]

The current study has a few limitations that need to be addressed. (a) In this investigation, we studied were only of European descent, so the findings may not apply to diverse ethnic groups. (b) While our research established a link between loneliness/social isolation and angina using Mendelian randomization, we were unable to differentiate between stable and unstable types of angina due to limited data. Future studies should address this by exploring how loneliness and social isolation affect different types of angina. (c) Our study only shows a causal relationship between loneliness/social isolation and the occurrence of angina. Still, more research is needed to understand their impact on the severity or frequency of angina attacks. (d) We did not analyze the data based on different age groups or sex. Future studies could consider these parameters for analysis. Finally, our study only used the two-sample Mendelian randomization method. In the future, it may be beneficial to use multivariable methods to account for potential confounding factors. Additionally, combining multiple databases for analysis could provide results that are more comprehensive.

Conclusion

This study utilized a two-sample Mendelian randomization approach to analyze the causal effects of loneliness and social isolation on angina. It was found that the risk of developing angina increases under conditions of loneliness and social isolation. However, there is currently no solid evidence to clarify further, how loneliness and social isolation affect the frequency or severity of angina occurrences. Moreover, the GWAS mainly included individuals of European descent, limiting the generalizability of the results to diverse racial and ethnic groups. Future research could further explore how to intervene in loneliness and social isolation to manage better and treat populations suffering from angina using diverse racial and ethnic participants.

Data Sharing Statement

The statistics data used in this study were publicly accessible. The data included in this study obey the ethical protocols and additional ethical approvals were unnecessary for this study.

Ethics Statement

Because this research is based on publicly available abstract-level data obtained from comprehensive genome-wide association studies (GWAS), the study was exempt from ethical approval.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

References

1. World Health Organization. Social isolation and loneliness among older people: advocacy brief. World Health Organization; 2021. Available from: https://www.who.int/publications/i/item/9789240030749. Accessed April 19, 2024.
2. National Academies of Sciences, Engineering, and Medicine; Division of Behavioral and Social Sciences and Education; Health and Medicine Division; Board on Behavioral, Cognitive, and Sensory Sciences; Board on Health Sciences Policy; Committee on the Health and Medical Dimensions of Social Isolation and Loneliness in Older Adults. Social isolation and loneliness in older adults: opportunities for the health care system. National Academies Press; 2020. Available from: https://nap.nationalacademies.org/catalog/25663/social-isolation-and-loneliness-in-older-adults-opportunities-for-The. Accessed April 19, 2024.
3. Serruys PW, Kageyama S, Garg S, Onuma Y. In the beginning there was angina pectoris, at the end there was still angina pectoris. *JACC Cardiovasc Interv*. 2022;15(24):2519–2522. doi:10.1016/j.jcin.2022.10.036
4. Taylor SH. Drug therapy and quality of life in angina pectoris. *Am Heart J*. 1987;114(1):234–240. doi:10.1016/0002-8703(87)90971-9
5. Berkman LF, Glass TA. Social network epidemiology. In: Berkman LF, Kawachi I, editors. *Social Epidemiology*. New York: Oxford University Press; 2014:234–289.
6. Hawkley LC, Cacioppo JT. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. *Ann Behav Med*. 2010;40(2):218–227. doi:10.1007/s12160-010-9210-8
7. Shankar A, McMunn A, Banks J, et al. Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychol*. 2011;30(4):377–385. doi:10.1037/a0022826
8. Steptoe A, Owen N, Kunz-Ebrecht SR, et al. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. *Psychoneuroendocrinology*. 2004;29(5):593–611. doi:10.1016/S0306-4530(03)00086-6
9. McAvay GJ, Seeman TE, Rodin J. A longitudinal study of change in domain-specific self-efficacy among older adults. *J Gerontol B Psychol Sci Soc Sci*. 1996;51(5):243–253. doi:10.1093/geronb/51B.5.P243
10. Grant N, Hamer M, Steptoe A. Social isolation and stress-related cardiovascular, lipid, and cortisol responses. *Ann Behav Med*. 2009;37(1):29–37. doi:10.1007/s12160-009-9081-z
11. Hawkley LC, Thisted RA, Masi CM, et al. Loneliness predicts increased blood pressure: 5-year cross-lagged analyses in middle-aged and older adults. *Psychol Aging*. 2010;25(1):132–141. doi:10.1037/a0017805
12. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol*. 2000;29(4):722–729. doi:10.1093/ije/29.4.722
13. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. doi:10.1136/bmj.k601
14. Day FR, Ong KK, Perry JRB. Elucidating the genetic basis of social interaction and isolation. *Nat Commun*. 2018;9(1):2457. doi:10.1038/s41467-018-04930-1
15. Dönertaş HM, Fabian DK, Fuentealba M, Partridge L, Thornton JM. Common genetic associations between age-related diseases. *Nature Aging*. 2021;1(4):400–412. doi:10.1038/s43587-021-00051-5
16. Lin SH, Thakur R, Machiela MJ. LDexpress: an online tool for integrating population-specific linkage disequilibrium patterns with tissue-specific expression data. *BMC Bioinf*. 2021;22(1):608. doi:10.1186/s12859-021-04531-8
17. Broadbent JR, Foley CN, Grant AJ, Mason AM, Staley JR, Burgess S. Mendelian Randomization v0.5.0: updates to an R package for performing Mendelian randomization analyses using summarized data. *Welcome Open Res*. 2020;5:252. doi:10.12688/wellcomeopenres.16374.2
18. Yan S, Wang H, Feng B, Ye L, Chen A. Causal relationship between gut microbiota and diabetic nephropathy: a two-sample Mendelian randomization study. *Front Immunol*. 2024;15:1332757. doi:10.3389/fimmu.2024.1332757
19. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. *Research on Aging*. 2004;26(6):655–672. doi:10.1177/0164027504268574
20. Sidik SM. Why loneliness is bad for your health. *Nature*. 2024;628(8006):22–24. doi:10.1038/d41586-024-00900-4
21. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart*. 2016;102(13):1009–1016. doi:10.1136/heartjnl-2015-308790
22. Cacioppo JT, Cacioppo S. The growing problem of loneliness. *Lancet*. 2018;391(10119):426. doi:10.1016/S0140-6736(18)30142-9
23. Halvorsen B, Espeland MZ, Andersen GØ. Increased expression of NAMPT in PBMC from patients with acute coronary syndrome and in inflammatory M1 macrophages. *Atherosclerosis*. 2015;243(1):204–210. doi:10.1016/j.atherosclerosis.2015.09.010
24. Attiq A, Afzal S, Ahmad W, Kandeel M. Hegemony of inflammation in atherosclerosis and coronary artery disease. *Eur. J. Pharmacol.* 2024;966:176338. doi:10.1016/j.ejphar.2024.176338
25. Wu B. Social isolation and loneliness among older adults in the context of COVID-19: a global challenge. *Glob Health Res Policy*. 2020;5(1):27. doi:10.1186/s41256-020-00154-3

26. Hoang P, King JA, Moore S. Interventions associated with reduced loneliness and social isolation in older adults: a systematic review and meta-analysis. *JAMA Network Open*. 2022;5(10):e2236676.
27. Li YN, Buys N, Ferguson S, Li ZJ, Sun J. Effectiveness of cognitive behavioral therapy-based interventions on health outcomes in patients with coronary heart disease: a meta-analysis. *World J Psychiatry*. 2021;11(11):1147–1166. doi:10.5498/wjp.v11.i11.1147
28. Menhas R, Yang L, Danish Nisar R. Community-based social healthcare practices in China for healthy aging: a social prescription perspective analysis. *Front Public Health*. 2023;11:1252157. doi:10.3389/fpubh.2023.1252157
29. Song Y, Zhu C, Shi B. Social isolation, loneliness, and incident type 2 diabetes mellitus: results from two large prospective cohorts in Europe and East Asia and Mendelian randomization. *E Clin Med*. 2023;64:102236.