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# A meta-analysis of the association of atrial septal abnormalities and atrial vulnerability

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## Abstract

**Background:** The mechanism of cryptogenic stroke (CS) in patients with atrial septal abnormalities remains unclear, and the increased incidence of atrial vulnerability may be one of the reasons. We performed this meta-analysis to clarify the association between atrial septal abnormalities and atrial vulnerability, and to provide evidence-based basis for the prevention and mechanism of CS.

**Methods:** We systematically searched for studies on the association between atrial septal abnormalities and atrial vulnerability, and pooled available data on types of atrial septal abnormalities, types of atrial vulnerability, and methods of atrial vulnerability detection. The primary endpoints were the occurrence of atrial arrhythmias or P wave abnormalities. Random-effects models were used to calculate odds ratios (OR) and 95% confidence intervals (CI).

**Results:** Twelve case-control studies were eligible. Compared with the control group, patients with atrial septal abnormalities had a higher risk of atrial vulnerability (OR: 1.93; 95% CI: 1.13-3.30, P = .02). Data based on stroke patients showed that the group with atrial septal abnormalities had a higher risk of atrial vulnerability than the control group (OR: 2.00; 95% CI: 1.13–3.53, P = .02). However, there was no significant difference in the incidence of atrial vulnerability between the 2 groups of nonstroke patients. Subgroup analysis showed that although atrial septal abnormality increased the risk of atrial vulnerability in the subgroup of atrial septal aneurysm (OR: 1.68; 95% CI: 0.47–5.95, P = .42), the subgroup of atrial fibrillation (AF)/atrial fluster (OR: 1.81; 95% CI: 0.94–3.46, P = .07) and the subgroup of subcutaneous recording system (OR: 1.33; 95% CI: 0.68–2.61, P = .41), the difference was not statistically significant.

**Conclusions:** Atrial septal abnormalities can increase the risk of atrial vulnerability, and atrial arrhythmia caused by atrial septal abnormalities may be one of the mechanisms of CS.

**Abbreviations:** AF = atrial fibrillation, ASA = atrial septal aneurysm, CI = confidence interval, CS = cryptogenic stroke, ECG = electrocardiograph, OR = odds ratios, PFO = patent foramen ovale.

**Keywords:** atrial septal aneurysm, atrial vulnerability, meta-analysis, patent foramen ovale

## 1. Introduction

Ischemic stroke has become a common disease endangering human life and health and is the second leading cause of death after ischemic heart disease.[1] Cryptogenic stroke (CS) accounts for about 40% of all ischemic strokes,[2] and the possible

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mechanisms include paradoxical embolism [3] and impairment of the left atrial function.[4] Paradoxical embolism refers to the clinical phenomenon of thromboembolism originating in the venous vasculature and traversing through an intracardiac shunt into the systemic circulation[5] which is currently considered to be the main pathogenic mechanism.[6] However, the current evidence is not sufficient to indicate the thrombus source of paradoxical embolism.[7] Some studies[5,8,9] have shown that left atrial dysfunction, such as interatrial block which can be caused by anatomic abnormality of the atrial septum, may be one of possible contributors of atrial septal abnormalities leading to ischemic events. Atrial vulnerability was defined by the prolongation of effective refractory period and atrial conduction time in electrophysiology, including interatrial block and biphasic P waves, and inducible atrial arrhythmia.[10–14] Atrial septal abnormalities present in part of those suffering from CS, in these patients, the association appears more than chance, and may be explained by the presence of atrial vulnerability. In view of the former considerations, we conducted a meta-analysis to evaluate the potential association between atrial septal abnormalities and atrial vulnerability, and to provide the evidence-based basis for the prevention and mechanism of CS.

## 2. Methods

This meta-analysis was performed according to the guidelines for a meta-analysis statement.[15] Because the data of this study were

based on published literature, ethical approval and patient consent were not needed.

### 2.1. Search strategy

We systematically searched databases of PubMed, Embase, and Web of Science from inception through May 2020 using the terms "patent foramen ovale (PFO)", "PFO", "right to left shunt", "RLS", "atrial septal abnormalities", "atrial septal aneurysm (ASA)", "electrocardiograph (ECG)", "atrial vulnerability", "P wave", "atrial fibrillation (AF)", "arrhythmia". All bibliography lists from the included articles were examined for identify potentially eligible studies.

### 2.2. Study selection and inclusion

The following inclusion criteria were used in our meta-analysis:

- Case-control studies on the association between atrial septal abnormality and atrial vulnerability in an adult population;
- The types of atrial septal abnormalities included ASA and/or PFO;
- The types of atrial vulnerability included AF, atrial flutter, interatrial block, and/or biphasic P waves. Our meta-analysis excluded the following studies: reviews, case reports, cross-sectional studies, conference summaries, repetitive articles.

### 2.3. Data extraction

Data extraction was independently completed by 2 researchers (Heng Sun and Liang Xu) according to inclusion criteria and exclusion criteria. Any conflicts between the 2 researchers were resolved by discussion or referral to a third researcher. The main endpoint of this meta-analysis was the occurrence of atrial vulnerability detected by ECG monitoring. The Newcastle–Ottawa scale was used to evaluate the bias risk of the included study.[16] The scores ranged from 0 to 9, with a score above 5 indicating reliable quality.

### 2.4. Statistical analysis

All analyses were performed using the Review Manager 5.3 software (The Cochrane Collaboration, Oxford, UK). Odds ratios (OR) and 95% confidence interval (CI) were used as the effect index for each study and pooled value. The $I^2$ statistic was used to assess statistical heterogeneity between studies. When $I^2$ was >50%, the random-effects model was used, and when $I^2$ was <50%, the fixed-effects model was used. $P$ value <.05 was considered as statistically significant. We planned prespecified subgroup analyses based on types of atrial vulnerability, methods of atrial vulnerability detection and types of atrial septal abnormalities and the sources of patients. Sensitivity analysis was used to evaluate the stability of meta-analysis results. Possible publication bias was assessed using funnel plots.

## 3. Results

### 3.1. Description of the included studies

The research selection process was shown in Figure 1. In our initial search, we identified 679 articles. After layer-by-layer screening, 12 qualified studies were selected for this meta-analysis, including 1215 patients with atrial septal abnormalities (PFO and/or ASA) and 1663 controls. The main descriptions and patient characteristics of the included studies were shown in Table 1.

### 3.2. Result of meta-analysis

The results of this meta-analysis showed that patients with atrial septal abnormalities were at higher risk of atrial vulnerability (15.7% vs 9.7%, OR: 1.93; 95% CI: 1.13–3.30, $P$ = .02, Fig. 2). Taking into account the different sources of the study subjects, we analyzed the association between atrial septal abnormalities and atrial vulnerability in different populations. The results showed that the incidence of atrial vulnerability in the stroke patients with atrial septal abnormalities was higher than that in the control group (33.6% vs 15.6%, OR: 2.00; 95% CI: 1.13–3.53, $P$ = .02). There was no significant difference in the incidence of atrial vulnerability between the 2 groups of nonstroke patients (7.1% vs 3.7%, OR: 1.73; 95% CI: 0.30–10.08, $P$ = .54). No statistically significant heterogeneity was observed in this study ($I^2$ = 0%, $P$ = .88) (Fig. 3).

### 3.3. Subgroup analyses

Subgroup analyses were planned in advance according to the types of atrial septal abnormalities, the types of atrial vulnerability and the types of ECG monitoring methods. Subgroup analysis based on the types of atrial septal abnormality and types of atrial vulnerability showed that although atrial septal abnormality increased the risk of atrial vulnerability in the subgroup of ASA (8.4% vs 5.7%, OR: 1.68; 95% CI: 0.47–5.95, $P$ = .42) and the subgroup of AF/atrial flutter (13.1% vs 8.6%, OR: 1.81; 95% CI: 0.94–3.46, $P$ = .07), the difference was not statistically significant (Figs. 4 and 5). No significant heterogeneity was found in subgroup analysis of the types of atrial septal abnormalities (Fig. 4) and the types of atrial vulnerability (Fig. 5).

Subgroup analysis based on different types of ECG monitoring methods showed that atrial vulnerability in the group with abnormal atrial septum was higher than that in the control group in the body surface ECG system (OR: 2.89; 95% CI: 1.50–5.58, $P$ = .002) and the intracardiac recording system (OR: 4.04; 95% CI: 1.66–9.83, $P$ = .002). However, there was no significant difference in the incidence of atrial vulnerability between the 2 groups which used subcutaneous recording system (13.3% vs 9.7%, OR: 1.33; 95% CI: 0.68–2.61, $P$ = .41) and clinical records to evaluate the incidence of atrial vulnerability (10.2% vs 16.9%, OR: 0.68; 95% CI: 0.38–1.19, $P$ = .18). Statistical heterogeneity was observed in this subgroup (Fig. 6).

### 3.4. Sensitivity analyses

Sensitivity analysis showed that the results did not change after excluding each study one by one [OR values range from 1.68 (95% CI: 1.00–2.83) to 2.21 (95% CI: 1.30–3.76)], which showed that the results had good stability.

### 3.5. Publication bias

Funnel plot showed that the points were basically symmetrical, which suggested that the possibility of publication bias was small (Fig. 7).
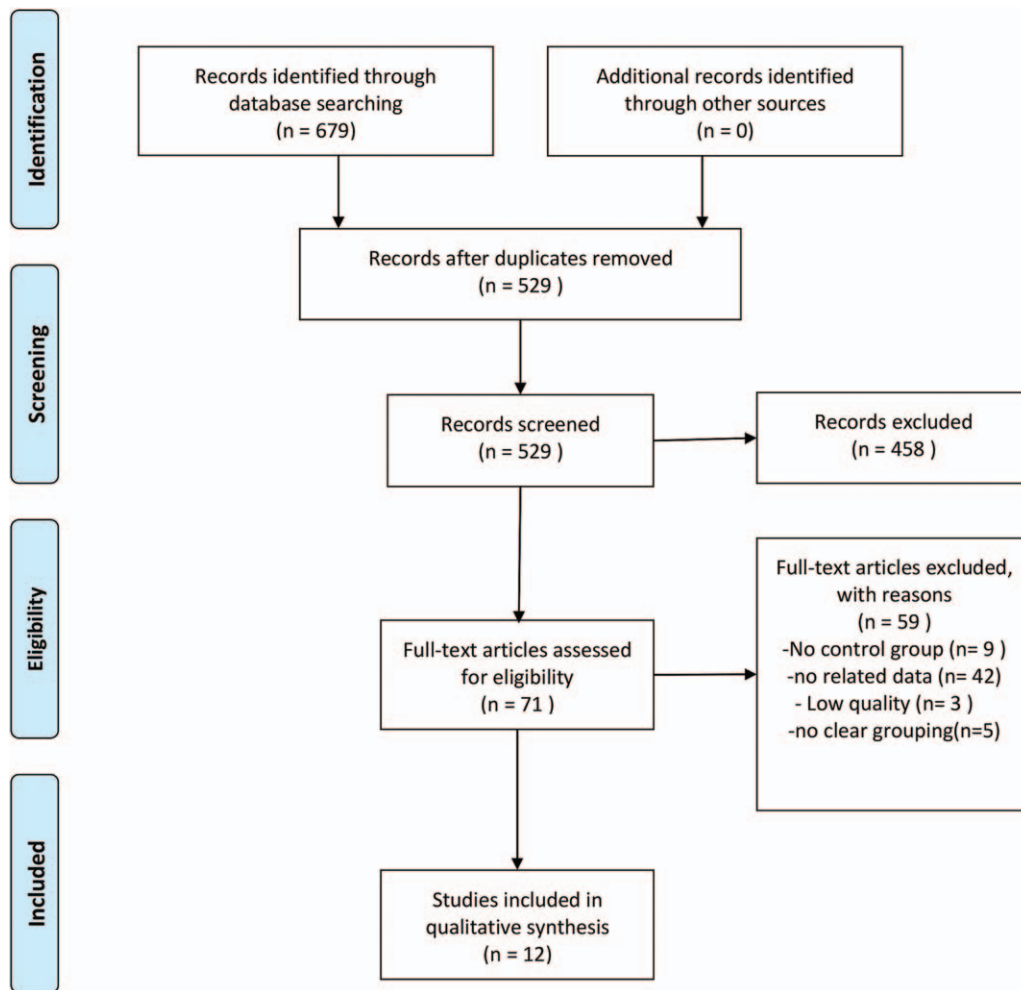
**Figure 1.** Flow diagram of study selection.

## 4. Discussion

Several studies have shown that the incidence of atrial septal abnormalities was higher in patients with CS.[17] However, the mechanism of CS caused by atrial septal abnormalities have been controversial.[18] In reviewing the literature, some studies.[19] reported that paradoxical embolism was the main mechanism of CS caused by PFO.[20] However, only a small number of patients with CS could find the source of paradoxical embolism. Furthermore, available data suggest that there was a lack of long-term monitoring of occult AF in patients with CS. Yasaka

**Table 1**

Main descriptions and patient characteristics of the included studies.

| Studies | Study population | Detection devices | Area | Atrial septal abnormalities | Atrial vulnerability | NOS score |
|---|---|---|---|---|---|---|
| Lucas 1994[34] | ICVD | Surface ECG systems | France | ASA | AF | 7 |
| Petty 1997[35] | ICVD | Clinical date | The United States | PFO | AF/af | 8 |
| Berthet 2000[10] | CS | Intracardiac recording systems | France | PFO/ASA | AF | 8 |
| Sugaya 2003[36] | NS | Clinical date | Japanese | ASA | AF/af | 7 |
| Rouesnel 2004[37] | ICVD | Intracardiac recording systems | France | PFO /ASA | AF | 6 |
| Belvís 2007[38] | CS | Surface ECG systems | Spain | PFO | P wave | 7 |
| Cotter 2011[39] | CS | Surface ECG systems | The United Kingdom | PFO | interatrial block | 7 |
| Cotter 2013[40] | CS | Subcutaneous recording systems | The United Kingdom | PFO | AF | 7 |
| Lantz 2013[41] | ICVD | Surface ECG systems | Sweden | PFO | AF | 6 |
| Sanna 2014[30] | IVCD | Subcutaneous recording systems | Multi-center study | PFO | AF | 7 |
| Mahfouz 2017[42] | CS | Surface ECG systems | Egypt | PFO | AF | 8 |
| Yetkin 2020[43] | NS | Surface ECG systems | Turkey | ASA | AF | 7 |

af = atrial flutter, AF = atrial fibrillation, ASA = atrial septal aneurysms, CS = cryptogenic stroke, ECG = electrocardiograph, ICVD = ischemic cerebrovascular disease, NOS = Newcastle–Ottawa scale, NS = no-stroke, PFO = patent foramen ovale.
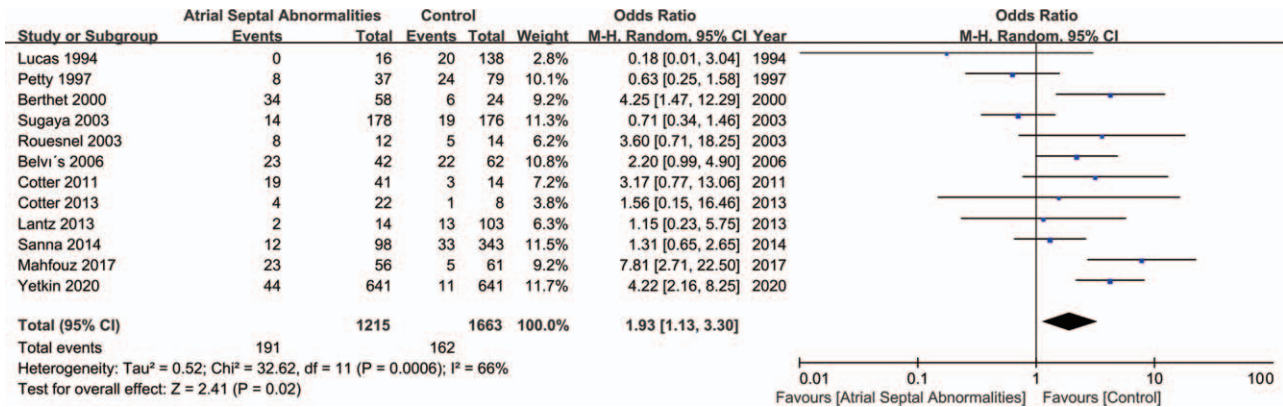
**Figure 2.** Forest plots comparing the incidence of atrial vulnerability between the group with atrial septal abnormalities and the control group. CI = confidence interval.

et al[21] found that patients with both AF and PFO have similar neuroradiological features to those with AF. Rigatelli et al[5] found that the left atrium of patients with atrial septal abnormalities had dysfunction simulating AF, which might further make these patients vulnerable to cardiogenic embolism. In a word, atrial arrhythmias play an important role in the process of CS with atrial septal abnormalities.

At present, most studies mainly focus on the association between PFO and CS,[22,23] while there are few studies on the embolization mechanism of CS.[24] Of note, our study was the first to analyze the association between atrial septal abnormalities and atrial vulnerability. Our meta-analysis included a total of 12 systematic case-control studies that evaluated the association between the presence of PFO and/or ASA and atrial vulnerability. We found that atrial septum abnormalities could lead to an increased risk of atrial vulnerability. The sensitivity analysis showed that there was no directional change in the pooled

outcome measures when we omitted any single study, which suggested that our results were reliable and had certain reference value. Our study found that there was a 2-fold increased risk of atrial vulnerability due to atrial septal abnormalities in patients with ischemic stroke, while there was no statistically significant difference in the association between atrial septal abnormalities and atrial vulnerability in patients with nonstroke. This may be related to the small number of literatures and the low incidence of atrial septal abnormalities in nonstroke patients.

Subgroup analysis results showed that atrial vulnerability detection devices might be a source of heterogeneity. In our meta-analysis, atrial vulnerability was mainly detected by body surface electrocardiogram. However, subcutaneous monitoring system, intracardiac monitoring system and clinical data were used relatively infrequently. We found that in the studies of using body surface electrocardiogram monitoring system or intracardiac monitoring system, atrial septal abnormalities were related to the
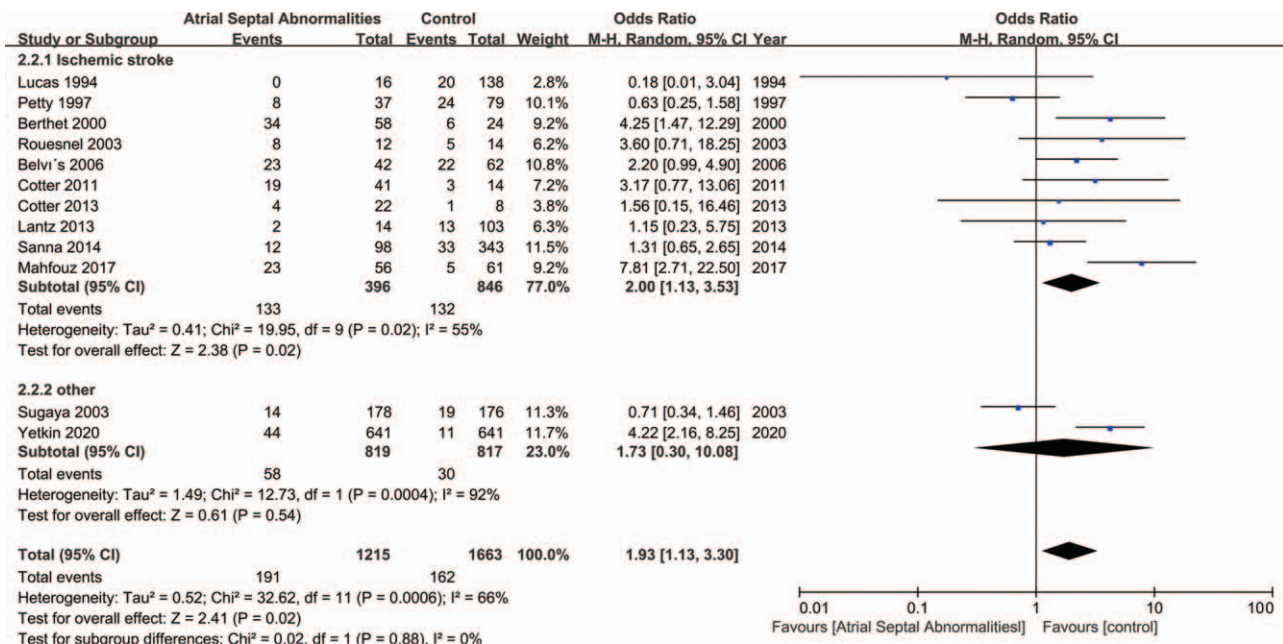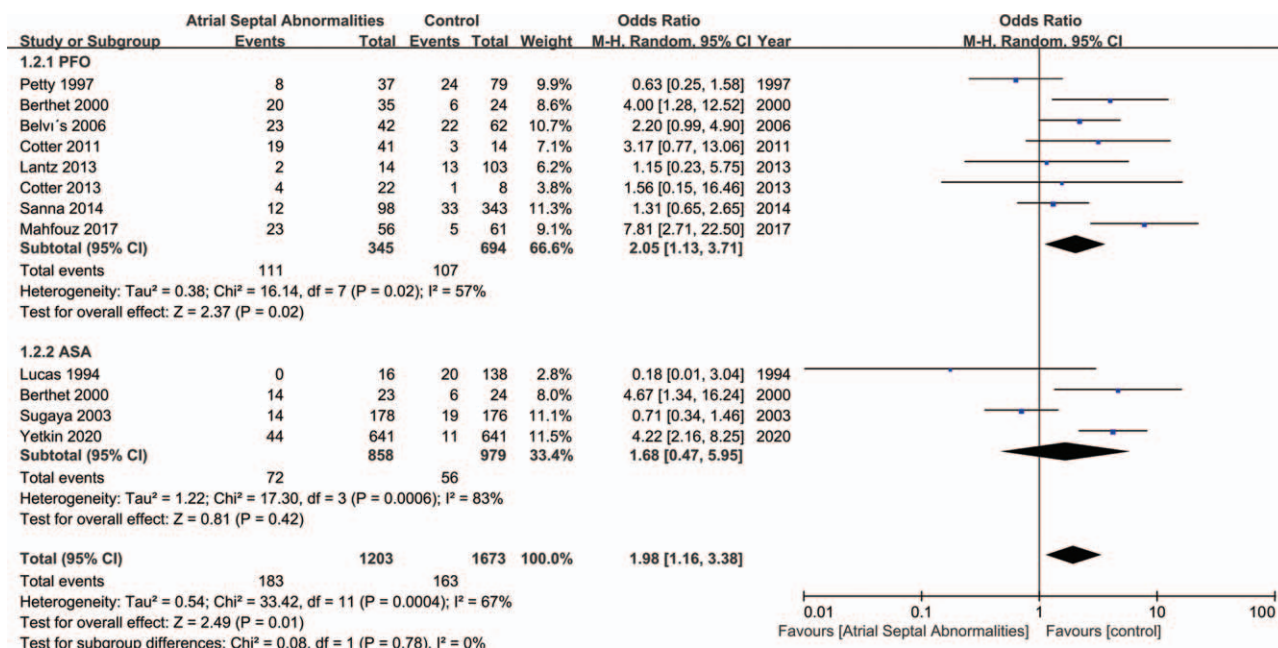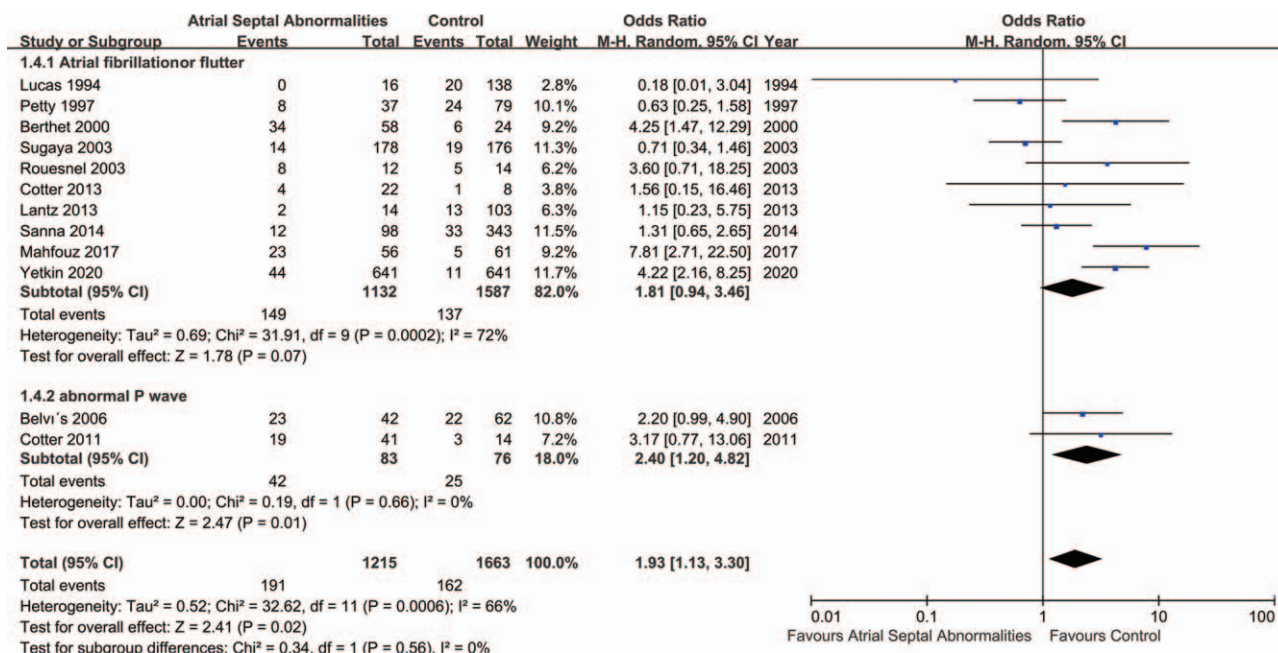


**Figure 3.** Forest plots comparing the incidence of atrial vulnerability between the group with atrial septal abnormalities and the control group in the stroke patients and in the nonstroke patients. CI = confidence interval.
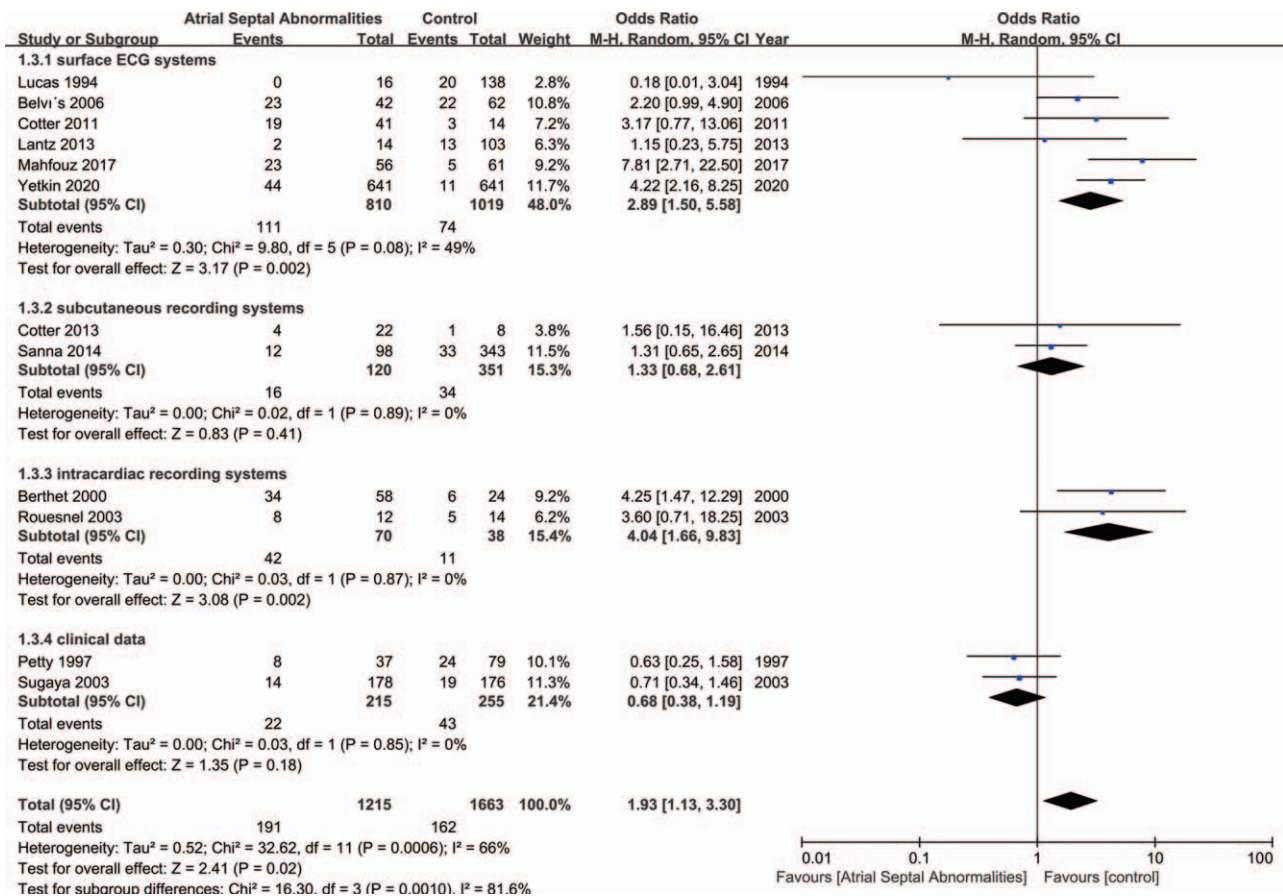
**Figure 4.** Forest plots comparing the incidence of atrial vulnerability between the group wtih PFO and without PFO and between the group with ASA and without ASA. ASA = atrial septal aneurysms, CI = confidence interval, PFO = patent foramen ovale.

increase of atrial vulnerability. Previous studies[25] showed that cardiac implanted electronic devices could detect atrial rapid arrhythmia with regular ventricular reactions and reduced the rate of missed diagnosis. The subcutaneous recording system may lead to a certain false positive due to excessive electromyography and premature atrial complex waves. The accuracy of clinical data collection was affected by strong subjectivity in the process of clinical data collection.

Subgroup analysis of the types of atrial septal abnormalities showed that the incidence of atrial vulnerability in the PFO group was 2.05 times that of the nonPFO group, while there was no statistical significance between the incidence of atrial vulnerability in the ASA group and the nonASA group. Previous studie [26,27] found that the existence of ASA increased atrial anatomical heterogeneity, which may affect the electrical stability of atrial stimulation waves and lead to arrhythmias. The larger the area of



**Figure 5.** Forest plots comparing the risk of AF or flutter between the group with atrial septal abnormalities and the control group and the risk of abnormal P wave between the 2 groups. CI = confidence interval.

**Figure 6.** Forest plots comparing the incidence of atrial vulnerability detected by different types of ECG monitoring methods between the group with atrial septal abnormalities and the control group. CI = confidence interval, ECG = electrocardiograph.

ASA, the more atypical aggregative cardiomyocytes similar to conductive cells, the greater the likelihood of AF.[28] The greater degree of ASA bulge and the diameter of the base, the easier it was to cause abnormal interatrial hemodynamics.[29] However, there is no research on the impact of ASA size on atrial vulnerability, so the association between ASA size and atrial vulnerability needs to
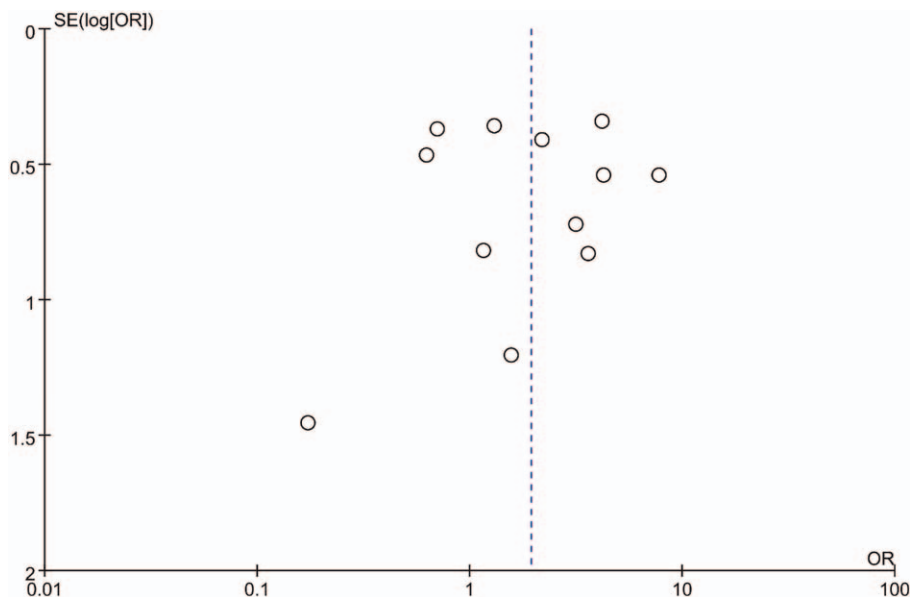


**Figure 7.** Funnel plot test for heterogeneity assessment. OR = odds ratios.

be further explored. Besides, some patients with ASA did not rule out atrial septal defect, PFO, or other related congenital heart diseases, which may cause false-negative results. Our study found that the incidence of atrial arrhythmias in the atrial septum abnormal group was higher than that in the control group, but there was no statistical difference between the 2 groups. The reasons for this negative result may be as follows: First of all, different ECG monitoring systems have different sensitivity to atrial arrhythmias[26]; Secondly, different monitoring times may cause false-negative[30]; Finally, P wave changes, such as interatrial block and biphasic P wave, occurred before the AF. Interatrial conduction delay forms a suitable substrate for induction and sustenance of atrial arrhythmias.[31,32]

Rigatelli et al[5] found that left atrial functional parameters were improved from PFO closure or ASA stabilization. What's more, recent meta-analysis of randomized controlled trials and observational showed that younger patients with stroke might be beneficial in reducing recurrent paradoxical embolism through PFO closure.[33] For patients with high risk of atrial vulnerability, early transcatheter closure can improve left atrial function and reduce the risk of stroke recurrence.

Our meta-analysis had several limitations. First of all, this study analyzed the susceptibility of atrial arrhythmia and P wave abnormality, and did not study the potential susceptibility index, which may have a certain selection bias. Secondly, only English literature was included, so there was the possibility of language bias. Finally, all the included studies were case-control studies, which might be a certain risk of selection, implementation, and measurement bias. In view of the limitations of inclusion in this meta-analysis, prospective cohort studies are needed for further verification in future studies to provide a more reliable basis for the screening of pathogenic atrial septal abnormalities.

## 5. Conclusions

Stroke patients with atrial septal abnormalities have a higher risk of atrial vulnerability compared with those without. Impairment of the left atrial function caused by atrial vulnerability may be one of the mechanisms of CS. Our study supports this possible mechanism and provides evidence-based basis for early clinical treatment.

## Author contributions

**Conceptualization:** Heng Sun, Liang Xu.
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**Formal analysis:** Heng Sun, Chang Zhou, Liang Xu.
**Funding acquisition:** Chang Zhou.
**Investigation:** Heng Sun, Liang Xu, Tao Xu.
**Methodology:** Heng Sun, Chang Zhou, Liang Xu.
**Project administration:** Liang Xu, Tao Xu.
**Resources:** Liang Xu.
**Software:** Heng Sun, Liang Xu.
**Supervision:** Chang Zhou.
**Writing – original draft:** Tao Xu.
**Writing – review & editing:** Chang Zhou, Tao Xu.

## References

[1] Hankey GJ. Stroke. Lancet 2017;389:641–54.
[2] Fonseca AC, Ferro JM. Cryptogenic stroke. Eur J Neurol 2015;22:618–23.
[3] Kamel H. The evolving concept of cryptogenic stroke. Continuum (Minneap Minn) 2020;26:353–62.
[4] Rigatelli G, Aggio S, Cardaioli P, et al. Left atrial dysfunction in patients with patent foramen ovale and atrial septal aneurysm: an alternative concurrent mechanism for arterial embolism? JACC Cardiovasc Interv 2009;2:655–62.
[5] Windecker S, Stortecky S, Meier B. Paradoxical embolism. J Am Coll Cardiol 2014;64:403–15.
[6] Rigatelli G, Roncon L, Braggion G, et al. Deep venous thrombosis before patent foramen ovale closure. Am J Med 2006;119:97–8.
[7] Lamy C, Giannesini C, Zuber M, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial septal aneurysm. Stroke 2002;33:706–11.
[8] Demir M, Aktaş İ, Çamci S. Left atrial mechanical function and stiffness in patients with atrial septal aneurysm: a speckle tracking study. Cardiol J 2015;22:535–40.
[9] Russo V, Rago A, Di Meo F, et al. Atrial septal aneurysms and supraventricular arrhythmias: the role of atrial electromechanical delay. Echocardiography 2015;32:1504–14.
[10] Berthet K, Lavergne T, Cohen A, et al. Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. Stroke 2000;31:398–403.
[11] Acampa M, Lazzerini PE, Guideri F, et al. Electrocardiographic predictors of silent atrial fibrillation in cryptogenic stroke. Heart Lung Circ 2019;28:1664–9.
[12] Platonov PG, Carlson J, Ingemansson MP, et al. Detection of inter-atrial conduction defects with unfiltered signal-averaged P-wave ECG in patients with lone atrial fibrillation. Europace 2000;2:32–41.
[13] Gencel L, Poquet F, Gosse P, Haissaguerre M, Marcus FI, Clementy J. Correlation of signal-averaged P wave with electrophysiological testing for atrial vulnerability in strokes of unexplained etiology. Pacing Clin Electrophysiol 1994;17:2118–24.
[14] Le Heuzey JY, Piot O, Copie X, Lavergne T, Guize L. Auricular vulnerability: what information can be obtained from the study of auricular vulnerability? How to perform this study? Ann Cardiol Angeiol (Paris) 1997;46:679–81.
[15] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
[16] Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[17] Albers GW, Comess KA, DeRook FA, et al. Transesophageal echocardiographic findings in stroke subtypes. Stroke 1994;25:23–8.
[18] Mas JL. Patent foramen ovale, atrial septal aneurysm and ischaemic stroke in young adults. Eur Heart J 1994;15:446–9.
[19] Kheiri B, Abdalla A, Osman M, Ahmed S, Hassan M, Bachuwa G. Patent foramen ovale closure versus medical therapy after cryptogenic stroke: an updated meta-analysis of all randomized clinical trials. Cardiol J 2019;26:47–55.
[20] Kent DM, Dahabreh IJ, Ruthazer R, et al. Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis. Eur Heart J 2015;36:2381–9.
[21] Yasaka M, Otsubo R, Oe H, Minematsu K. Is stroke a paradoxical embolism in patients with patent foramen ovale? Intern Med 2005;44:434–8.
[22] Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? Stroke 2009;40:2349–55.
[23] Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology 2000;55:1172–9.
[24] Kitsios GD, Dahabreh IJ, Abu Dabrh AM, Thaler DE, Kent DM. Patent foramen ovale closure and medical treatments for secondary stroke prevention: a systematic review of observational and randomized evidence. Stroke 2012;43:422–31.
[25] Seet RC, Friedman PA, Rabinstein AA. Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. Circulation 2011;124:477–86.
[26] Janion M, Kurzawski J. Atrial fibrillation in patients with atrial septal aneurysm. Cardiol J 2007;14:580–4.
[27] Yetkin E, Atalay H, Ileri M. Atrial septal aneurysm: prevalence and covariates in adults. Int J Cardiol 2016;223:656–9.
[28] Mitrofanova LB, Gorshkov AN, Lebedev DS, Mikhaylov EN. Evidence of specialized tissue in human interatrial septum: histological, immuno-histochemical and ultrastructural findings. PLoS One 2014;9:e113343.
[29] Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 1993;24:1865–73.

[30] Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478–86.

[31] Chhabra L, Devadoss R, Chaubey VK, Spodick DH. Interatrial block in the modern era. Curr Cardiol Rev 2014;10:181–9.

[32] Soliman EZ, Prineas RJ, Case LD, et al. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2009;40:1204–11.

[33] Xu L, Pan X, Zhou C, Li J, Wang F. Long-term efficacy after closure of patent foramen ovale for ischemic neurological events in young adults: A systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e18675.

[34] Lucas C, Goullard L, Marchau MJr, et al. Higher prevalence of atrial septal aneurysms in patients with ischemic stroke of unknown cause. Acta Neurol Scand 1994;89:210–3.

[35] Petty GW, Khandheria BK, Chu CP, Sicks JD, Whisnant JP. Patent foramen ovale in patients with cerebral infarction. A transesophageal echocardiographic study. Arch Neurol 1997;54:819–22.

[36] Sugaya T, Yasu T, Fujii M, et al. Effect of atrial septal aneurysm on risk of cerebrovascular events in Japanese patients. Int J Cardiol 2004;93:253–6.

[37] Rouesnel P, Babuty D, Fauchier L, et al. Comparative study of atrial vulnerability in patients with unexplained ischemic stroke or lone atrial paroxysmal fibrillation. Ann Cardiol Angeiol 2003;52:220–5.

[38] Belvís R, Leta RG, Martínez-Domeño A, et al. Electrocardiographic findings in patients with cryptogenic ischemic stroke and patent foramen ovale. J Electrocardiol 2007;40:168–71.

[39] Cotter PE, Martin PJ, Pugh PJ, Warburton EA, Cheriyan J, Belham M. Increased incidence of interatrial block in younger adults with cryptogenic stroke and patent foramen ovale. Cerebrovasc Dis Extra 2011;1:36–43.

[40] Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. Neurology 2013;80:1546–50.

[41] Lantz M, Sjöstrand C, Kostulas K. Ischemic stroke and patent foramen ovale: risk factors and genetic profile. J Stroke Cerebrovasc Dis 2013;22:841–5.

[42] Mahfouz RA, Alawady WS, Salem A, Abdelghafar AS. Atrial dyssynchrony and left atrial stiffness are risk markers for cryptogenic stroke in patients with patent foramen ovale. Echocardiography 2017;34:1888–94.

[43] Yetkin E, Ileri M, Korkmaz A, Ozturk S. Association between atrial septal aneurysm and arrhythmias. Scand Cardiovasc J 2020;54:169–73.