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Association between patent foramen ovale and migraine without aura: a community-based cross-sectional study

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(3 supplemental tables were in the Supplemental material).

Abstract

Objectives We evaluated the ratio and grade of patent foramen ovale and migraine in the communities of Western China and controlled the baseline characteristics by propensity score to investigated their relationship.

Design Propensity-matched cross-sectional study.

Setting Residents older than 20 years recruited in the fifteen communities of Western China from July 2020 to October 2020.

Participants 3741 residents accepting contrast-transthoracic echocardiography and standard structured questionnaire were evaluated for the relationship between patent foramen ovale and migraine without aura.

Primary and secondary outcome measures: The primary outcome measures were the prevalence and grade of patent foramen ovale, the ratio of migraine in different degrees of shunting.

Results The ratio of patent foramen ovale was 23.5%. The positive rate of migraine without aura in the patent foramen ovale group was 12.83%, significantly higher than another (7.83%, $p < 0.0001$). After adjustment, patent foramen ovale remains a higher morbidity risk of migraine without aura (12.79% vs. 8.12%; $p < 0.001$; OR = 1.71, 95%CI = 1.19 – 2.47). Besides, the positive rate of migraine without aura in the patent foramen ovale group with large shunts was 13.6%, significantly higher than that in the participants without patent foramen ovale (7.8%, $p < 0.0001$; OR = 1.65, 95%CI = 1.23 - 2.22).

Conclusion This community-based cross-sectional study suggested that there is a strong association between patent foramen ovale and migraine without aura, especially when the

shunt is large. Future work will continue tracking respective cerebrovascular events and seek to understand if better managing of patent foramen ovale condition improves the migraine and whether primary screening for patent foramen ovale should be carried out on a routine basis in patients with migraine.

Clinical trial No. ChiCTR1900024623.

Keywords migraine, cardiology, epidemiology

Strengths and limitations of this study

- This was the first community-based study investigating whether PFO can increase the risk of migraine without aura.
- The continuous follow-up for participants through high-quality registries was another major strength of this study.
- To reduce bias, we used multiple statistical models on a propensity score matching process.
- The data are cross-sectional, not longitudinal

1.Introduction

Migraine is the major disability disease under 50 years old [1]which causes a great burden on social and individual economy. The prevalence of migraine is high, from 9.3% [2] to 14.4%[3]. Accurate recognition and appropriate treatment are necessary to reduce the burden of migraine and improve patient satisfaction.[4] Unfortunately, plenty of patients with migraine have been historically underdiagnosed and under-treated.[5] Although numerous drugs have been available, few patients are able to insist on standardized preventive treatment.[6] Opioids are still frequently abused in migraines across all ages and clinical settings especially in underdeveloped regions [7, 8], which lead to a high risk of medication overuse headache[9], disease chronification[10, 11], addiction and drug abuse. Retrospective cohort study found that using opioids in patients with migraine, even one exposure, can increased future health resource utilization and ultimately lead to substantial health resource costs.[12] Therefore, internists and researchers are still looking for new treatments. In the long-term exploration, numerous studies suggested that patent foramen ovale (PFO) may be the potential etiology or risk factor of migraine[13, 14].

PFO, described as a “back door to the brain”[15], is the most common congenital intracardiac right to left shunt in adult and has been implicated in the pathogenesis of many neurologic conditions. Micro-embolism, vasoactive biochemical, or diluted blood, bypassing the pulmonary circulation from the systemic venous circulation directly to the brain, giving rise to cortical spreading depression, which may cause migraine attacks.[16] Guideline[16] has suggested primary screening for PFO in patients with migraine with aura (MA), but the relationship between PFO and migraine without aura (MO) remains

controversial[17, 18]. In the past decade related studies are almost case-control studies based on hospitals which may lead to admission bias. [6]. Their results could eliminate some uncertainties and be much better convinced if expanding the sources of participants to the community.

Here we used contrast-transthoracic echocardiography (cTTE) and a standard structured questionnaire to evaluate the ratio and severity of PFO and migraine in the communities of Western China, and control the baseline characteristics by propensity score to explore the relationship between PFO and MO. Besides, this study tried the feasibility of carrying out these technologies in the community-oriented primary care and would continue tracking respective cerebrovascular events.

2.Data and Methods

2.1. Study design

This study was a community-based cross-sectional study, approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (2018-491) and registered at the Chinese Clinical Trial Register (ChiCTR1900024623). We obtained written informed consent from all participants or their legal guardians. All participants were recruited from fifteen communities around the city of Chengdu, Sichuan, China by the sequential cluster sampling from July 2020 to October 2020.

2.2. Patient and Public Involvement

No patient involved.

2.3. Participants

In this study, we recruited urban residents older than 20 years who lived in the

communities for more than six months and won't move house in the last ten years. According to the outcome of cTTE, they were divided into two groups: with and without PFO. Enrolled Participants were excluded from the study if they meet the exclusion criteria: a) with a history of significant head trauma or migraine with aura; b) with other cardiac abnormalities (except for PFO); c) In the acute stage of vascular embolism or hypercoagulable state; d) inadequate cubital venous access; e) unable to perform the Valsalva manoeuvre (VM) because of severe heart or lung disease.

2.4. Variables

Detailed demographic information was obtained from enrolled participants via face-to-face interviews based on a standard structured questionnaire. All baseline data information was collected by trained workers under strict quality control. The following information were collected, such as age, gender, educational level, BMI, smoking, alcohol drinking, regular tea, regular coffee, clinical history of headache, family history of migraine, and mental health status.

Physical examinations and diagnosis were performed by neurological internists. Each participant was asked for a past history of migraine and a three-item identification of migraine [19] for current symptoms. Primary screening positive was defined as a positive answer to either, who will accept another systematic and detailed examination questionnaire referred to the International Classification of Headache Disorders III[20], including frequency, duration of headache, pain type, sensitivity to light and sound, visual disturbances, nausea, focal neurological symptoms, and medications.

Educational levels were divided into primary (less than 6 years of education), middle

(6 to 9 years), high (9 to 12 years) and advanced (more than 12 years). BMI was divided into underweight (<18.5kg·m−2), normal (≥ 18.5kg·m−2), overweight (≥ 24kg·m−2) and obesity (≥ 28kg·m−2). Smoking was defined at least one cigarette a day for more than one year. Alcohol drinking was defined at least once a week for more than half a year. Regular tea was defined at least three times a week for more than half a year, same with regular coffee. Mental health symptoms were evaluated with Pittsburgh sleep quality index[21], the 9-item Patient Health Questionnaire [22], the 7-item Generalized Anxiety Disorder scale [23].

2.5. PFO Screening test

cTTE data were acquired using a Philips IE 33 with 1-5 MHz or 3-8MHz multiplane transducers to identify PFO; this was performed by 2 experienced sonographers who also reviewed jointly all videotapes and were unaware of participants' clinical data.

A microbubble bolus from agitated solution of 8 ml saline, 1 ml blood, and 1 ml air was injected into antecubital veins for increased sensitivity.[24] Before the examination, sonographers informed participants about VM. Participants were assessed for PFO at rest and during provocative maneuvers (VM and coughing). Positive for the presence of a PFO was considered to be present if microbubbles were present in the left atrium or ventricle within 3 cardiac cycles from maximum right atrial opacification.[24] The degree of right-left shunt (RLS) was quantified based on detected microbubble per frame in the left atrium: grade I(1–10); grade II(11–30); grade III(>30 or the left atrium is filled with microbubble). [24]

2.6. Statistical analysis

Continuous variables were described as mean and standard deviation (mean ± SD) and

compared by means of t test. Categorical variables were described as frequencies and percentages and compared by means of Chi-square test. All analysis were performed using SAS (version 9.4) and R (version 4.1.0). Two-sided p<0·05 was considered statistically significant.

Chained equations (fully conditional specification) were used for the multiple imputation of absent data and the imputation number was increased to 25. We used Rubin's rules to merge the outcomes of multiple data sets. Baseline characteristics of with and without PFO groups were matched using the propensity score method of 1:2 nearest neighbor matching with a caliper (the caliper was set 0.2 times the pooled estimate of the standard deviation of the propensity score). In order to ensure the stability of the multiple imputation of absent data, two binary logistic regression model were set up to estimate the individual propensities for PFO, one only adjusted for age and gender (no missing values) and another adjusted for all variables (age, gender, educational level, BMI, smoking, alcohol drinking, regular tea, regular coffee, family history of migraine, and mental health status). Covariate balance was assessed by the standardized mean difference. Afterwards, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) to explore risk of migraine among PFO. Then we conducted additional sensitivity analyses to prove the stability of our model, including 1:1 nearest neighbor matching, 1:3 nearest neighbor matching, variable ratio matching, full matching, and inverse probability of treatment weighting.

Additionally, generalized overlap weighting[25] was adopted to calculate the association between RLS severity and MO. Similarly, the estimation of generalized propensity scores was used by multinomial logistic model: in one model, we examined the association between

RLS and MO with controlling for the effects of age and gender only; in another, we adjusted all variables above. The estimation of standard error and confidence interval was based on robust variance estimator.

3. Results

3.1. Demographics and Operative Details

Figure 1 shows the flow of participants through this study. 3741 participants fulfilled all inclusion/exclusion criteria and agreed to participate to the study.

Mean age (SD) of these participants was 50.90 (7.37) years, and largely female (74.5%, 2786/3741). Among them, 881 (23.5%) participants were diagnosed as PFO positive (666 females, mean age (SD): 50.27 (7.53) years) and 2860 as PFO negative (2120 females, mean age (SD): 51.09 (7.31) years). After more detailed division, 2.25% (84 of 3741) had an RLS of grade I, 5.21% (195 of 3741) had an RLS of grade II, and 16.09% (602 of 3741) had an RLS of grade III.

The positive rate of MO in the PFO group was 12.83%, significantly higher than without PFO group (7.83%, $p < 0.0001$). More baseline features were reported in the Table.1 and the indicate number of participants with missing data for each variable were reported in the Supplemental Table A.

Table.1 Demographic characteristics after multiple imputation

Variable	Without PFO (n=2860)	With PFO (n=881)	SMD	P
propensity score	0.2337(0.0361)	0.2413(0.0383)	0.1993	0.0060
Mean (SD) age, years	51.09(7.31)	50.27(7.53)	0.1106	0.0038
Gender, n (%)			0.0339	0.3816
Female	2120(74.13)	666(75.60)		
Male	740(25.87)	215(24.40)		
BMI, n (%)				0.7874
Underweight	76(2.65)	21(2.33)	0.0204	

Normal	1451(50.72)	464(52.62)		
Overweight	1051(36.76)	312(35.38)	0.0287	
Obesity	282(9.88)	85(9.67)	0.0076	
Educational level, n (%)				0.1878
Primary	940(32.86)	254(28.84)		
Middle	1349(47.18)	439(49.84)	0.0533	
High	416(14.56)	140(15.88)	0.0368	
Advanced	154(5.40)	48(5.44)	0.0073	
Smoking, n (%)	476(16.64)	143(16.20)	0.0126	0.7564
Alcohol, n (%)	430(15.03)	134(15.23)	0.0077	0.8492
Tea, n (%)	801(28.01)	232(26.29)	0.0387	0.3286
Coffee, n (%)	36(1.25)	15(1.68)	0.0352	0.3917
Sleep quality, mean (SD)	3.82(2.48)	3.71(2.46)	0.0451	0.2691
Anxiety, mean (SD)	1.01(2.28)	1.10(2.42)	0.0355	0.3734
Depression, mean (SD)	1.03(2.10)	1.10(2.14)	0.0320	0.4232
Family migraine, n (%)	355(12.41)	141(16.05)	0.1042	0.1001

Abbreviations: SD, standard deviation; SMD, standardized mean difference

3.2 Propensity-score matching for groups with and without PFO

After 1:2 matching, the standardized mean differences of all variables were less than 0.1 without exception which mean the balance was better (Details were shown in Supplemental Table B). Propensity-score-matched populations were generated to adjust baseline differences and reported in Table.2 with outcomes.

Table.2 Demographic characteristics (Matched)

Variable	Matched			
	Without PFO (n=1747)	With PFO (n=880)	SMD	P
propensity score	0.2404(0.0370)	0.2411(0.0379)	0.0004	0.6645
Mean (SD) age, years	50.37(7.53)	50.28(7.51)	0.0090	0.7850

Gender, n (%)			0.0128	0.7710
Female	1323(75.75)	665(75.59)		
Male	424(24.25)	215(24.41)		
BMI, n (%)				0.9760
Underweight	39(2.21)	20(2.33)	0.0108	
Normal	923(52.81)	463(52.59)		
Overweight	618(35.37)	312(35.41)	0.0107	
Obesity	168(9.61)	85(9.67)	0.0146	
Educational level, n (%)				0.9880
Primary	503(28.77)	254(28.86)		
Middle	874(50.04)	439(49.84)	0.0152	
High	277(15.88)	140(15.87)	0.0118	
Advanced	93(5.31)	48(5.44)	0.0128	
Smoking, n (%)	283(16.19)	143(16.22)	0.0113	0.8218
Alcohol, n (%)	263(15.08)	134(15.24)	0.0126	0.7824
Tea, n (%)	453(25.90)	231(26.28)	0.0147	0.7437
Coffee, n (%)	27(1.55)	14(1.63)	0.0090	0.8082
Sleep quality, mean (SD)	3.70(2.41)	3.71(2.46)	0.0137	0.8725
Anxiety, mean (SD)	1.06(2.39)	1.09(2.41)	0.0108	0.7587
Depression, mean (SD)	1.07(2.20)	1.10(2.13)	0.0096	0.8023
Family migraine, n (%)	266(15.21)	141(15.98)	0.0111	0.6238

Abbreviations: SD, standard deviation; SMD, standardized mean difference

Participants diagnosed with PFO showed a marked rise of MO ratio compared with another (12.79% vs 8.12%, p = 0.0004, Table.2). After full adjustment, logistic regression

analyses showed that PFO increased the risk of migraine (OR = 1.71, 95%CI = 1.19 – 2.47). The association remains significant in adjustment model only by age and gender (OR = 1.66, 95%CI = 1.18 – 2.32). Multiple additional sensitivity analyses in two adjustment models yielded the similar results (Details was shown in Figure 2).

3.3 The relationship between RLS severity and MO

Details of generalized overlap weighting were shown in Supplemental Table C and D. Controlling for the effects of age and gender, individuals who had a PFO with large shunts were 1.69 times more likely to report experiencing MO (OR = 1.69, P<0.0001, 95%Cl = 1.25 - 2.29). This significant effect was partially strengthened after controlling for the full variables. In the fully adjusted model, individuals who had a PFO with large shunts were 1.65 times more likely to report experiencing MO (OR = 1.65, P<0.0001, 95%Cl = 1.23 - 2.22). However, a PFO with moderate-sized or small shunts was not.

4. Discussion

This is the first community-based study in China investigating whether PFO can increase the risk of migraine without aura. Besides, all subjects were obtained from a prospective population cohort study in Southwest China and could receive continuous follow-up in the future. This was a useful complement to existing epidemiological data and clinical researches of PFO and MO in Southwest China and indicated that MO ratio is higher in participants with PFO as compared to controls especially in the groups with large shunts.

The autopsy study of Hagen on 965 normal hearts discovered that PFO possessed a prevalence of 25.4% during the 4th through 8th decades.[26] In order to eliminate interference of extracardiac shunt, we used cTTE to evaluate the existence of PFO in this study. Our ratio

of PFO in the general population was 23.4%, similar to the universal recognition. Our findings also estimated the ratio of MO in Han Chinese from Sichuan Province, similar to that in the Southeast Coast[27] or whole mainland of China[2].

The pathogenesis of migraine is complex. Current evidence demonstrated that there are various factors could increase the risk of migraine, including age, female sex, smoking, alcohol, obesity, low educational status, family history and dietary factors.[28-31] Based on these known findings, we included all the variables above in the propensity score model to balance the baseline characteristics as much as possible. By using various sensitivity analysis, we ensured ulteriorly the robustness of the results.

Our outcome are in line with and extend the results of a large-scale case-control study by Wang et al who found the prevalence of RLS in MO was significantly higher than that of the healthy group (39.9% vs. 29.4%, $p < 0.001$).[13] While other studies determined that the prevalence of MO is similar in both populations with and without PFO.[17, 18] However, as the author mentioned in the article they ignored cohort studies, which are the best method for determining the incidence and natural history of a condition.[18]

Our outcomes considered that routine screening for PFO in migraine may be necessary. With the help of various portable medical devices, it is feasible to carry out migraine and PFO screening in the community even in underdeveloped regions like Southwest China. Given the finding that only 25% of patients who consulted a healthcare professional received an accurate migraine diagnosis,[5] it may be more meaningful to disseminate and implement migraine guidelines to community-oriented primary care than neurologist, which can markedly improve access to high-quality management for patients with migraine reducing

the consumption of health resources and socio-economic burden. Figure 3 displays our recommended stepwise approach to migraine.

There are some limitations in this study: first, recall bias could not be excluded due to retrospective design. Second, PFO increase the risk of cryptogenic stroke, some residents failed to participate in this study due to the death or physical disability from stroke, thus the prevalence of migraine in PFO group may be underestimated.

5. Conclusion

In summary, in this study with the first based on community population hitherto in China, we corroborated that PFO can increase the risk of MO especially in the groups with large shunts, proposing the need of routine screening for PFO in migraine. Future work will continue tracking respective cerebrovascular events and seek to understand if better managing of patent foramen ovale condition improves the migraine and whether primary screening for patent foramen ovale should be carried out on a routine basis in patients with migraine.

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Contributions Lei Chen and Yusha Tang conceived and designed the work. Yusha Tang conducted the study, carried out the statistical analysis and drafted the manuscript. Anjiao Peng and Bo Peng were involved in data collection and interpretation. Lei Chen involved in critical revision of the article and final approval of the version to be published. Shixu He,

Xia Zhao, Yuanfeng Zhu, Na Yang, Wanlin Lai, and Tingting Song contributed to the acquisition of data. All authors have agreed to be accountable for all aspects of the work.

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Competing interests None declared.

Ethics approval This study involves human participants and was approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (2018-491).

Data availability statement No additional data available.

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DOI: 10.1177/0333102418764888

Figure 1

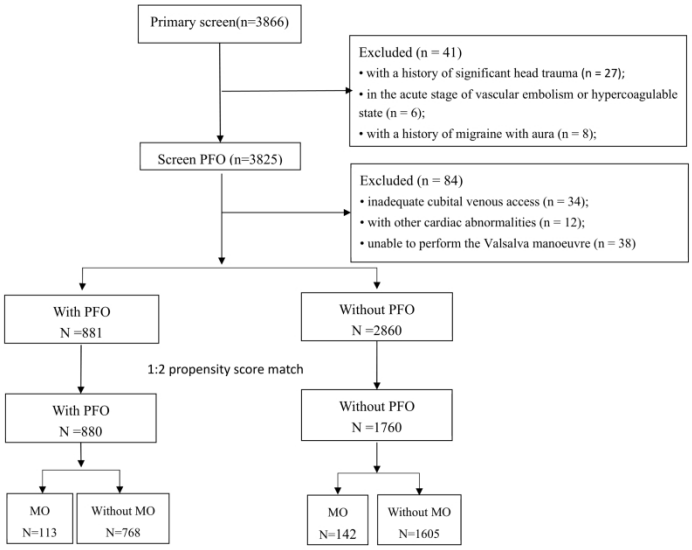
The flow of participants through this study

Figure 2

The multiple additional sensitivity analyses in two adjustment models for groups with and without PFO

Figure 3

Our proposed stepwise approach to migraine



The flow of participants through this study

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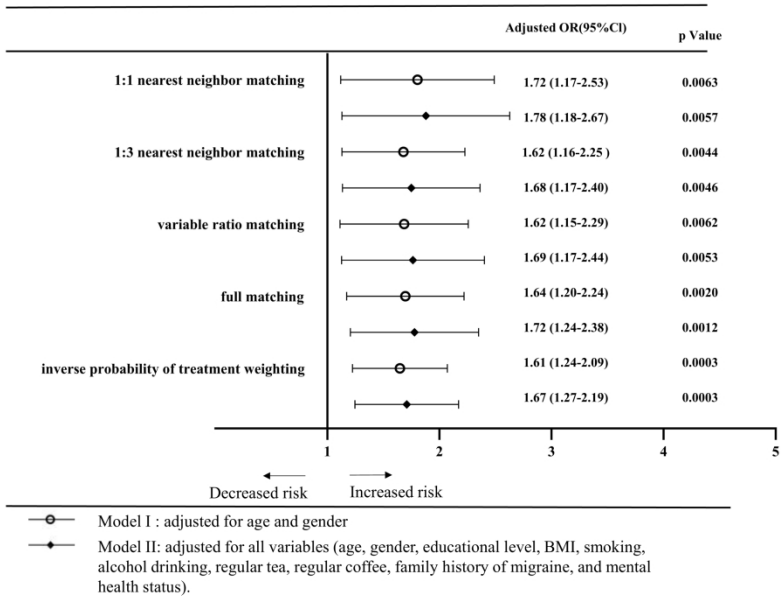

The multiple additional sensitivity analyses in two adjustment models for groups with and without PFO

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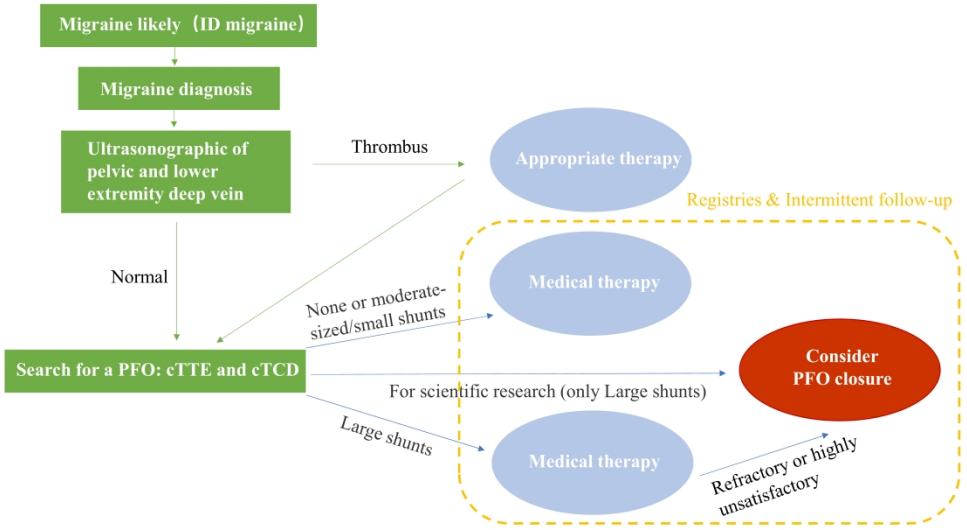


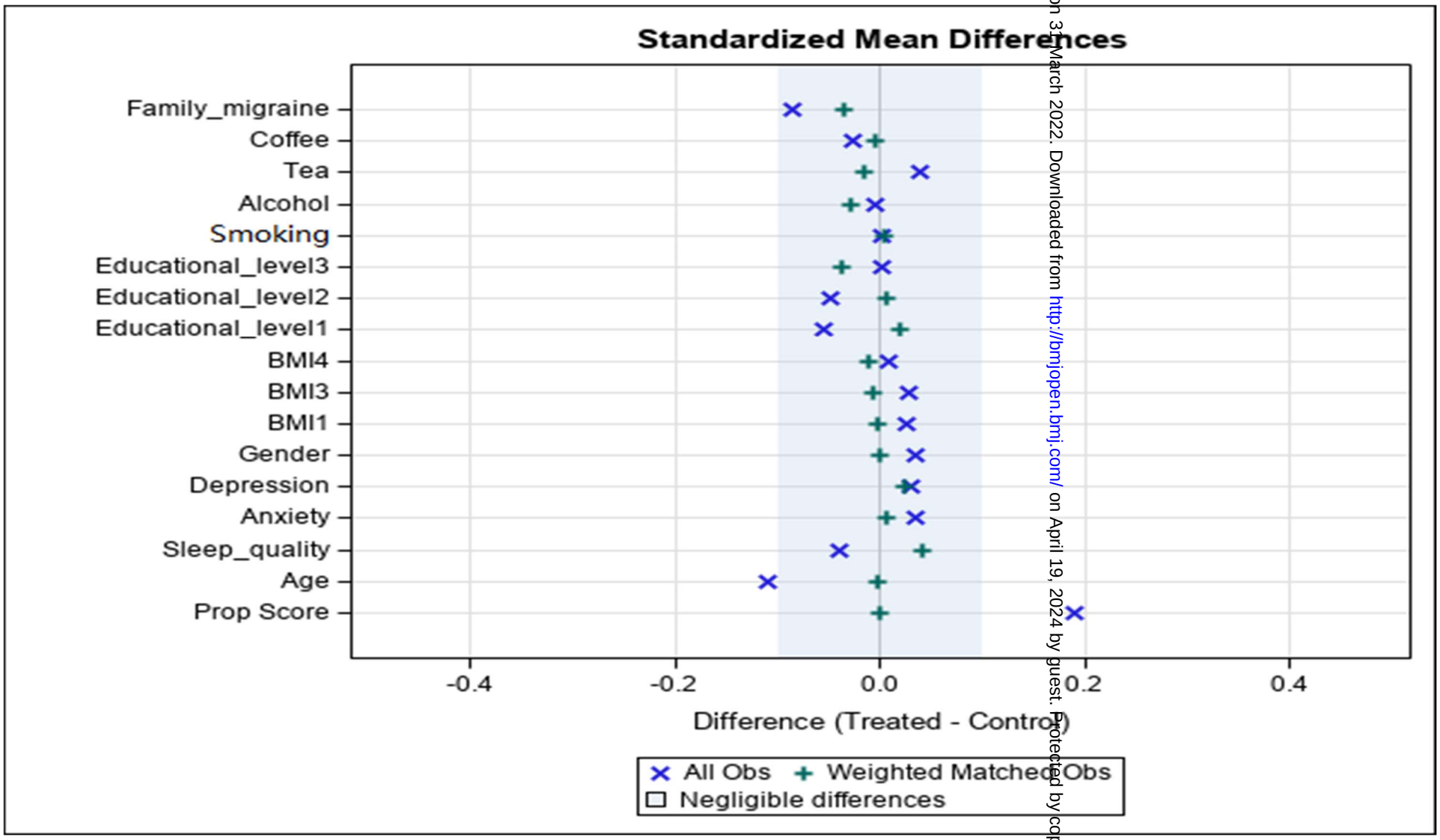
Our proposed stepwise approach to migraine

998x705mm (119 x 119 DPI)

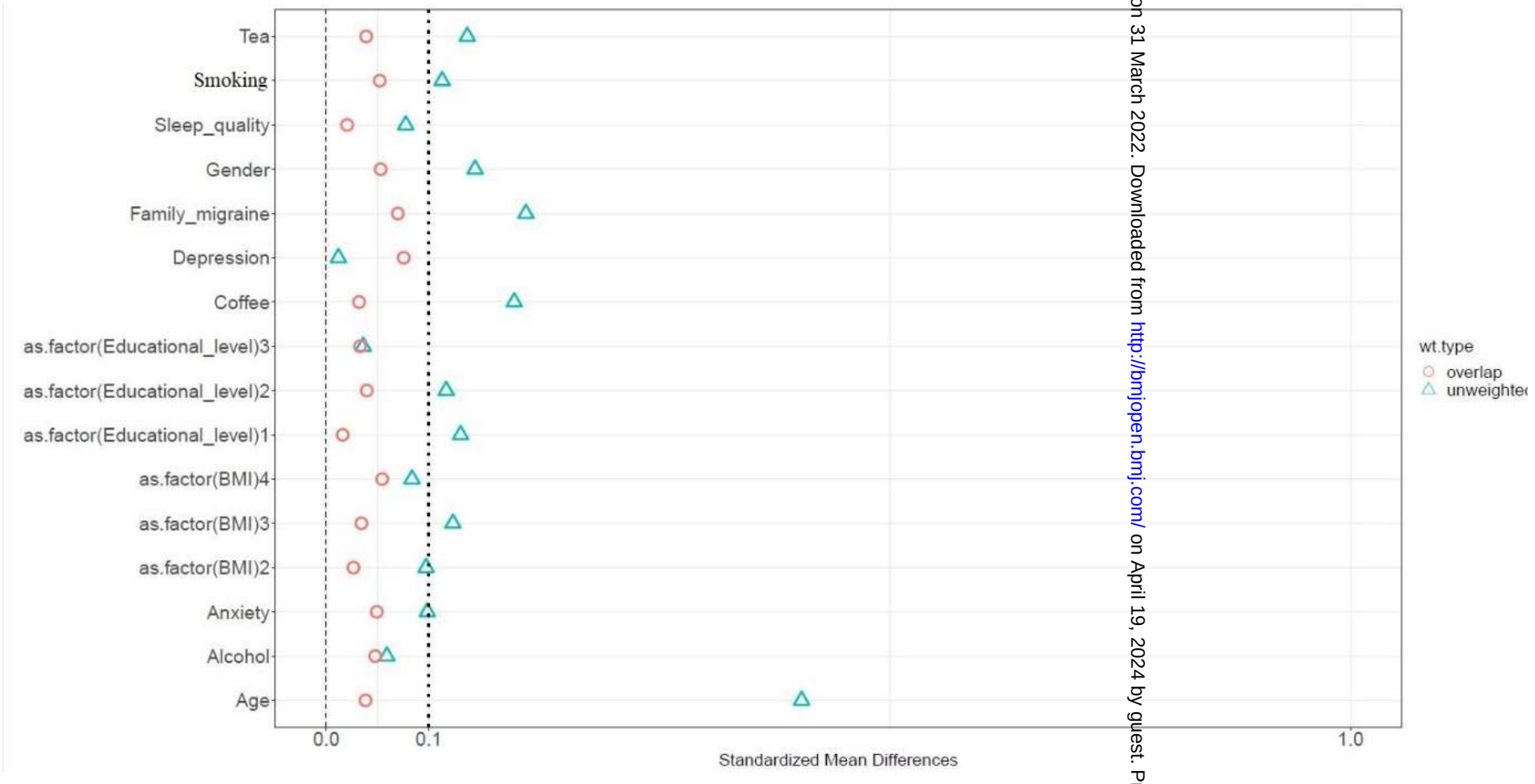
Supplemental Table A. The indicate number of participants with missing data

Value	Number	Missing data
Screening for PFO	3741	none
Age	3741	none
Gender	3741	none
BMI	3639	102
Educational level	3557	184
Smoking	3624	117
Alcohol	3505	236
Tea	3598	143
Coffee	3598	143
Sleep quality	3599	142
Anxiety	3614	127
Depression	3608	133
Family history of migraine	2752	99

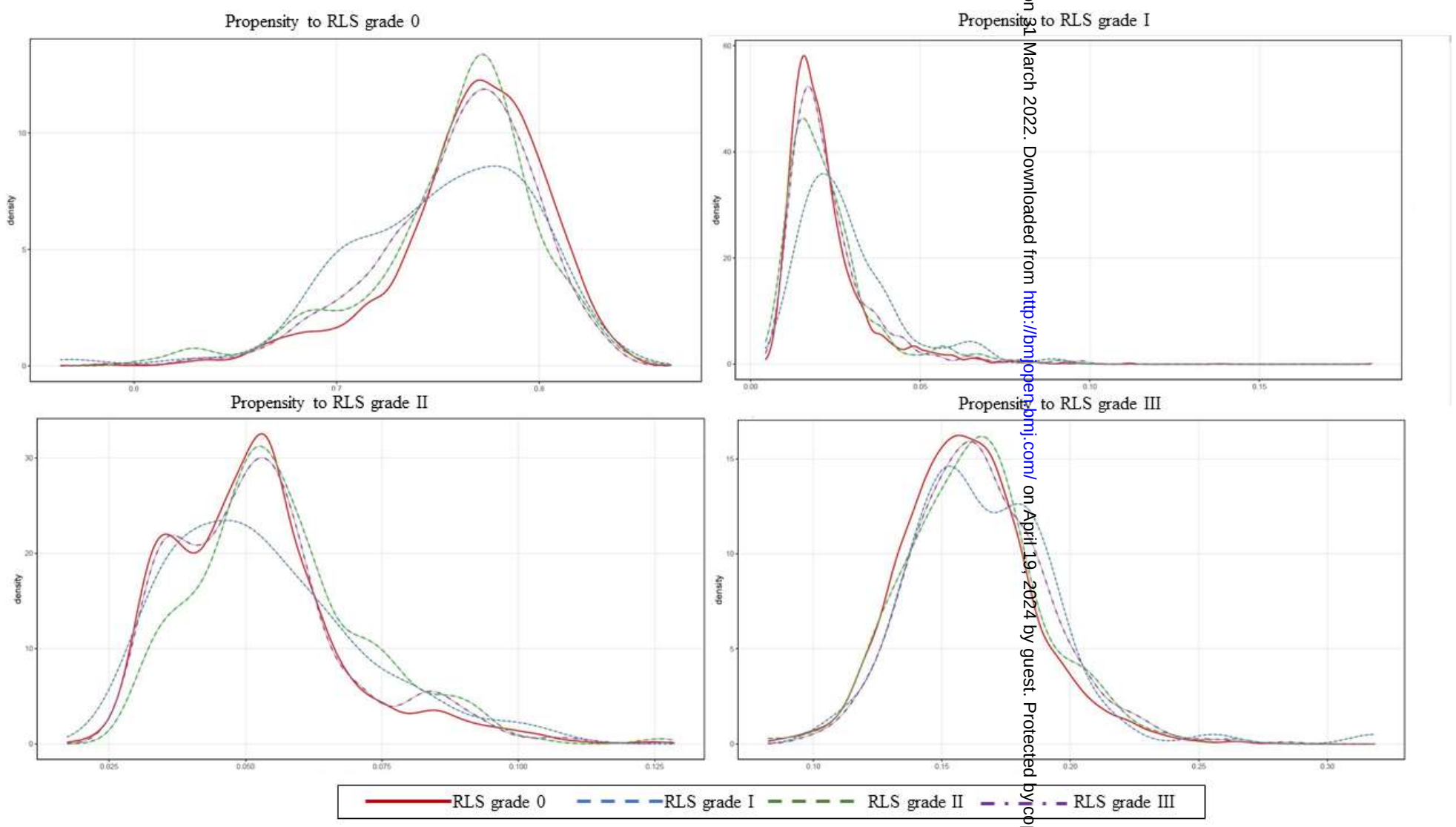
Supplemental Table B. The standardized mean differences of all variables before and after 1:2 nearest neighbor matchingfor groups with and without PFO



Supplemental Table C. The standardized mean differences of all variables before and after generalized overlap weighting for groups with different degrees of right-left shunt



Supplemental Table D. Marginal distributions of the estimated RLS degrees generalized propensity scores



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between patent foramen ovale and migraine without aura: a community-based cross-sectional study in China

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Association between patent foramen ovale and migraine without aura: a community-based cross-sectional study in China

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Word count: 2542 words, 2 figures, 2 tables
(4 supplemental tables were in the Supplemental material).

Abstract

Objectives: To assess the influence of patent foramen ovale on the prevalence of migraine without aura based on propensity score-matched samples in Southwest China.

Design: Propensity-matched cross-sectional study

Participants: Residents over 20 years of age were recruited from 15 communities of Western China from July 2020 to October 2020. A total of 3741 residents having accepted to undergo contrast-transthoracic echocardiography and a standard structured questionnaire were assessed for the relationship between patent foramen ovale and migraine without aura.

Primary and secondary outcome measures: The primary outcome measures were the prevalence of migraine without aura across different degrees of right-left shunts.

Results: A total of 3741 participants were included. Among them, 881 participants were diagnosed with PFO. The prevalence of migraine without aura in the patent foramen ovale group was 12.83%, significantly higher than the other group (7.83%, $p < 0.0001$). Analyses of the matched samples showed that the presence of a patent foramen ovale increased the morbidity risk of migraine without aura ($p < 0.001$; OR = 1.71, 95% CI = 1.19–2.47).

Conclusion: This community-based cross-sectional study pointed to a strong association between patent foramen ovale and migraine without aura, especially when the shunt is large.

Clinical trial No. ChiCTR1900024623.

Keywords migraine, cardiology, epidemiology

Strengths and limitations of this study

- This was the first community-based study to assess whether PFO can increase the risk of migraine without aura.
- Another major strength of this study was the continuous follow-up of participants through high-quality registries.
- To reduce bias, we used multiple statistical models in a propensity score-matching process.
- The data are cross-sectional, not longitudinal.

INTRODUCTION

Migraine is a major disabling disease affecting individuals under 50 years of age [1]which incurs a hefty burden on both individual and social well-being. The prevalence of migraine is high, ranging from 9.3% [2] to 14.4%[3]. Accurate recognition and appropriate treatment are necessary to reduce the burden of migraine and improve patient satisfaction.[4] Unfortunately, many patients with migraine have been historically underdiagnosed and undertreated.[5] Pharmacological treatment remains the first choice for patients with migraine. However, long-term pharmacological treatments may have low compliance rates, low effectiveness, or undesirable side effects, and new drugs such as calcitonin gene-related peptide monoclonal antibodies are too expensive.[6, 7] Although numerous drugs have been available, few patients are able to insist on receiving a standardised preventive treatment protocol.[8] Opioids are still abused among individuals with migraines across all ages and clinical settings, especially in underdeveloped regions [9, 10], resulting in a high risk of medication overuse headache[11], disease chronification[12, 13], addiction, and drug abuse. Therefore, internists and researchers are still looking for new treatments for patients with refractory or highly unsatisfactory medical therapy. In the context of long-term assessments, many studies have suggested that a patent foramen ovale (PFO) may be the potential aetiology or risk factor underpinning migraine.[14, 15]

PFO, described as a 'back door to the brain',[16] is the most common congenital intracardiac right-to-left shunt in adults and has been implicated in the pathogenesis of many neurological conditions. Micro-embolism, vasoactive biochemical, or diluted blood, bypassing the pulmonary circulation from the systemic venous circulation directly to the

brain, giving rise to cortical spreading depression, may result in migraine attacks.[17] Guidelines[17] have recommended the primary screening of patients \ with migraine with aura (MA) for PFO, but the relationship between PFO and migraine without aura (MO) remains controversial[18, 19]. In the past decade, related studies have mostly consisted of case-control studies based in hospitals, which may have incurred a certain degree of admission bias. [8] Their results may eliminate some uncertainties and be more convincing if of the sources of study participants are expanded across the community.

Here, we used contrast-transthoracic echocardiography (cTTE) and a standard structured questionnaire to assess the ratio and severity of PFO and migraine in the communities of Western China and control the baseline characteristics by propensity score to probe the relationship between PFO and MO. In addition, this study sought to determine the feasibility of deploying these technologies in community-oriented primary care settings and for the continuous tracking of cerebrovascular events.

DATA AND METHODS

2.1. Study design

This study was a community-based cross-sectional study approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (2018-491) and registered at the Chinese Clinical Trial Register (ChiCTR1900024623). Written informed consent was obtained from all participants or their legal guardians. Text message recruitment letters and banner advertisements in local communities were used to recruit interested participants from 15 communities around the city of Chengdu, Sichuan, China, from July 2020 to October 2020.

2.2. Patient and Public Involvement

No patient was involved.

2.3. Participants

In this study, we recruited urban residents over 20 years of age who had lived in communities for more than six months. Patients were divided into two groups according to the outcome of cTTE: with and without PFO. Enrolled participants were excluded from the study if they met the following exclusion criteria: a) a history of significant head trauma or migraine with aura; b) with other cardiac abnormalities (except for PFO); c) in the acute stage of vascular embolism or hypercoagulable state; d) inadequate cubital venous access; e) unable to perform the Valsalva manoeuvre (VM) due to severe heart or lung disease.

2.4. Variables

Detailed demographic information was obtained from the enrolled participants via face-to-face interviews based on a standard structured questionnaire. All baseline data were collected by trained workers, undergoing strict quality control assessments. The following information was assessed: age, gender, educational level, BMI, smoking, alcohol drinking, regular tea, regular coffee, clinical history of headache, family history of migraine, and mental health status.

Physical examinations and diagnoses were performed by the neurological internists. Each participant was asked if they had a history of migraine and answered a three-item identification questionnaire assessing the presence of migraine [20] for current symptoms. A positive primary screening result was defined as a positive answer to either question; thereafter, patients underwent an additional systematic and detailed examination

questionnaire, the International Classification of Headache Disorders III[21], assessing onset age, frequency, duration of headache, pain type, sensitivity to light and sound, visual disturbances, nausea, focal neurological symptoms, and medications. An aura was defined as fully reversible visual, sensory, speech, or other central nervous system symptoms which developed gradually, followed by migraine attacks or associated migraine symptoms.

Educational levels were divided into primary (less than 6 years of education), middle (6 to 9 years), high (9 to 12 years), and advanced (more than 12 years). BMI was divided into underweight (<18.5 $kg \cdot m^{-2}$), normal ($\geqslant$ 18.5 $kg \cdot m^{-2}$), overweight ($\geqslant$ 24 $kg \cdot m^{-2}$), and obesity ($\geqslant$ 28 $kg \cdot m^{-2}$) according to the categorisation of BMI groups for Chinese adults released by the Ministry of Health of the People's Republic of China[22]. Smoking was defined as having at least one cigarette per day for more than one year. Alcohol consumption was defined as having at least one drink a week for more than half a year. Regular tea was defined as having tea at least three times a week for more than half a year, similar to regular coffee. Mental health symptoms were evaluated using the Pittsburgh Sleep Quality Index [23], the 9-item Patient Health Questionnaire [24], and the 7-item Generalised Anxiety Disorder Scale [25].

2.5. PFO Screening test

Next, cTTE data were acquired using a Philips IE 33 with 1-5 MHz or 3–8 MHz multiplane transducers to assess for the presence of a PFO. This was performed by two experienced sonographers who also jointly reviewed all videotapes and were unaware of the participants' clinical data.

A microbubble bolus from an agitated solution of 8 ml saline, 1 ml blood, and 1 ml air

was injected into the antecubital veins to increase sensitivity.[26] Prior to the examination, the sonographers informed the participants about VM. Participants were assessed for PFO at rest and during provocative manoeuvres (VM and coughing). Positive for the presence of a PFO was considered to be present if microbubbles were present in the left atrium or ventricle within three cardiac cycles from maximum right atrial opacification.[26] The degree of right-left shunt (RLS) was quantified based on the maximum value of detected microbubbles per frame in the left atrium at rest or during provocative manoeuvres: grade I (1–10), grade II (11–30), and grade III (>30 or the left atrium is filled with microbubbles).[26]

2.6. Statistical analysis

Continuous variables were described as mean and standard deviation (mean ± SD) and compared using a t-test. Categorical variables were described as frequencies and percentages and compared using a chi-square test. All analyses were carried out using SAS (version 9.4) and R (version 4.1.0). A value of $p<0{\cdot}05$ was considered statistically significant.

Chained equations (fully conditional specification) were used for the multiple imputation of absent data, and the imputation number was increased to 25. We used Rubin's rules to merge the outcomes of multiple datasets. Baseline characteristics of patients with and without PFO were matched using the propensity score method of 1:2 nearest neighbour matching with a calliper of 0.02 times the pooled estimate of the standard deviation of the propensity score. In order to ensure the stability of the multiple imputation of absent data, two binary logistic regression models were set up to estimate the individual propensities for PFO, one model only adjusting for age and gender (no missing values), and another model adjusting for all variables (age, gender, educational level, BMI, smoking, alcohol drinking,

regular tea, regular coffee, family history of migraine, and mental health status). Covariate balance was assessed by the standardised mean difference and considered good when the absolute standardised mean difference was under 0.1. Next, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) to probe the risk of migraine among patients with PFO. We then conducted additional sensitivity analyses to prove the stability of our model, including 1:1 nearest neighbour matching (with a calliper of 0.02 times the pooled estimate), 1:3 nearest neighbour matching (with a calliper of 0.02 times the pooled estimate), variable ratio matching (without calliper), full matching (without calliper), and inverse probability of treatment weighting (with stabilised IPTW weights).

We further analysed how PFO differentially influenced the development of migraine without aura disease across different RLS grades by generalised overlap weighting[27]. Similarly, the estimation of generalised propensity scores was used by a multinomial logistic model. In one, we controlled for the effects of age and gender; in another, we adjusted all aforementioned variables. Subsequently, each grade of the RLS will have a propensity score. In the case of the four groups, since any two groups can be compared, each covariate has multiple standardised differences. For simplicity, we used the maximum value of the absolute value of multiple standardised differences for each covariate. Because generalised overlap weighting smoothly down-weighted the units with propensity scores close to 0 or 1, we considered it a continuous version of direct trimming. Finally, we estimated the standard error and confidence interval based on the robust variance estimator.

RESULTS

3.1. Demographics and Operative Details

Figure 1 represents the flow of the participants in this study. A total of 3741 participants fulfilled all inclusion/exclusion criteria and agreed to participate in the study.

The mean age (SD) of these participants was 50.90 (7.37) years, and the ratio of female was 74.5% (2786/3741). Among them, 881 (23.5%) participants were diagnosed as PFO-positive (666 females, mean age (SD): 50.27 (7.53] years) and 2860 as PFO-negative (2120 females, mean age (SD): 51.09 (7.31] years). Following a more detailed division, 2.25% (84 of 3741) had an RLS of grade I, 5.21% (195 of 3741) had an RLS of grade II, and 16.09% (602 of 3741) had an RLS of grade III.

The positive rate of MO in the PFO group was 12.83%, which was significantly higher than that in the group without PFO (7.83%, $p < 0.0001$). Additional baseline features are reported in Table 1 and the number of participants with missing data for each variable is reported in Supplemental Table A.

Table.1 Demographic characteristics after multiple imputation

Variable	Without PFO (n=2860)	With PFO (n=881)	SMD	P
propensity score	0.2337(0.0361)	0.2413(0.0383)	0.1993	0.0060
Mean (SD) age, years	51.09(7.31)	50.27(7.53)	0.1106	0.0038
Gender, n (%)			0.0339	0.3816
Female	2120(74.13)	666(75.60)		
Male	740(25.87)	215(24.40)		
BMI, n (%)				0.7874
Underweight	76(2.65)	21(2.33)	0.0204	
Normal	1451(50.72)	464(52.62)		
Overweight	1051(36.76)	312(35.38)	0.0287	
Obesity	282(9.88)	85(9.67)	0.0076	
Educational level, n (%)				0.1878
Primary	940(32.86)	254(28.84)		
Middle	1349(47.18)	439(49.84)	0.0533	
High	416(14.56)	140(15.88)	0.0368	
Advanced	154(5.40)	48(5.44)	0.0073	
Smoking, n (%)	476(16.64)	143(16.20)	0.0126	0.7564
Alcohol, n (%)	430(15.03)	134(15.23)	0.0077	0.8492

Tea, n (%)	801(28.01)	232(26.29)	0.0387	0.3286
Coffee, n (%)	36(1.25)	15(1.68)	0.0352	0.3917
Sleep quality, mean (SD)	3.82(2.48)	3.71(2.46)	0.0451	0.2691
Anxiety, mean (SD)	1.01(2.28)	1.10(2.42)	0.0355	0.3734
Depression, mean (SD)	1.03(2.10)	1.10(2.14)	0.0320	0.4232
Family migraine, n (%)	355(12.41)	141(16.05)	0.1042	0.1001

Abbreviations: SD, standard deviation; SMD, standardized mean difference

3.2 Propensity-score matching for groups with and without PFO

Following 1:2 matching, the standardised mean differences of all variables were less than 0.1 without exception, meaning that the balance was better (details are shown in Supplemental Table B). Propensity-score-matched populations were generated to adjust for baseline differences and are reported in Table 2 with outcomes.

Participants diagnosed with PFO showed a marked increase in the MO ratio compared with the other participants (12.79% vs. 8.12%, p = 0.0004, Table 2). Following full adjustment, logistic regression analyses showed that PFO increased the risk of migraine (OR = 1.71, 95% CI = 1.19–2.47). The association remains significant in the adjustment model only by age and sex (OR = 1.66, 95% CI = 1.18–2.32). Multiple additional sensitivity analyses in the two adjustment models yielded similar results (details are shown in Figure 2).

Table.2 Demographic characteristics (Matched)

Variable	Matched			
	Without PFO (n=1747)	With PFO (n=880)	SMD	P
propensity score	0.2404(0.0370)	0.2411(0.0379)	0.0004	0.6645
Mean (SD) age, years	50.37(7.53)	50.28(7.51)	0.0090	0.7850

Gender, n (%)			0.0128	0.7710
Female	1323(75.75)	665(75.59)		
Male	424(24.25)	215(24.41)		
BMI, n (%)				0.9760
Underweight	39(2.21)	20(2.33)	0.0108	
Normal	923(52.81)	463(52.59)		
Overweight	618(35.37)	312(35.41)	0.0107	
Obesity	168(9.61)	85(9.67)	0.0146	
Educational level, n (%)				0.9880
Primary	503(28.77)	254(28.86)		
Middle	874(50.04)	439(49.84)	0.0152	
High	277(15.88)	140(15.87)	0.0118	
Advanced	93(5.31)	48(5.44)	0.0128	
Smoking, n (%)	283(16.19)	143(16.22)	0.0113	0.8218
Alcohol, n (%)	263(15.08)	134(15.24)	0.0126	0.7824
Tea, n (%)	453(25.90)	231(26.28)	0.0147	0.7437
Coffee, n (%)	27(1.55)	14(1.63)	0.0090	0.8082
Sleep quality, mean (SD)	3.70(2.41)	3.71(2.46)	0.0137	0.8725
Anxiety, mean (SD)	1.06(2.39)	1.09(2.41)	0.0108	0.7587
Depression, mean (SD)	1.07(2.20)	1.10(2.13)	0.0096	0.8023
Family migraine, n (%)	266(15.21)	141(15.98)	0.0111	0.6238
MO, n (%)	142(8.12)	113(12.79)		0.0004

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MO, migraine without aura

3.3 The relationship between RLS severity and MO

The details of the generalised overlap weighting are presented in the Supplemental

Tables C and D. Controlling for the effects of age and gender, individuals who had a PFO with large shunts were 1.69 times more likely to report experiencing MO (OR = 1.69, P<0.0001, 95% Cl = 1.25–2.29). This significant effect was partially strengthened after controlling for all variables. In the fully adjusted model, individuals who had a PFO with large shunts were 1.65 times more likely to report experiencing MO (OR = 1.65, P<0.0001, 95% Cl = 1.23–2.22). However, a PFO with moderate or small shunts was not.

DISCUSSION

This is the first community-based study in China to probe whether PFO can increase the risk of migraine without aura. In addition, all subjects were obtained from a prospective population cohort study in Southwest China and could undergo continuous follow-ups. This was a useful addition to existing epidemiological data and clinical research on PFO and MO in Southwest China. It showed that the MO ratio was higher in participants with PFO than in controls, especially in groups with large shunts.

An autopsy study of Hagen in 965 normal hearts revealed that PFO had a prevalence of 25.4% during the 4th through 8th decades.[28] In order to eliminate any possible interference of an extracardiac shunt, we used cTTE to evaluate the existence of PFO in this study. Our prevalence of PFO in the general population was 23.4%, which is similar to its universal prevalence. Our findings also estimated the ratio of MO in Han Chinese from the Sichuan Province to be similar to that in the Southeast Coast[29] or the Chinese mainland[2].

The pathogenesis of migraine is complex. Current evidence demonstrates that various factors may increase the prevalence of migraine, including age, female sex, smoking, alcohol consumption, obesity, low educational status, and family history.[30-32] Based on these known

findings, we included all above variables in the propensity score model to balance the baseline characteristics as much as possible. By using various sensitivity analyses, we ensured the robustness of the results.

Our results are consistent with and extend the results of a large-scale case-control study by Wang et al., who found that the prevalence of RLS in MO was significantly higher than that in the healthy group (39.9% vs. 29.4%, $p < 0.001$).[14] Other studies have found that the prevalence of MO is similar in both populations with and without PFO.[18, 19] However, as the author mentioned in the article, they ignored cohort studies, which are the best method for determining the incidence and natural history of a condition.[19]

Our outcomes suggest that routine screening for PFO in migraine patients who are not responsive to treatments or find their medical therapy dissatisfactory. With the help of various portable medical devices, it is possible to carry out migraine and PFO screening in the community, even in underdeveloped regions such as Southwest China. Given the finding that only 25% of patients who consulted a healthcare professional received an accurate migraine diagnosis,[5] it may be more meaningful to disseminate and implement migraine guidelines to community-oriented primary care than neurologists, which can markedly improve access to high-quality management for patients with migraine, reducing the consumption of health resources and socioeconomic burden.

There are some limitations to this study: First, a recall bias could not be excluded. Second, PFO increases the risk of cryptogenic stroke, and some residents failed to participate in this study due to death or physical disability from stroke. Thus, the prevalence of migraine in the PFO group may be underestimated.

CONCLUSION

In summary, in this study, based on the community population hitherto in China, we confirmed that PFO can increase the risk of MO, especially in groups with large shunts. Future work will continue to track respective cerebrovascular events and seek to understand if better management of PFO conditions improves migraine and whether primary screening for PFO should be carried out on a routine basis in patients with migraine who are not responsive to treatments or find their medical therapy dissatisfactory.

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Competing interests None declared.

Author contributions

Lei Chen and Yusha Tang conceived and designed the work. Yusha Tang conducted the study, carried out the statistical analysis and drafted the manuscript. Anjiao Peng and Bo Peng were involved in data collection and interpretation. Lei Chen involved in critical revision of the article and final approval of the version to be published. Shixu He, Xia Zhao, Yuanfeng Zhu, Na Yang, Wanlin Lai, and Tingting Song contributed to the acquisition of data. All authors have agreed to be accountable for all aspects of the work.

Data sharing No additional data available.

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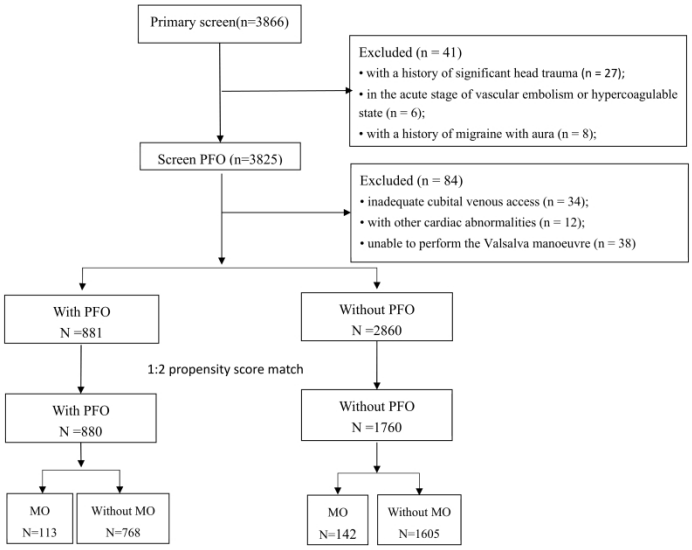
Figure Legends

Figure 1

The flow of participants in this study

Figure 2

Multiple additional sensitivity analyses in two adjustment models for groups with and without PFO



The flow of participants in this study

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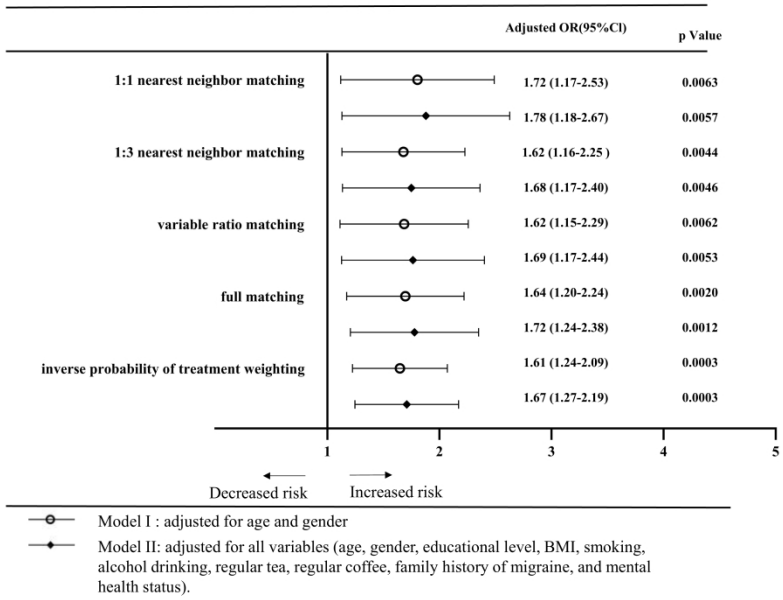


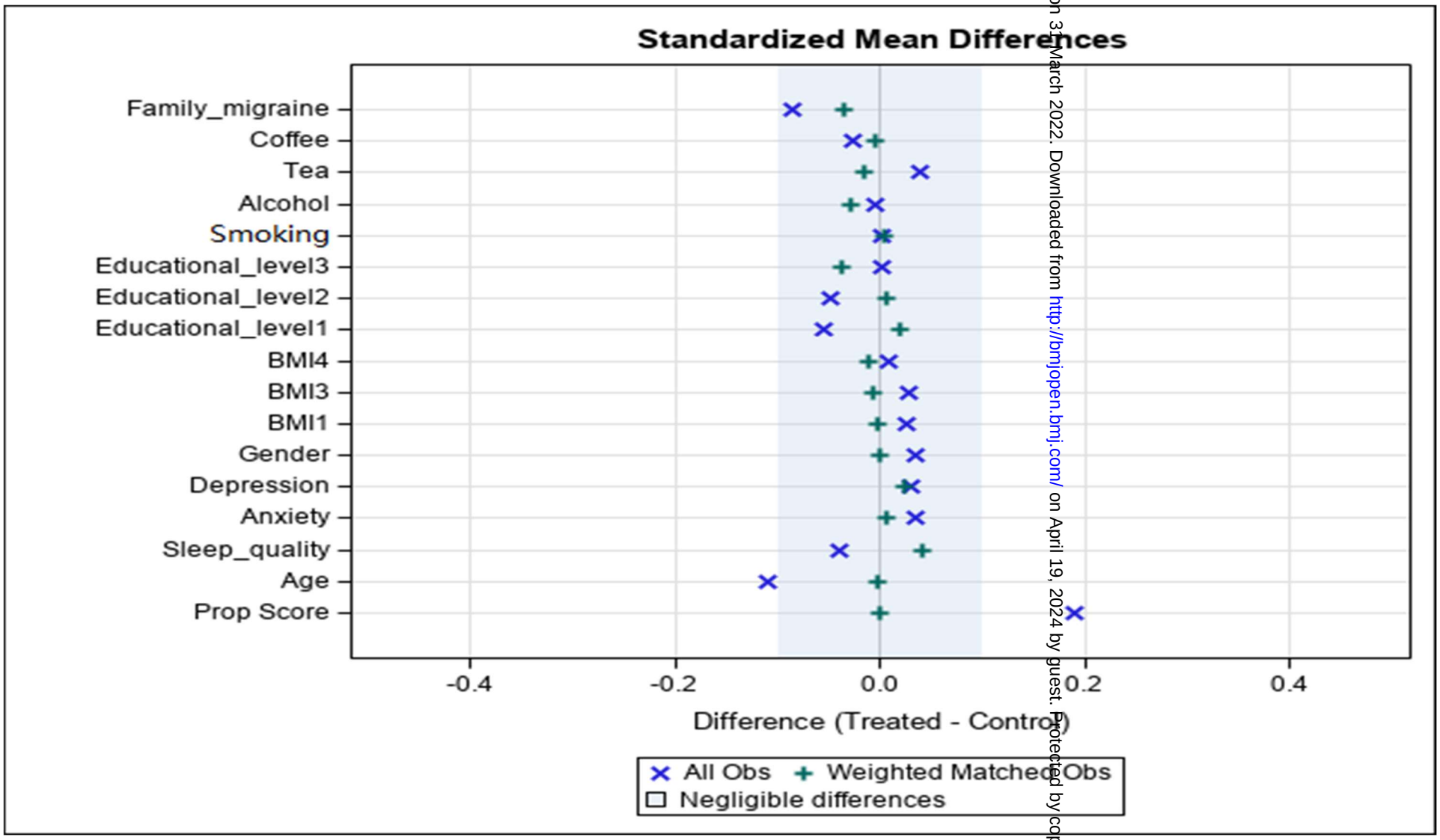
Multiple additional sensitivity analyses in two adjustment models for groups with and without PFO

296x209mm (400 x 400 DPI)

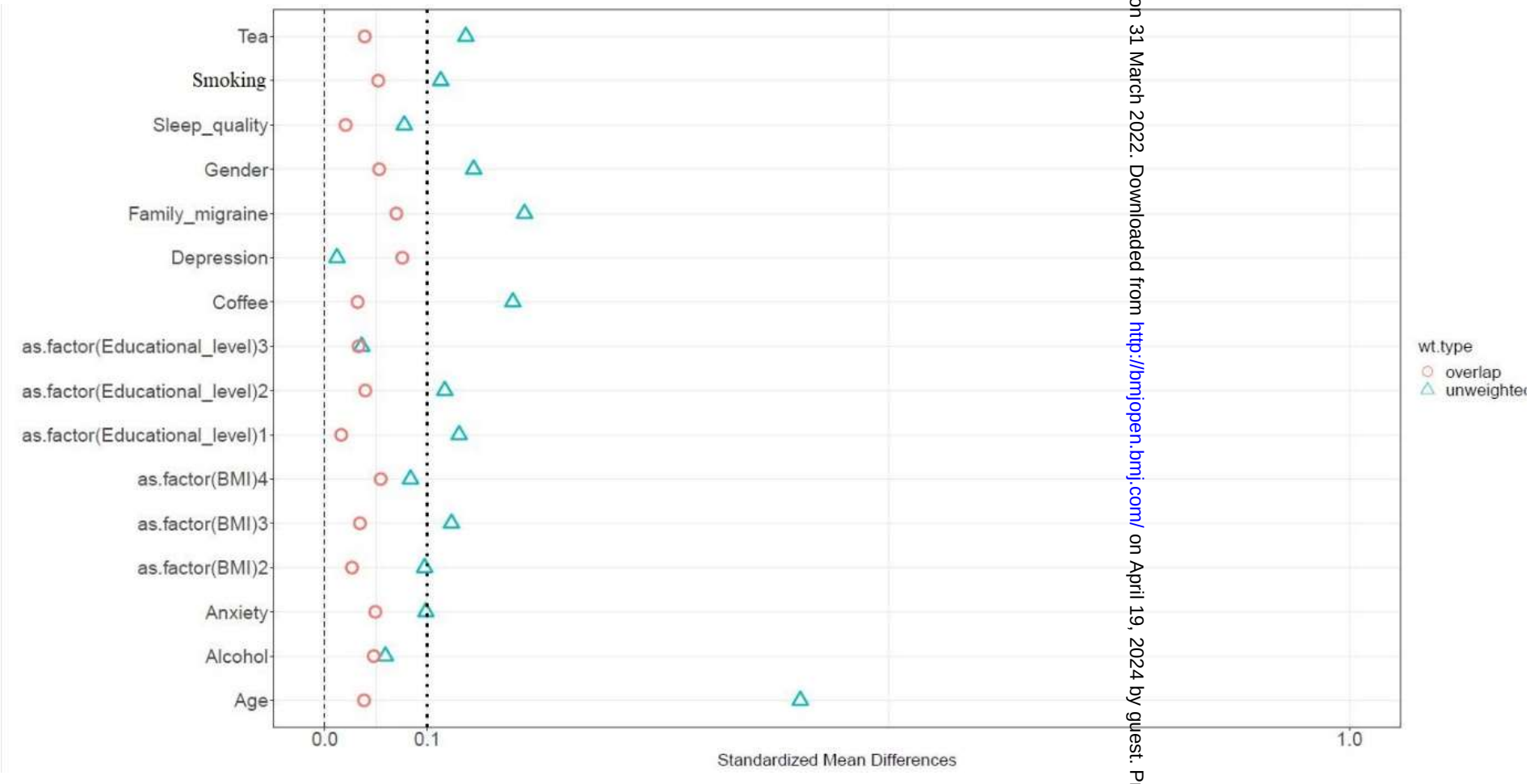
Supplemental Table A. The indicate number of participants with missing data

Value	Number	Missing data
Screening for PFO	3741	none
Age	3741	none
Gender	3741	none
BMI	3639	102
Educational level	3557	184
Smoking	3624	117
Alcohol	3505	236
Tea	3598	143
Coffee	3598	143
Sleep quality	3599	142
Anxiety	3614	127
Depression	3608	133
Family history of migraine	2752	99

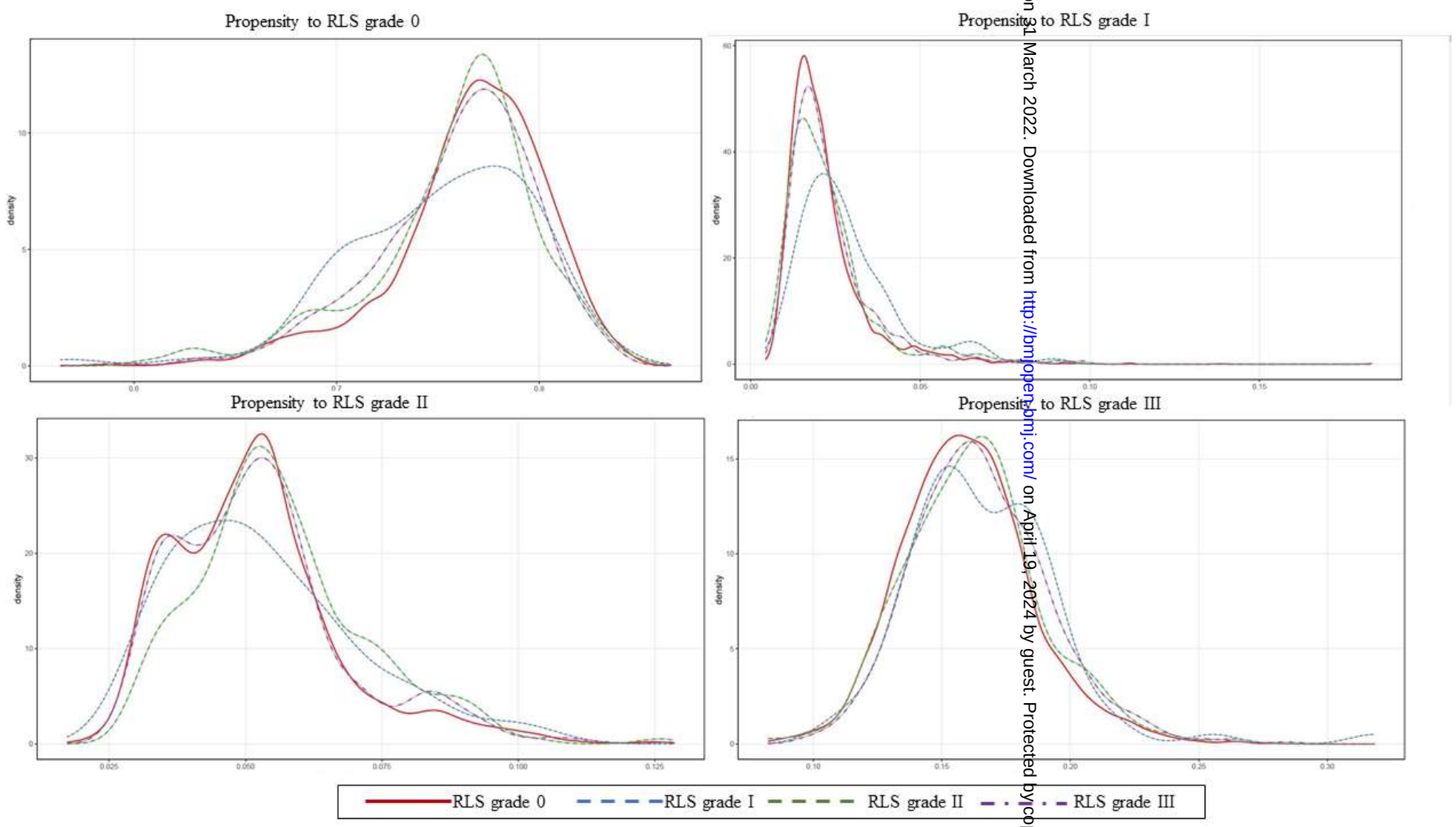
Supplemental Table B. The standardized mean differences of all variables before and after 1:2 nearest neighbor matchingfor groups with and without PFO



Supplemental Table C. The standardized mean differences of all variables before and after generalized overlap weighting for groups with different degrees of right-left shunt



Supplemental Table D. Marginal distributions of the estimated RLS degrees generalized propensity scores



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.