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Original Research Article

The Prevalence of Mitral Valve Prolapse in Panic Disorder: A Meta-Analysis

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Background: *Although most studies have suggested that mitral valve prolapse (MVP) is more prevalent in patients with panic disorder (PD) than in healthy controls, there is a substantial uncertainty in the rates of MVP across studies.* **Objective:** *To investigate, through systematic review and meta-analysis, the relative risk of MVP in patients with PD compared to controls.*
Methods: *Embase, Proquest, Pubmed, and Google Scholar electronic databases were searched up to September 2018. All studies published in peer-reviewed journals, which included both PD and controls groups, were selected. Events (presence of MVP) and nonevents (absence of MVP) in PD and control groups were recorded. The main outcome was the measure of relative risk (RR) pooled with 95% confidence intervals, using fixed-effects model. Heterogeneity, small publication effect, and publication bias were evaluated.*

Results: *Fourteen studies, including 1146 participants, met eligibility criteria. There was no significant heterogeneity or publication bias. The prevalence of MVP in PD and healthy controls was 27.20% and 9.21%, respectively. Patients with PD had a significantly increased relative risk of MVP compared to controls in the pooled sample (RR = 2.469, 95% confidence interval = 1.848–3.300). Age did not significantly modify the RR.*
Conclusions: *MVP is significantly more prevalent in patients with PD than in controls. This meta-analysis of published studies is sufficient to establish an association between PD and MVP; nevertheless, it is not clear that the association is specific to PD. Patients with PD should be evaluated for MVP to decrease possible negative adverse consequences of MVP.*
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Key Words: panic disorder, cardiovascular disease, agoraphobia, mitral valve prolapse, relative risk, meta-analysis.

INTRODUCTION

Panic disorder (PD) is an anxiety disorder characterized by reccurring unexpected panic attacks and agoraphobia in the vast majority of individuals with PD.[1] The lifetime prevalence of PD and recurrent panic attacks without a diagnosis of PD in the general adult population is 5.2% and 7% respectively.[2,3] PD is associated with high disability and with severe symptoms. Among those, cardiovascular symptoms, such as tachycardia, palpitations, fatigue, dyspnea, dizziness and fainting, are key features of panic attacks, in addition to marked distress and anticipatory anxiety.[1]

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Despite the extensive research, we do not understand the etiology of PD.

The prevalence of mitral valve prolapse (MVP) in the general population is reported to be 2.4% using recent echocardiography criteria.[4] However, in previous community studies using an older echocardiographic technique, equipment and diagnostic criteria, the prevalence of MVP was reported as 5%.[5] The cardiovascular symptoms listed previously for PD also occur in MVP.

For the last 40 years there have been multiple discussions on whether MVP is associated with PD. Some researchers speculated that PD could lead to or be caused by MVP given the similarity of symptoms in PD and MVP.[6,7] However, the etiological connection, previously postulated between these two conditions, has not been confirmed, and the field now accepts that PD and MVP can co-exist independently.[1,8–10] The literature on the comorbidity of PD and MVP is inconsistent in terms of the magnitude of association. The prevalence of MVP in patients with PD has been reported as between 0% and 57%, which makes the results inconclusive.[11–13] The high variability of these results may be related to sampling biases, small study samples, and to inconsistent diagnostic criteria for PD and MVP. Furthermore, the differences in echocardiography techniques have been shown to strongly influence estimates of the prevalence of MVP diagnosis.[14,15]

The relationship between the DSM-III category of anxiety neurosis, panic attacks, chronic anxiety, and MVP has been reviewed in earlier studies without a meta-analytical process.[8,9] However, the contents and classifications of variables of interest have been subject to change over time. For example, situationally-predisposed panic attacks can also be observed in other anxiety disorders, including social phobia, generalized anxiety disorder or simple phobias. Moreover, no current DSM-5 entity corresponds precisely to the DSM-III concept of "anxiety neurosis," which was frequently used in the older literature investigating the association of PD and MVP. On the other hand, later DSM classifications have defined PD and agoraphobia as successive, related, and overlapping disorders.[1,16,17] For these reasons, we have limited this meta-analysis to those patients who were diagnosed with PD and/or agoraphobia and comparing them with a control group.

We aimed to perform a systematic review of the literature and a meta-analysis on the prevalence of MVP in PD and agoraphobia vs controls.

METHODS

Data Sources

We performed a literature search that focused on reporting MVP prevalence in adults with PD (with or without agoraphobia), and with agoraphobia only. We searched major electronic bibliographic indexing services Google Scholar, Embase, Proquest, and Pubmed using keywords "mitral valve prolapse AND panic," "mitral valve prolapse AND panic disorder" and "mitral valve prolapse AND agoraphobia." We included in our screen all articles written in English, Spanish, and Turkish and published in a peer-reviewed journal, from the earliest dates available through September 2018. Then, the reference lists of identified studies were searched manually for additional articles.

Description of Included Studies

The criteria for including studies in the meta-analysis was that (1) the patients must have been diagnosed with either PD or agoraphobia (PD/A), (2) the study must have included cases and controls, and (3) the study must have reported the prevalence of MVP in both groups. For studies comparing MVP prevalence among multiple psychiatric diagnostic groups (e.g., generalized anxiety disorder, social phobia) with a control group, only the data of the PD/A groups were extracted. We excluded studies using as comparator only psychiatric diagnoses associated with situationally-predisposed panic attacks (such as GAD with panic attacks, social phobia with panic attacks). For reports classifying the MVP diagnosis as definite, probable, or possible, only the definite numbers were included in the meta-analysis. The minimum acceptable criteria for the diagnosis of MVP were mitral leaflet interfaces moving posteriorly from the C-D line $\geq$2 mm in late systole, or $\geq$3 mm posterior systolic movement of the mitral valve, in accordance with the criteria of the American Society of Echocardiography[18] and others.[19] All the studies included were controlled, and the diagnosis of MVP was made or excluded in PD/A and controls with

TABLE 1. Studies Comparing the Prevalence of MVP in Patients With PD to Control Group

Study	Year	Echocardiography	PD and Agoraphobia			Controls		
			N (F/M)	Age	Rate of MVP (%, *n*)	*n* (F/M)	Age	Rate of MVP (%, *n*)
Kantor et al.[7]	1980	Ausc/M-Mode	25 (25/0)	41.9 ± 9.4	32%, 8	23 (23/0)	42	8.7%, 2
Venkatesh et al.[21]	1980	Ausc/M-Mode	21 (15/16)	37	38.1%, 8	20 (14/6)	37	10%, 2
Shear et al.[22]	1984	M-Mode	25 (14/11)	35.8	8%, 2	25 (14/11)	37	4%, 1
Nesse et al.[23]	1985	Ausc/M-Mode	20 (16/4)	32.0 ± 11	35%, 7	3 (NR)	26.0 ± 5.2	0%, 0
Dager et al.[24]	1986	M-Mode and 2D	35 (NR)	NR	34.3%,12	20 (10/10)	36.6	15%, 3
Gorman et al.[25]	1988	M-Mode and 2D	36 (18/18)	35.4 ± 7.3	39%/14	22 (12/10)	29.3 ± 8.5	18%, 4
Arkonac et al.[26]	1990	M-Mode and 2D	56 (30/26)	32.7 ± 9.1	54%, 30	40 (16/24)	32.9 ± 8.7	12.5%, 5
Carney et al.[27]	1990	Cineangiography	20 (11/9)	52 ± 11	40%, 8	28 (15/13)	56 ± 9	7%, 2
Ozer et al.[28]	1993	M-Mode and 2D	40 (24/16)	31.5 ± 6.59	45%,18	57 (31/26)	32.8 ± 6.17	17.5%, 10
Arik et al.[29]	1998	M-Mode and 2D	51 (33/18)	38.1 ± 10.0	17.6%, 9	60 (41/19)	38.7 ± 12.3	5%, 3
Hamada et al.[30]	1998	M-Mode and 2D	121 (55/66)	38.3 ± 1.2	32.2%, 39	37 (15/22)	31.6 ± 1.3	16.7%, 6
Martin-Santos et al.[31]	1998	M-Mode and 2D	84 (NR)	NR	9.5%, 8	34 (NR)	NR	17.7%, 6
Tamam et al.[32]	2000	M-Mode and 2D	50 (34/16)	33 ± 8	12%, 6	50 (28/22)	31 ± 9	5.7%, 3
Filho et al.[33]	2011	M-Mode and 2D	41 (19/22)	37.8 ± 9.0	2.4%, 1	102 (67/35)	22.3 ± 2.7	1%, 1

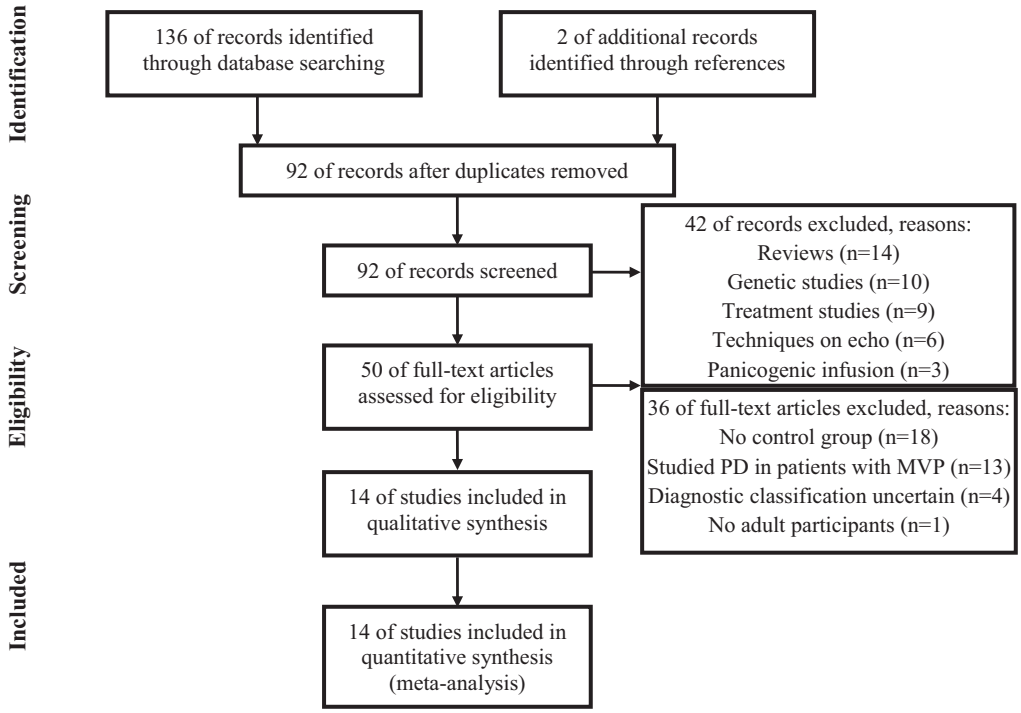
Ausc = auscultation; NR = not reported; 2D = two dimension.

echocardiography (in 13 studies), using the best echo standards for the MVP diagnosis available at the time, or by cineangiography (in one study) (see Table 1). As far as medical and psychiatric diagnoses, in all studies the diagnosis of PD/A was made with standardized interviews (e.g., SCID) according to the DSM criteria applicable at the time. However, the exclusion criteria for comorbid psychiatric diagnoses were not reported in 8 out of 14 studies for the PD/A group. In 4 studies the control groups were determined to have no psychiatric diagnosis via SCID, in 7 studies the exclusion for controls was made with psychiatric interviews; medical illness was excluded in 11 of 14 studies based on a medical interview; and in 3 of 14 studies the authors did not explain the selection process for controls. A flowchart of the article selection according to the Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement[20] has been summarized in Figure 1. Since this meta-analysis focused on the risk ratio of MVP in PD/A compared to controls as the main output, we recorded the sample size, the number of positive outcome (MVP+), and the number of negative outcomes (MVP−) from the selected studies. The general features of the included studies (e.g., publication year, gender distribution, mean ages, and echocardiography methods) were summarized in Table 1.

Statistics

The event (MVP+) and nonevents (MVP−) in PD/A and control groups extracted from the studies were entered into the dataset as raw numbers. The pooled data included number of events, number of nonevents, sample size of the PD/A, and the control groups. The risks of MVP for cases (PD/A) and controls, and the risk ratios (RR) for each study were calculated. The significance of pooled RR's was tested by z tests. The homogeneity of the effect sizes across the studies was tested with the Cochrane's Q test, and the magnitude of heterogeneity was expressed by the I^2 (inconsistency) test. If the homogeneity assumption was not violated ($I^2 < 25\%$, $p < 0.1$), we accepted the relative risk and weighted percentages from fixed effect model calculations (Mantel-Haenszel test). In addition to visual inspection of the funnel plots, publication bias and small study effects were assessed by the Harbord and Egger's tests. We performed a sensitivity analysis by investigating the effect of individual studies on the overall meta-analysis: the meta-analysis was re-estimated by omitting each study, sequentially, to determine the robustness of results. All statistical analyses were performed with Stata 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The overall statistical level of significance was set to 2 tailed $p \leq 0.05$.

FIGURE 1. PRISMA Flowchart of the Article Selection Process



RESULTS

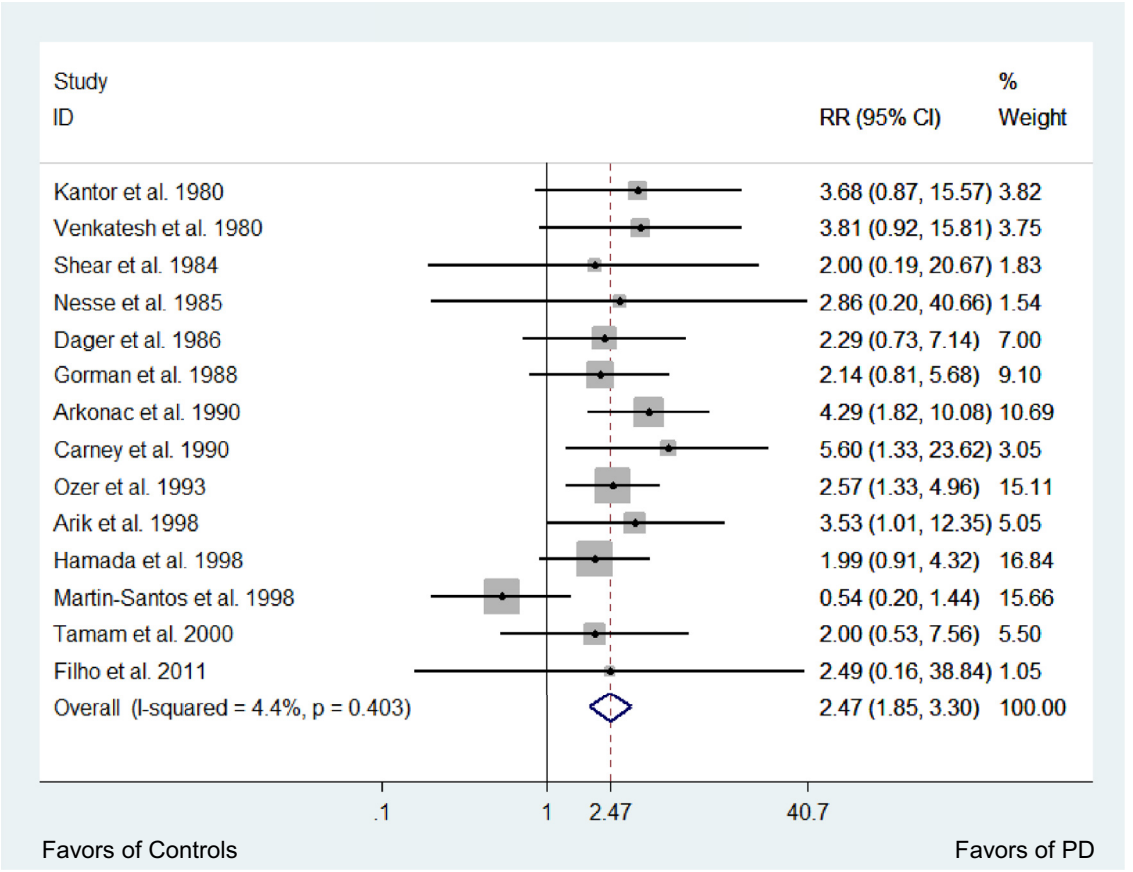
Methodologic Quality of Included Studies

The diagnostical assessments for PD/A were done according to DSM classifications in all of the included 14 studies.[7,21-33]. Again, the diagnosis of MVP was made according to accepted standards, and confirmed using combinations of methods in all the included studies. In most of the studies, the clinicians assessing MVP were blinded to research groups. The main output measures were clearly expressed in all studies. Overall, the quality of studies included in the meta-analysis was evaluated as high. Nevertheless, 5 of the included studies did not report mean age ($n = 2$) and standard deriva-tion ($n = 3$) either in cases or controls (Table 1). Without the 5 studies which did not report mean age or SD, the mean age of participants with PD/A was higher (36.76 ± 6.81, $n = 435$) than controls (33.40 ± 7.60, $n = 399$) in the pooled sample, but the difference did not reach statistical significance (SMD = 1.015, SE = 0.523, t = 1.941, $p = 0.06$). The distribution of genders was not reported in 3 studies (in PD/A group $n = 2$, in controls $n = 1$). In the remaining studies there were no significant differences in gender distribution between cases (female $n = 279$ out of 497, 56.14%) and controls (female $n = 276$ out of 464, 59.48%) in the pooled sample ($\chi^2 = 0.968$, df = 1, $p = 0.325$).

Main Meta-analysis

The total pooled sample size was 1136 and consisted of 14 studies which have reported the main outcome and met the eligibility criteria of the meta-analysis. One-hundred seventy out of 625 PD/A patients (27.2%) and 48 out of 521 controls (9.2%) met criteria for MVP. In the pooled sample, the RR for MVP+ was significantly higher in patients with PD/A (RR = 2.469, 95%CI = 1.848−3.300) compared to controls (z = 6.110, $p < 0.001$, Figure 2). The odds ratio for MVP+ was 3.146 (95%CI = 2.199−4.500) for patients with PD/A (z = 6.275, $p < 0.001$). There was no evidence of heterogeneity in the effect sizes of pooled studies (Q = 13.593,

FIGURE 2. Forrest Plot of Increased Relative Risk of MVP in PD Compared to Controls



df = 13, $p = 0.403$). Overall, high consistency was observed in the pooled effect sizes, with a low inconsistency index ($I^2 = 4.36\%$). The forest plot of RRs including 95% confidence intervals (CI) and weighted percentages across the studies using fixed effect approach can be seen at Figure 2. Visual inspection of funnel plots and Galbraith plots suggested there was no publication bias (Figures 3 and 4). Furthermore, Egger's (bias = 0.348, $p = 0.658$) and Harbord tests (bias = −0.057, $p = 0.936$) provided no indications of small study effects or publication bias in the calculated RR. The Labbe plot showed a smooth increase in RR of having MVP+ in favors of PD/A (Figure 5). The sensitivity analysis, done by omitting sequentially each individual study and re-calculating the meta-analysis supported the robustness of results. Omitting each study sequentially caused a modest variability in RR, between

FIGURE 3. Funnel Plot of Publication Bias

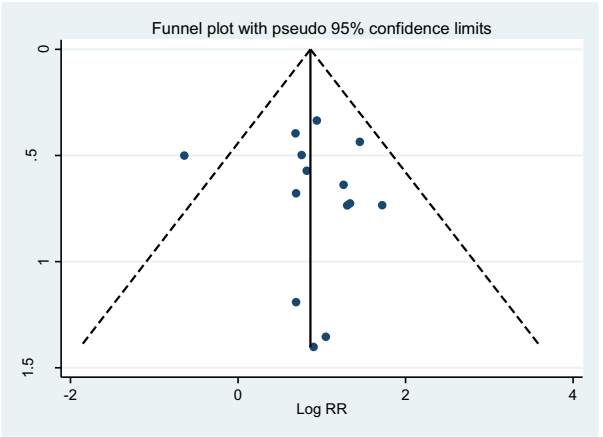


FIGURE 4. Galbraith Graphic for Publication Bias and Small Study Effect

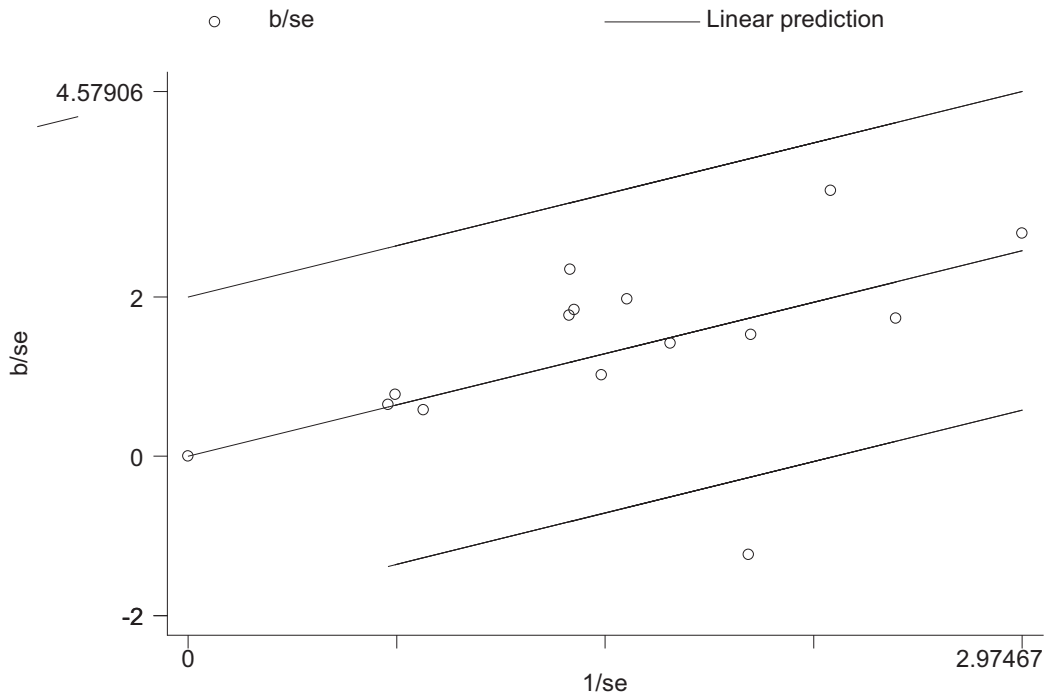
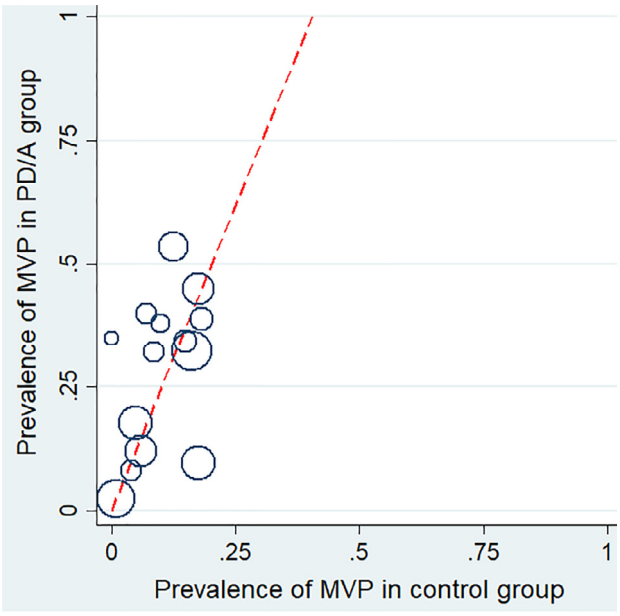


FIGURE 5. Labbe Plot of RR. Dashed Line Represents Regression Line on RR = 2.47



2.252 and 2.827 (95%CI = 1.848−3.300). Although we have not observed significant heterogeneity among studies, it was important to test whether the age difference between groups might have contributed to the calculated RR, since we found marginal statistical differences in age between the pooled PD and control groups. Univariate metaregression confirmed that there was no significant effect of mean age on the pooled RR ($\beta = -0.035$, 95%CI = −0.147−0.076, $p = 0.500$).

DISCUSSION

Our results verified the increased prevalence of MVP in patients with PD/A compared to controls. The pooled prevalence of MVP in PD/A was 27.2%; approximately 1 out of 4 patients with PD/A had MVP. In comparison with controls, patients with PD/A have a RR for MVP of 2.5, and an odds ratio for having MVP of 3.1.

However, there are no biologic explanations for the strong relationship between MVP+ and PD/A. Remaining unanswered questions include whether the observed

association between PD and MVP is causal, or resulting from overlapping symptoms. Also, we do not know how MVP modifies the course of PD, for example by changing the severity of PD in patients with MVP, or by changing the response to antidepressants or cognitive-behavioral therapy in this comorbid population. For this latter question two case reports suggest that β-blockers may help ameliorate panic symptoms in PD subjects with comorbid MVP, but no comparison with PD without MVP was provided.[34,35] One study suggests an amelioration in MVP severity following naturalistic treatment for PD, which was hypothesized to reduce autonomic drive.[36]

According to epidemiological research data, PD is more frequent in women than in men. The expected starting age of PD shows a bimodal dispersion at the age of 15–25 and 45–54, and then the prevalence begins to decrease as the age progresses.[37] In contrast, MVP has no gender differences and almost equal distribution between ages 30 and 80 years.[4] Despite the differences in the epidemiological distribution between PD and MVP, this meta-analysis could not find a significant effect of age on MVP risk. On the other hand, we do not know whether any anxiety disorder other than PD/A associated with MVP. Some studies have suggested that the incidence of MVP may be higher in patients with GAD[24,38] and social anxiety disorder.[33]

Several clinical implications may arise from the results of our meta-analysis. Firstly, MVP is one of the major causes leading to mitral regurgitation in developed countries.[39] Secondly, there may be an association between MVP+ and sudden cardiac death,[40] with a prevalence of MVP of 2.4% in sudden cardiac death victims.[4] Also, arrhythmias that could cause sudden death were significantly increased in patients with MVP compared to healthy controls.[41] This highlights the need of a careful cardiac examination in patients with PD, many of which also suffer from MVP.

Limitations

As in any meta-analysis, our study is dependent on the available literature. We had to remove studies which did not meet our quality criteria, but in doing so we may have reduced our sample and introduced potential bias (although none was observed on our statistical tests). In general, the most important limitation of earlier studies investigating the relationship between MVP and PD is that the definitions of PD/A and of MVP are not clear. Many of the early studies, which we excluded from our meta-analysis, have not clearly documented the distinction between panic attacks and PD. The studies before DSM-III-R used terms such as chronic anxiety, anxiety neurosis, and panic attacks as psychiatric diagnoses. The current diagnostic classification considers panic attacks not as a diagnostic entity, but as a symptom which can be observed during the course of several anxiety and mood disorders. If studies using the old nomenclature were included in the meta-analysis, it might skew the results. Only articles using rigorous diagnostic criteria were included in our meta-analysis, which contributes to homogeneity and strength of our study. However, since the cardiac echography criteria for diagnosing MVP have changed over time,[42] although all the studies included used the best echo criteria available, those criteria are different between the 5 studies published before 1985 and the 9 studies published afterward (see Table 1). Another potential limitation is that the frequency of MVP in the control group is relatively low, which may lead to instability of the results by causing significant change in the relative risk and the odds ratios.

CONCLUSIONS

We have confirmed through this meta-analysis that MVP is more prevalent in patients with PD than in controls. Clinicians treating patients with PD should be aware of the high prevalence of MVP and of its possible consequences. However, more studies are needed to explore the biologic shared mechanisms between MVP and PD/A.

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Lundbeck, MyndAnalytics (CNS Response), Sunovion; he received research funds (through his academic institution) from Alkermes, LiteCure, Minerva Neosync, and Roche.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: APA; 2013
2. Angst J: Panic disorder: history and epidemiology. Eur Psychiatry 1998; 13(Suppl. 2):51–55
3. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU: Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the united states. Int J Methods Psychiatry Res 2012; 21:169–184
4. Freed LA, Levy D, Levine RA, et al: Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med 1999; 341:1–7
5. Savage DD, Levy D, Garrison RJ, et al: Mitral valve prolapse in the general population. 3. Dysrhythmias: the Framingham Study. Am Heart J 1983; 106:582–586
6. Gorman JM, Fyer AF, Gliklich J, King D, Klein DF: Effect of imipramine on prolapsed mitral valves of patients with panic disorder. Am J Psychiatry 1981; 138:977–978
7. Kantor JS, Zitrin CM, Zeldis SM: Mitral valve prolapse syndrome in agoraphobic patients. Am J Psychiatry 1980; 137:467–469
8. Filho AS, Maciel BC, Martín-Santos R, Romano MM, Crippa JA: Does the association between mitral valve prolapse and panic disorder really exist? Primary Care Companion J Clin Psychiatry 2008; 10:38–47
9. Margraf J, Ehlers A, Roth WT: Mitral valve prolapse and panic disorder: a review of their relationship. Psychosom Med 1988; 50:93–113
10. Pollack RD: Mitral valve prolapse syndrome—myth or reality? West J Med 1987; 146:381–382
11. Bass C, Wade C: Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med 1984; 14:51–61
12. Hickey AJ, Andrews G, Wilcken DE: Independence of mitral valve prolapse and neurosis. Br Heart J 1983; 50:333–336
13. Matuzas W, al-Sadir J, Uhlenhuth EH, Glass RM, Easton C: Correlates of mitral valve prolapse among patients with panic disorder. Psychiatry Res 1989; 28:161–170
14. Gorman JM, Shear MK, Devereux RB, King DL, Klein DF: Prevalence of mitral valve prolapse in panic disorder: effect of echocardiographic criteria. Psychosom Med 1986; 48:167–171
15. Weisse AB: Mitral valve prolapse: now you see it; now you don't: recalling the discovery, rise and decline of a diagnosis. Am J Cardiol 2007; 99:129–133
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3rd ed. Washington, DC: APA; 1980
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3rd ed revised. Washington, DC: APA; 1987
18. Sahn DJ, DeMaria A, Kisslo J, Weyman AE: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58:1072–1083
19. Devereux RB, Kramer-Fox R, Shear MK, et al: Diagnosis and classification of severity of mitral valve prolapse: methodologic, biologic, and prognostic consideration. Am J Heart 1987; 113:1265–1280
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6:e1000097
21. Venkatesh A, Pauls DL, Crowe R, et al: Mitral valve prolapse in anxiety neurosis (panic disorder). Am Heart J 1980; 100:302–305
22. Shear MK, Devereux RB, Kramer-Fox R, Mann JJ, Frances A: Low prevalence of mitral valve prolapse in patients with panic disorder. Am J Psychiatry 1984; 141:302–303
23. Nesse RM, Cameron OG, Buda AJ, McCann DS, Curtis GC, Huber-Smith MJ: Urinary catecholamines and mitral valve prolapse in panic-anxiety patients. Psychiatry Res 1985; 14:67–75
24. Dager SR, Comess KA, Dunner DL: Differentiation of anxious patients by two-dimensional echocardiographic evaluation of the mitral valve. Am J Psychiatry 1986; 143:533–535
25. Gorman JM, Goetz RR, Fyer M, et al: The mitral valve prolapse panic disorder connection. Psychosom Med 1988; 50:114–122
26. Arkonaç O, Gültekin N, Özer S, Üner S, Toker F, Erkoç S: Panic disorders and mitral valve prolapse. Dusunen Adam: J Psychiatry Neurol Sci 1990; 3:7–12. [Turkish]
27. Carney RM, Freedland KE, Ludbrook PA, Saunders RD, Jaffe AS: Major depression, panic disorder, and mitral valve prolapse in patients who complain of chest pain. Am J Med 1990; 89:757–760
28. Ozer S, Uner S, Ozmen E, Gultekin N, Erkmen H: Prevalence of mitral valve prolapse in agoraphobia without panic history. Dusunen Adam: J PsychiatryNeurol Sci 1993; 6:35–38. [Turkish]
29. Arık AC, Yılmaz O, Altıntop L, Şahin AR, Özdemir G: Panic disorder and mitral valve prolapse. Dusunen Adam: J Psychiatry Neurol Sci 1998; 11:16–18. [Turkish]
30. Hamada T, Koshino Y, Misawa T, Isaki K, Gejyo F: Mitral valve prolapse and autonomic function in panic disorder. Acta Psychiatry Scand 1998; 97:139–143
31. Martín-Santos R, Bulbena A, Porta M, Gago J, Molina L, Duró JC: Association between joint hypermobility syndrome and panic disorder. Am J Psychiatry 1998; 155: 1578–1583

32. Tamam L, Ozpoyraz N, San M, Bozkurt A: Association between idiopathic mitral valve prolapse and panic disorder. Croat Med J 2000; 41:410–416
33. Filho AS, Maciel BC, Romano MM, et al: Mitral valve prolapse and anxiety disorders. Br J Psychiatry 2011; 199: 247–248
34. Bachmann S, Muller-Werdan U, Huber M, Kasel M, Werdan K, Schmidt H: Positive impact of the β-blocker celiprolol on panic, anxiety, and cardiovascular parameters in patients with mitral valve prolapse syndrome. J Clin Psychopharmacol 2011; 31:783–785
35. Zwanzger P, Baghai T, Schule C, Rupprecht R: Treatment of mitral valve prolapse and panic disorder with metoprolol. World J Biol Psychiatry 2000; 1:124–125
36. Coplan JD, Papp LA, King DL, Gorman JM: Amelioration of mitral valve prolapse after treatment for panic disorder. Am J Psychiatry 1992; 149:1587–1588
37. Eaton WW, Kessler RC, Wittchen HU, Magee WJ: Panic and panic disorder in the United States. Am J Psychiatry 1994; 151:413–420
38. Ozer S, Uner S, Ozmen E, Arkonac O, Gultekin N: Prevalence of mitral valve prolapse in generalized anxiety disorder. Dusunen Adam: J Psychiatry Neurol Sci 1991; 4:49–52. [Turkish]
39. Narayanan K, Uy-Evanado A, Teodorescu C, et al: Mitral valve prolapse and sudden cardiac arrest in the community. Heart Rhythm 2016; 13:498–503
40. Spartalis M, Tzatzaki E, Spartalis E, et al: Mitral valve prolapse: an underestimated cause of sudden cardiac death-a current review of the literature. J Thorac Dis 2017; 9:5390–5398
41. Hodzic E: Assesment of rhythm disorders in classical and nonclassical mitral valve prolapse. Med Arch 2018; 72: 9–12
42. Levine RA, Stathogiannis E, Newell JB, Harrigan P, Weyman AE: Reconsideration of chocardiographic standards for mitral valve prolapse: lack of association between leaflet displacement isolated to the apical four chamber view and independent echocardiographic evidence of abnormality. J Am Coll Cardiol 1988; 11:1010–1019