

# Methamphetamine-associated pulmonary arterial hypertension: data from the national biological sample and data repository for pulmonary arterial hypertension (PAH Biobank)

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**To cite:** Charoenpong P, Dhillon N, Murnane K, et al. Methamphetamine-associated pulmonary arterial hypertension: data from the national biological sample and data repository for pulmonary arterial hypertension (PAH Biobank). *BMJ Open Respir Res* 2023;**10**:e001917. doi:10.1136/bmjresp-2023-001917

Received 27 June 2023  
Accepted 7 November 2023

## ABSTRACT

**Objective** This study compares the clinical and haemodynamic severity of methamphetamine-associated pulmonary arterial hypertension (MA-PAH) with idiopathic pulmonary arterial hypertension (IPAH) and connective tissue-associated pulmonary arterial hypertension (CTD-PAH). It also examines sex differences in clinical and physiological parameters among those with MA-PAH.

**Design** This is a cross-sectional study using clinically derived data from the National Biological Sample and Data Repository for Pulmonary Arterial Hypertension (PAH biobank), a US-based registry, to compare clinical and physiological characteristics between males and females with MA-PAH.

**Population** The analysis included 1830 patients enrolled in the PAH biobank, with a diagnosis of MA-PAH (n=42), IPAH (n=1073), or CTD-PAH (n=715).

**Main outcome measures** The study assessed and compared the clinical and haemodynamic parameters of patients with MA-PAH, IPAH and CTD-PAH.

**Results** Among the patients analysed, 42 had MA-PAH, with 69.1% being female. There were no statistically significant differences in functional class among patients with MA-PAH, IPAH and CTD-PAH. The per cent predicted 6-min walk distance (6MWD) was comparable between the three groups. Patients with MA-PAH had similar mean pulmonary artery pressure and pulmonary vascular resistance to patients with IPAH but higher compared with patients with CTD-PAH. Male patients with MA-PAH exhibited a worse functional class and lower per cent predicted 6MWD, but no significant differences in haemodynamic findings were observed between the sexes.

**Conclusion** There were no differences in haemodynamic between MA-PAH and IPAH but we found that MA-PAH differed from CTD-PAH. The study did not find evidence of sex differences in MA-PAH. Further research is necessary to identify risk factors and underlying mechanisms of MA-PAH, particularly considering the increasing prevalence of methamphetamine use. Such investigations will contribute to the development of effective prevention and treatment strategies for this condition.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has indicated that patients with methamphetamine-associated pulmonary arterial hypertension (MA-PAH) exhibit more adverse haemodynamic profiles and poorer outcomes compared with individuals with idiopathic pulmonary arterial hypertension (IPAH). Additionally, there is some nascent evidence of a higher relative risk of MA-PAH among female MA users. However, our understanding of the pathomechanism of MA-PAH and gender differences in this condition remains limited.

## WHAT THIS STUDY ADDS

⇒ Surprisingly, our study found no significant differences in hemodynamics between MA-PAH and IPAH, in contrast to previous reports. Moreover, within our PAH Biobank cohort, we were unable to identify any gender-related distinctions specific to MA-PAH disease severity. Sample size may limit our ability to observe any differences. Our analysis of haemodynamic parameters revealed significant differences in pulmonary vascular resistance and mean pulmonary artery pressure between MA-PAH and connective tissue disease-associated pulmonary arterial hypertension. However, these parameters did not exhibit significant differences between MA-PAH and IPAH.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The unexpected absence of significant haemodynamic differences between MA-PAH and IPAH, contrary to previous reports, underscores the need for further research to validate these findings. Exploring gender variations in MA-PAH is essential for advancing pathophysiological understanding, enabling personalised care and treatment. Furthermore, further research on the extent and duration of MA exposure is vital for the development of diagnostic criteria for MA-PAH and will aid in its management and prognosis.



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## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare but life-threatening disease, characterised by endothelial cell proliferation and smooth muscle hypertrophy. Exposure to structurally-related drugs/toxins, including certain appetite suppressants and illicit drugs, has been associated with PAH (group 1.3 in the current clinical classification of pulmonary hypertension).<sup>1</sup>

Methamphetamine (MA), a derivative of amphetamine, is a dangerous and addictive psychomotor stimulant. MA acts by enhancing catecholamine (dopamine, norepinephrine) signalling and inhibiting catecholamine catabolising enzyme, thereby increasing catecholamine concentrations. Through a variety of mechanisms,<sup>2</sup> MA use has been associated with damage to organ systems including neurotoxicity, myocardial infarction, cardiomyopathy, pulmonary haemorrhage, pulmonary oedema, acute lung injury and pulmonary hypertension<sup>2-8</sup>

Originally recognised as a public health issue in the 1960s,<sup>9</sup> MA abuse is a growing epidemic. In 2019, approximately 27 million people worldwide had used amphetamine-type stimulants, behind only cannabis (200 million) and opioids (62 million).<sup>10</sup> The global number of amphetamine-type users has increased to 34 million in 2020.<sup>11</sup> In the USA, the prevalence of MA users (12 or older) has increased since 2015 from 0.6% to 0.9% (2.5 millions) in 2020. Percentages increased with age groups—0.5% of adults aged 18–25 (171 000); 1.1% of adults aged ≥26 (2.4 millions).<sup>12</sup> The purity and potency of seized MA exceed 90%,<sup>13</sup> and costs of manufacture have declined; ease of access and purity may contribute to the trend of increasing MA abuse.

MA was initially suspected to be associated with PAH from a 1993 case report of severe PAH in a truck driver with long-term inhalation of MA,<sup>14</sup> and the body of evidence supporting an association between MA exposure and PAH has grown. A retrospective cohort study found that patients with idiopathic pulmonary arterial hypertension (IPAH) were 10 times more likely to have a history of stimulant use (MA, cocaine, or amphetamines—with MA being the most common) than patients with PAH with known risk factors and about 8 times more than patients with chronic thromboembolic pulmonary hypertension.<sup>15</sup> In 2017, a study by Zamanian *et al*<sup>16</sup> compared 90 MA-PAH and 97 patients with IPAH, revealing that patients with MA-PAH exhibited worse haemodynamic findings and outcomes (including hospitalisations) compared with patients with IPAH. Based on the growing evidence including this report, MA was reclassified as having a definite association with PAH at the most recent World Symposium on Pulmonary Hypertension.<sup>1</sup>

MA comes in several forms and can be smoked, snorted, injected or ingested orally. Unlike some other illicit drugs, the prevalence of MA use is relatively similar between sexes,<sup>17</sup> though there are differences in how the drug is consumed between the sexes and by geographical region.<sup>18</sup>

While the strength of the association has been recognised, specifics regarding the presentation and outcomes in MA-PAH are less well understood. In recent studies by Zamanian *et al*<sup>16</sup> and Kolaitis *et al*,<sup>19</sup> a comparative analysis was conducted between 90 patients diagnosed with MA-PAH and 97 patients with IPAH, and between 118 patients with MA-PAH and 423 patients with IPAH, respectively. The results revealed that those with MA-PAH presented with a worse functional status and haemodynamic findings (lower cardiac index (CI)) than patients with IPAH.<sup>16 19</sup> They also had lower scores of PAH-specific health-related quality of life (HRQL; emphasis-10).<sup>19</sup> While the findings from the two studies hold significant importance, it is essential to recognise that these are the largest reports on the clinical characteristics of patients with MA-PAH. This underscores the need for additional research in the realm of MA-PAH to deepen our understanding of its pathophysiology and outcomes.

The term ‘oestrogen paradox’ is used to describe the paradoxical relationship between sex and disease outcomes, specifically, increased susceptibility to PAH in females but at the same time better clinical outcomes. Researchers have explored various factors that may contribute to the oestrogen paradox, including the potential protective effects of oestrogen hormones in women. However, the exact mechanisms behind this phenomenon are still not fully understood. This phenomenon was previously reported in IPAH<sup>20</sup> and other PAH subgroups such as connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) and portopulmonary hypertension-associated PAH.<sup>21 22</sup>

Our understanding of sex differences in MA-PAH remains limited. Zamanian *et al*<sup>16</sup> reported that the relative risk (RR) of receiving an ICD-coded likely PAH diagnosis among MA users was higher in women (RR=3.32) compared with men (RR=2.16); however, this is the only effort to date that explores this.

To address this knowledge gap, our study used data from a PAH registry to report the clinical and physiological status of MA-PAH, compared with IPAH and CTD-PAH. Additionally, we compare males and females with MA-PAH on measures of disease severity, investigating sex differences among participants with MA-PAH.

## METHOD

### Study cohort and variables

We use data from the National Biological Sample and Data Repository for Pulmonary Arterial Hypertension (PAH Biobank), a National Heart, Lung, and Blood Institute funded biorepository ([www.pahbiobank.org](http://www.pahbiobank.org)) overseen by the Cincinnati Children’s Hospital Medical Center (CCHMC). Thirty-eight North American PH centres identified and enrolled consenting participants beginning in 2012. Participants were diagnosed by the treating centres with the WHO PH Group 1 classification. The diagnosis and aetiology of PAH were determined

by the treating physicians and the diagnosis had to be confirmed by right heart catheterisation.

Electronic case report forms captured details of the evaluation, including demographic, anthropometric, participant's state of origin and cardiopulmonary physiology. To classify participants' state origins effectively, we employed the Census Regions and Divisions of the United States, resulting in four distinct regions: the Northeast, Midwest, South and West.

Specimens banked from participants' whole blood included DNA, plasma, serum, RNA, cDNA and immortalised cell lines. These specimens underwent whole-genome genotype sequencing using the Illumina HumanOmni 5M system, coding sequence data on genes known to be implicated in PAH with the Illumina TruSeq Custom Amplican system, and dosage data on bone morphogenetic protein receptor type 2 (BMP2), ALK1 and ENG using Multiplex Ligation-dependent Probe Amplification, which was subsequently confirmed by TaqMan Gene Expression Assay.<sup>23</sup>

Written informed consent was obtained from participants and/or legal guardians through a process approved by the institutional review board (IRB) at CCHMC and the local IRB at each participating PH centre including the IRB of Louisiana State University Health Sciences Center at Shreveport (as an enrolling centre). Additionally, written informed consent for the purpose of publication was secured at the time of enrolment.

The data, including genetic information, were deidentified by CCHMC, and no 'identifiable private information or identifiable biospecimens' were provided. Our study using the entire dataset was determined not to constitute human subjects research under the Common Rule by the Louisiana State University Health Sciences Center at Shreveport Institutional Review Board (STUDY00002052), as we did not receive identifiable private information.

### Statistical analysis

Our primary objective was to perform a comparative analysis involving three distinct groups: MA-PAH, IPAH and CTD-PAH. IPAH was chosen as a natural comparator, aligning with previous research, and our goal was to validate the findings established in earlier studies. Given concerns about the misidentification of MA-PAH as IPAH due to under-reporting of MA use, we also compared the MA-PAH participants to CTD-PAH, who have a clear risk factor for PAH.

We restricted 'hypothesis testing' to those comparisons where we had an a priori hypothesis that the differences between groups may relate to the mechanism/biology of the disease; these included comparisons of pulmonary vascular haemodynamics between MA-PAH and IPAH, MA-PAH and CTD-PAH, and between males and females among those with MA-PAH.

Continuous variables were shown as mean±SD or median (IQR), depending on distribution. Categorical

variables were shown as counts (percentages). Base-line demographic, clinical variables including symptoms, functional class, 6-min walk distance (6MWD) and haemodynamics at the time of diagnosis were compared between participants with MA-PAH and IPAH and between MA-PAH and CTD-PAH using the analysis of variance (ANOVA) with pairwise comparisons or Kruskal-Wallis followed by Dunn's test for continuous variables and  $\chi^2$  or Fisher's exact test for categorical variables, using STATA, V.14.2. To compare male and female MA-PAH participants, we employed the Student's t-test to assess continuous variables and used the  $\chi^2$  or Fisher's exact test to compare categorical variables.

In addressing missing data for each metric, we opted for the deletion method, specifically employing complete case analysis; individuals with incomplete information for a particular analysis were not included in that specific analysis, but they were not removed from our dataset altogether. Where appropriate, we also conducted sensitivity analysis by performing data normalisation; however, the results were unchanged, and the primary analyses were presented.

### Patient and public involvement

None.

## RESULT

### MA-PAH versus IPAH/CTD-PAH

#### Participant cohort

MA-PAH was less prevalent in our cohort than either IPAH or CTD-PAH. Forty-two participants (1.6%) had a diagnosis of MA-PAH, 1073 participants (42.1%) had a diagnosis of IPAH and 715 participants (28%) had a diagnosis of CTD-PAH from a total of 2550 participants in PAH Biobank database (table 1). At diagnosis, participants with MA-PAH were younger than participants with IPAH and CTD-PAH, and the proportion of females within the MA-PAH group (69.1%) was lower when compared with the IPAH group (78.4%) and to the CTD-PAH group (90.9%). The majority of participants in all groups were Caucasian. Notably, the MA-PAH group had a low representation of African Americans, accounting for just 2.4% in this group. Furthermore, all groups exhibited similar anthropometric characteristics. A higher percentage (78.57%) of MA-PAH cases lived in the West region, whereas there was no distinct geographical predominance observed in IPAH or CTD-PAH.

Notably, the MA-PAH group exhibited a higher proportion of participants with underlying cardiomyopathy (9.5%) in contrast to the IPAH group (1.6%) or the CTD-PAH group (1.7%). Additionally, both MA-PAH and CTD-PAH had elevated rates of renal insufficiency (9.5% and 6.7%, respectively) compared with IPAH (4.5%). Nevertheless, the prevalence of other comorbidities among MA-PAH, IPAH and CTD-PAH participants was similar.

While use of selective serotonin reuptake inhibitors (SSRIs) was similar between groups, the rates of

**Table 1** Baseline patient demographic and clinical characteristics between methamphetamine-associated pulmonary arterial hypertension (MA-PAH), idiopathic pulmonary arterial hypertension (IPAH) and connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH)

	MA-PAH (n=42)	IPAH (n=1073)	CTD-PAH (n=715)
<b>Demographic, anthropometrics and comorbidities</b>			
Age at diagnosis, year (n=1782)	43.59 (10.34)	48.75 (25.87)	56.95 (19.82)
Sex, female, n (%)	29 (69.1%)	841 (78.4%)	650 (90.9%)
Weight, kg	80.2 (28.38)	78.45 (29.75)	71.8 (23.64)
Height, cm	167.62 (13)	162.6 (12.52)	162.56 (10.16)
BMI, kg/m <sup>2</sup>	29.03 (10.47)	28.99 (10.25)	27.11 (8.33)
Race, n (%)			
White, non-Hispanic	32 (76.2%)	792 (73.8%)	488 (68.3%)
Black, non-Hispanic	1 (2.4%)	121 (11.3%)	131 (18.3%)
Asian	4 (9.5%)	33 (3.1%)	20 (2.8%)
Hispanic	3 (7.1%)	105 (9.8%)	63 (8.8%)
Other	2 (4.8%)	22 (2%)	13 (1.8%)
US census regions			
Northeast	0 (0%)	225 (21%)	164 (23%)
Midwest	2 (4.7%)	285 (26.5%)	205 (28.7%)
South	7 (16.7%)	327 (30.5%)	234 (32.8%)
West	33 (78.6%)	226 (21.1%)	108 (15.1%)
Others (Canada, Puerto Rico, Germany, New Zealand, Saudi Arabia)	0 (0%)	10 (0.9%)	3 (0.4%)
Comorbidities			
Ischaemic cardiovascular event, n (%)	4 (9.5%)	81 (7.6%)	74 (10.4%)
Valvular heart disease, n (%)	1 (2.4%)	59 (5.5%)	38 (5.3%)
Cardiomyopathy, n (%)	4 (9.5%)	17 (1.6%)	13 (1.8%)
Hypertension, n (%)	12 (28.6%)	377 (35.1%)	251 (35.1%)
Interstitial lung disease, n (%)	0 (0%)	20 (1.9%)	166 (23.2%)
Diabetes mellitus, n (%)	7 (16.7%)	166 (15.5%)	70 (9.8%)
Renal insufficiency, n (%)	4 (9.5%)	48 (4.5%)	53 (7.4%)
Venous thromboembolism, n (%)	4 (9.5%)	54 (5%)	48 (6.7%)
Obstructive sleep apnoea, n (%)	14 (33.3%)	336 (31.3%)	150 (21%)
Depression, n (%)	11 (26.2%)	133 (12.4%)	85 (11.9%)
Medications			
Selective serotonin reuptake inhibitors, n (%)	10 (23.8%)	217 (20.2%)	140 (19.6%)
Antipsychotics, n (%)	9 (21.4%)	106 (9.9%)	62 (8.7%)
History of recreational drug use, n (%)	41 (97.6%)	93 (9.8%)	48 (7.6%)
History of appetite suppressant use, n (%)	8 (20.5%)	133 (14%)	59 (9.5%)
BMP2 mutation carrier, n (%)	20 (47.6%)	493 (46%)	297 (41.54%)
<b>Symptoms and 6MWD</b>			
Symptoms at diagnosis			
Orthopnoea, n (%)	2 (4.76%)	51 (4.75%)	29 (4.06%)
Syncope, n (%)	10 (23.81%)	298 (27.77%)	77 (10.77%)
Oedema, n (%)	17 (40.48%)	298 (27.77%)	195 (27.27%)
Time from onset of symptoms to diagnosis, days (n=1030)	251 (565)	365 (825)	341 (911)
6MWD at diagnosis, m (n=1179)	372.11 (130.5)	336.79 (150.32)	326 (164.41)
Predicted 6MWD*, % (n=1218)	59.97 (18.99)	61.94 (21.08)	61.3 (23.51)

Continued

**Table 1** Continued

	MA-PAH (n=42)	IPAH (n=1073)	CTD-PAH (n=715)
<b>PAH treatment</b>			
PAH treatment naïve at enrolment, n (%)	6 (14.29%)	39 (3.63%)	37 (5.17%)
Parenteral PAH medications, n (%)	5 (13.16%)	288 (26.74%)	123 (16.8%)
Diuretics, n (%)	35 (83.33%)	767 (71.48%)	518 (72.45%)
Oxygen supplement, n (%)	16 (38.1%)	357 (33.27%)	246 (34.41%)
Peak oxygen flow rate (LPM) (n=501)	2.5 (2)	3 (2)	3 (2)

All values are presented as mean(SD) or median (IQR) for continuous variables, and number (percentage) for categorical variables.

\*Per cent predicted 6 min walk distance: calculated as (actual 6MWD/predicted 6MWD) × 100. The predicted 6MWD is determined using different formulas for males and females based on height, age and weight.<sup>33</sup>

BMI, body mass index; BMPR2, bone morphogenetic protein receptor type 2; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; MA-PAH, methamphetamine-associated pulmonary arterial hypertension; 6MWD, 6-min walk distance.

depression and antipsychotic use were higher in MA-PAH. MA-PAH had the highest rate of appetite suppressant use and, unsurprisingly, recreational drug use. Of note, within the MA-PAH group, there was one paediatric participant who had been exposed to MA in utero and did not have a personal history of MA misuse. In the other groups, a history of various recreational drug use was reported, including marijuana, narcotics, opiates, heroin, barbiturates and methadone. Additionally, 35 (0.03%) of the participants with IPAH and 15 (0.02%) of those with CTD-PAH had a history of amphetamine or cocaine use. However, these cases were not classified

as drug and toxin-associated PAH by the physicians enrolling the participants.

The prevalence of BMPR2 mutation carrier in our group was highest among participants with MA-PAH (47.6%), compared with IPAH or CTD-PAH (46% and 41.5%, respectively) (table 1).

#### PAH treatment at enrolment

Participants with MA-PAH were more likely to be treatment naïve and less likely to be on parenteral PAH medication than participants with IPAH (table 1), despite non-statistically significant lower CI, pulmonary artery

**Table 2** Baseline haemodynamics from diagnostic right heart catheterisation between methamphetamine-associated pulmonary arterial hypertension (MA-PAH), idiopathic pulmonary arterial hypertension (IPAH) and connective tissue-associated pulmonary arterial hypertension (CTD-PAH)

	MA-PAH (n=42)	IPAH (n=1073)	P value*	CTD-PAH (n=715)	P value*
Heart rate, beats/min (n=1057)	72.5 (27)	78 (21)	0.63	80 (19)	0.35
Mean right atrial pressure, mm Hg (n=1782)	9 (6)	8 (7)	0.3	8 (7.25)	0.07
Mean pulmonary artery pressure, mm Hg (n=1828)	53 (14)	51 (19)	0.34	44 (16)	<0.001
PAPi† (n=1765)	4.94 (3.5)	5.64 (5.24)	0.2	5.38 (5.22)	0.32
Pulmonary capillary wedge pressure, mm Hg (n=1786)	11 (5)	10 (6)	0.3	10 (6)	0.19
Cardiac output by thermodilution (L/min) (n=1135)	4.42 (1.31)	4.3 (1.89)	0.99	4.49 (1.88)	1
Cardiac index by thermodilution‡ (L/min/m <sup>2</sup> ) (n=1115)	2.17 (0.55)	2.28 (0.97)	0.67	2.48 (0.98)	0.05
Pulmonary arterial oxygen saturation, % (n=1124)	63 (14)	64 (12)	0.25	65 (12.3)	0.15
Pulmonary vascular resistance§, WU (n=1111)	9.01 (5.22)	9.59 (7.03)	1	7.5 (5.46)	0.04
Positive vasodilator testing, n (%) (n=942)	2 (8.7%)	103 (17.9%)	0.4	38 (11%)	1

All values are presented as mean (SD) or median (QR) for continuous variables, and number (percentage) for categorical variables

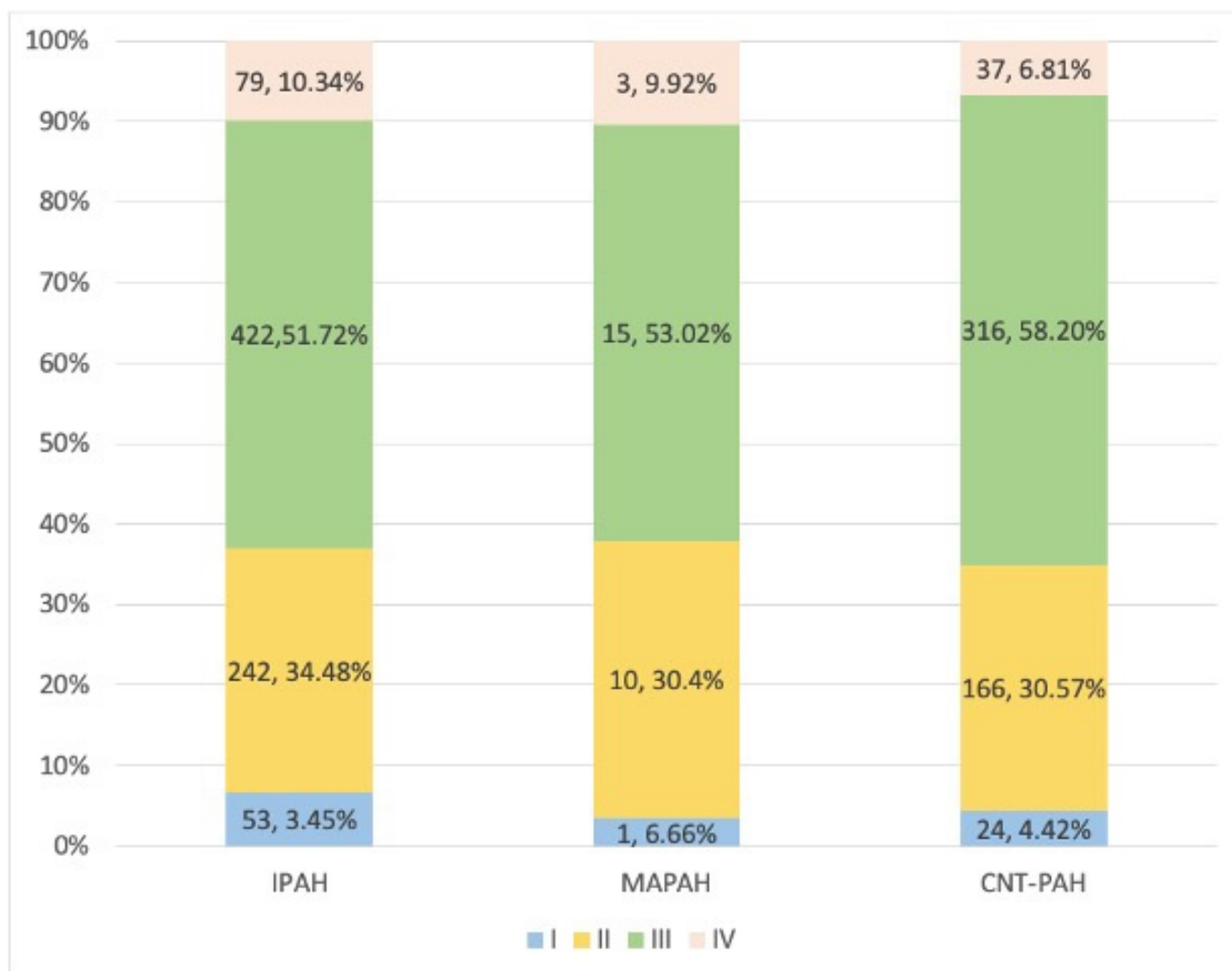
\*P values from comparison with MA-PAH group.

†Pulmonary Artery Pulsatility Index (PAPi): calculated as (sPAP – dPAP)/mrap, where sPAP is systolic pulmonary artery pressure, dPAP is diastolic pulmonary artery pressure and mrap is mean right atrial pressure.

‡Cardiac index by thermodilution: calculated as cardiac output/body surface area

§Pulmonary vascular resistance (PVR): calculated as (mPAP – pcwp)/CO, where mPAP is mean pulmonary artery pressure, pcwp is pulmonary capillary wedge pressure, and CO is cardiac output.

CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; MA-PAH, methamphetamine-associated pulmonary arterial hypertension; PAPi, pulmonary artery pulsatility index; WU, Wood unit.



**Figure 1** WHO functional class of methamphetamine-associated pulmonary arterial hypertension (MA-PAH) (n=42), idiopathic pulmonary arterial hypertension (IPAH) (n=1073), and connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) (n=715).

pulsatility index (PAPi) and pulmonary artery (PA) oxygen saturation (table 2). Similarly, when compared with those with CTD-PAH, participants with MA-PAH were more likely to be treatment naïve and had lower parenteral treatment use (table 1), despite a higher mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR), and lower CI (table 2). There was no difference in diuretics use, and oxygen supplement requirement in the MA-PAH group compared with other groups.

#### Symptoms and functional status at diagnosis

Participants with MA-PAH tended to have the shortest time from symptoms onset to diagnosis (251 days) compared with participants with IPAH (365 days) and participants with CTD-PAH (341 days). While rates of syncope were similar between IPAH and MA-PAH, oedema was more prevalent in participants with MA-PAH. The functional status between MA-PAH and IPAH/CTD-PAH was similar (figure 1). The majority of participants were functional

class 3, and only about one-third of participants in each group were functional class 1 or 2 (figure 1). Similarly, functional status measured by per cent predicted 6min walk test was similar between the groups (table 1).

#### Haemodynamics at diagnosis

There was no difference of mPAP or PVR between participants with MA-PAH and IPAH. However, these parameters of participants with MA-PAH were significantly higher than participants with CTD-PAH. There was no difference in pulmonary capillary wedge pressure, CI by thermodilution, PAPi or PA oxygen saturation between MA-PAH and IPAH or CTD-PAH groups. There was no statistically significant difference of vasodilatory response between MA-PAH and IPAH or CTD-PAH (table 2).

#### Gender differences among participants with MA-PAH

Of the total 42 participants with MA-PAH, almost 70% were female and the age at diagnosis was similar between

the sexes (table 3). Females had a shorter time from symptom onset to diagnosis compared with males. Female participants were more likely to be PAH treatment naïve, compared with males. No difference in diuretics use and oxygen supplement requirement among both sexes was found. Male participants were more likely to have cardiovascular comorbidities including ischaemic cardiovascular events and cardiomyopathy, compared with females. There were no significant differences in other medical comorbidities or history of recreational drug use. There was comparable prevalence of depression among both sexes, but females were more likely to take SSRIs. More female participants used appetite suppressants compared with males.

Table 3 indicates that 6MWD and per cent predicted 6MWD at diagnosis were higher among women. In figure 2, we compared the functional status between male and female participants with MA-PAH. Notably, a greater proportion of male participants with MA-PAH fall into functional class 3 or 4 compared with female participants with MA-PAH. Furthermore, the prevalence of BMPR2 mutation carriers in female MA-PAH was slightly higher than in male MA-PAH (48.3% and 46.2%, respectively) (table 3).

Haemodynamically, females were found to have higher mPAP, slightly lower CI by thermodilution, lower PAPi, lower PA oxygen saturation and lower PVR compared with males. However, these did not reach statistical significance. Additionally, there was no difference in the vasodilator response among both sexes, as shown in table 4.

## DISCUSSION

From PAH Biobank clinical database, a majority of participants with MA-PAH were Caucasian, and predominantly female (around 70%), although this predominance was less pronounced than in IPAH, where females accounted for 80% of cases. Participants with MA-PAH were younger at diagnosis and had a shorter time from symptoms to diagnosis, compared with participants with IPAH. Participants with MA-PAH were more likely to be PAH treatment naïve at enrolment and were less likely to be on parenteral medications at enrolment. These findings align with previous studies.<sup>16 19</sup> In comparisons to CTD-PAH groups, similar findings were noted, although with more prominent differences.

The geographical distribution of MA-PAH in the PAH Biobank closely resembled the patterns observed in a previous study by Kolaitis *et al*<sup>19</sup> within the PHAR cohort, showing a significant Western predominance. This geographical correlation may be attributable to the higher prevalence of MA abuse in the western regions of the USA. In contrast, there was no such predominance observed in the cases of IPAH or CTD-PAH.

Participants with MA-PAH were found to have a significantly higher prevalence of depression. Moreover, the rate of taking antipsychotics was also highest in the MA-PAH group. These findings were in agreement with

the previous study<sup>19</sup> which found that participants with MA-PAH reported worse generic mental HRQL which may reflect concurrent psychiatric diseases in drug abuse patients rather than being a cause of MA-PAH.

Interestingly, participants with MA-PAH had the highest rate of history of appetite suppressant use (20.5%). It is known that appetite suppressants are classified as a definite association for PAH (drug and toxin-induced PAH) and the possible mechanism involves serotonin metabolism derangement as these drugs are serotonin agonists. Preclinical studies have shown that serotonin mediates PAH through vasoconstriction, proliferation and remodelling of PA smooth muscle cells. In addition, preclinical studies have also shown MA increases serotonin levels by increasing synthesis, reducing metabolism, increasing accumulation and promoting the release of serotonin,<sup>24–26</sup> leading to a hypothesis that the serotonin pathway may contribute to the pathophysiology of MA-PAH as well. Given that MA-PAH and anorexic-induced PAH may share the underlying mechanism of developing PAH through the serotonin pathway, previous use of anorexic agents could potentially increase the susceptibility of developing PAH in MA users and could potentially explain the higher prevalence of appetite suppressant use in MA-PAH groups.

The prevalence of cardiovascular comorbidities specifically, cardiomyopathy in participants with MA-PAH was higher than in participants with IPAH. Additionally, prevalence of oedema was also higher in MA-PAH group. These support concomitant direct cardiotoxicity from MA in MA-PAH group.<sup>27</sup> Interestingly, none of the participants with MA-PAH had a history of interstitial lung diseases which was in contrast to previous findings from animal studies that suggested lung toxicity from MA-PAH.<sup>28</sup> However, subclinical changes cannot be ruled out, and there were no data on lung function or chest imaging in the database to further investigate this matter. Differences in route of MA intake may also contribute to variations in any parenchymal lung toxicity from MA.

There was no difference in WHO functional class at diagnosis between participants with MA-PAH, IPAH and CTD-PAH as shown in figure 1. However, the per cent predicted 6MWD was found to be lower in the MA-PAH group than in the other groups. It should be noted that the discrepancy between WHO functional class and 6MWD may be due to missing data and a small sample size. Haemodynamically, participants with MA-PAH had less favourable findings than participants with IPAH, with lower CI, PAPi, PA oxygen saturation and less vasoreactivity. These findings were consistent with previous studies.<sup>18 19</sup> When compared with participants with CTD-PAH, participants with MA-PAH had higher mPAP, lower CI by thermodilution and significantly higher PVR than CTD-PAH, suggesting a more severe disease in MA-PAH and a possible shared pathomechanism with IPAH as the findings were similar between the two groups compared with CTD-PAH.

**Table 3** Baseline patient demographic and clinical characteristics between female and male methamphetamine-associated pulmonary arterial hypertension (MA-PAH)

	Female (n=29)	Male (n=13)
<b>Demographic, anthropometrics and comorbidities</b>		
Age at diagnosis, year (n=42)	43.65 (10.34)	43.25 (7.95)
BMI, kg/m <sup>2</sup>	31.03 (8.90)	27.87 (6.55)
Race, n (%)		
White, non-Hispanic	20 (68.9%)	12 (92.3%)
Black, non-Hispanic	1 (3.4%)	0 (0%)
Asian	4 (13.7%)	0 (0%)
Hispanic	2 (7%)	1 (7.7%)
Other	2 (7%)	0 (0%)
US census regions		
Northeast	0 (0%)	0 (0%)
Midwest	0 (0%)	2 (15.4%)
South	4 (13.8%)	3 (23.1%)
West	25 (86.2%)	8 (61.5%)
Others (Canada, Puerto Rico, Germany, New Zealand, Saudi Arabia)	0 (0%)	0 (0%)
Comorbidities		
Ischaemic cardiovascular event, n (%)	1 (3.45%)	3 (23.1%)
Valvular heart disease, n (%)	0 (0%)	1 (7.7%)
Cardiomyopathy, n (%)	2 (6.9%)	2 (15.4%)
Hypertension, n (%)	10 (34.5%)	2 (15.4%)
Interstitial lung disease, n (%)	0 (0%)	0 (0%)
Diabetes mellitus, n (%)	6 (20.7%)	1 (7.7%)
Venous thromboembolism, n (%)	2 (6.9%)	2 (15.4%)
Renal insufficiency, n (%)	1 (3.5%)	3 (23.1%)
Obstructive sleep apnoea, n (%)	9 (31%)	5 (38.5%)
Depression, n(%)	8 (27.6%)	3 (23.1%)
Medications		
Selective serotonin reuptake inhibitors, n (%)	9 (31%)	1 (7.7%)
Antipsychotics, n (%)	7 (24.1%)	2 (15.4%)
History of recreational drug use, n (%)	28 (96.6%)	13 (100%)
History of appetite suppressant use, n (%)	7 (25.9%)	1 (8.3%)
BMPR2 mutation carrier	14 (48.3%)	6 (46.2%)
<b>Symptoms and 6MWD</b>		
Symptoms at diagnosis		
Orthopnoea	2 (6.9%)	0 (0%)
Syncope	7 (24.1%)	3 (23.1%)
Oedema	14 (48.3%)	3 (23.1%)
Time from onset of symptoms to diagnosis, days	217.5 (426.5)	456.5 (1005.5)
6MWD at diagnosis, m (n=26)	413 (90)	318 (139)
Predicted 6MWD*, % (n=26)	66.59 (18.31)	48.94 (15.64)
<b>PAH treatment</b>		
PAH treatment naïve at enrolment, n (%)	5 (17.2%)	1 (7.7%)
Parenteral PAH medications, n (%)	3 (11.5%)	2 (16.7%)
Diuretics, n (%)	25 (86.2%)	10 (76.9%)

Continued



**Table 3** Continued

	Female (n=29)	Male (n=13)
Oxygen supplement, n (%)	11 (37.9%)	5 (38.5%)
Peak oxygen flow rate (LPM)	2 (2)	3 (2)

All values are presented as mean (SD) or median (IQR) for continuous variables, and number (percentage) for categorical variables

\*Per cent predicted 6 min walk distance: calculated as (actual 6MWD/predicted 6MWD) × 100. The predicted 6MWD is determined using different formulas for males and females based on height, age and weight.<sup>33</sup>

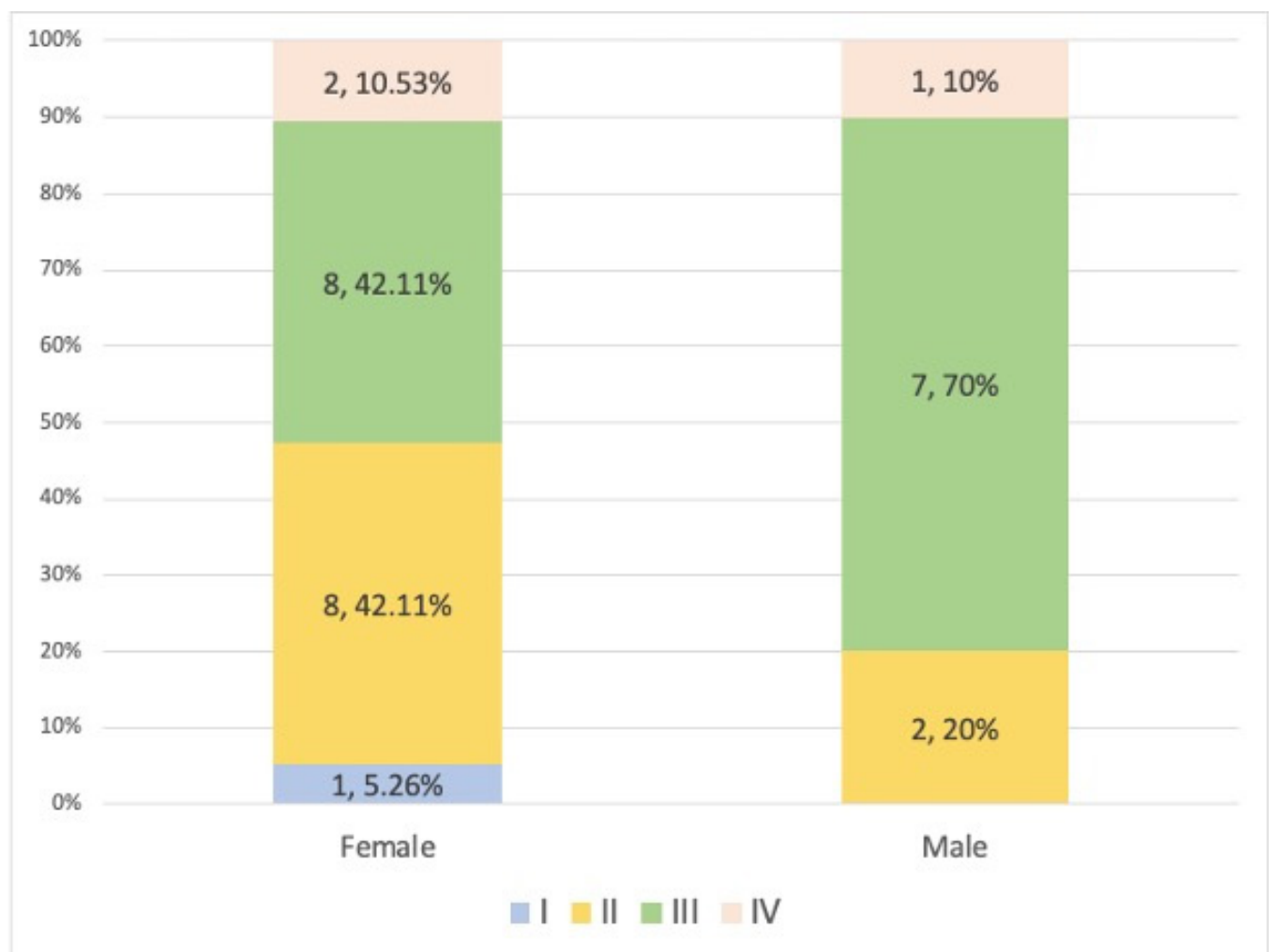
BMI, body mass index; BMPR2, bone morphogenetic protein receptor type 2; 6MWD, 6-min walk distance;

Similar to a previous study,<sup>29</sup> which reported that 9% (3 out of 33) of participants with fenfluramine derivatives-associated PAH but none of the healthy participants had BMPR2 mutation, our study found that the prevalence of BMPR2 mutation carriers in participants with MA-PAH was 47.6%. This is higher than the prevalence in IPAH (46% in our study, and previously reported to be 14%–42% in participants with IPAH<sup>30</sup>) and participants with CTD-PAH (41.5%). Our findings suggest that genetic factors, such as BMPR2 mutations, may increase

the risk of developing PAH in patients with MA-PAH and may also affect the severity of the disease.

This study marks the first to report and compare clinical characteristics, and haemodynamic findings between male and female participants with MA-PAH. While substantial evidence exists regarding gender differences in other groups of PAH, limited data are available in MA-PAH.

Previous studies<sup>16 19</sup> showed that MA-PAH, like IPAH, predominantly affects females, although IPAH has a more



**Figure 2** WHO functional class of female (n=29) and male (n=13) methamphetamine-associated pulmonary arterial hypertension.

**Table 4** Baseline haemodynamics from diagnostic right heart catheterisation between female and male methamphetamine-associated pulmonary arterial hypertension (MA-PAH)

	Female MA-PAH (n=29)	Male MA-PAH (n=13)	P value
Heart rate, beats/min (n=18)	76.8 (17.40)	83.34 (18.58)	0.56
Mean right atrial pressure, mm Hg (n=42)	9 (6)	8 (4)	0.76
Mean pulmonary artery pressure, mm Hg (n=42)	54(13)	49(14)	0.54
PAPi* (n=42)	4.83 (4.07)	5 (2.33)	0.79
Pulmonary capillary wedge pressure, mm Hg (n=41)	11.28 (3.98)	9.167 (3.54)	0.12
Cardiac output by thermodilution (L/min) (n=32)	4.33 (1.3)	4.74 (1.03)	0.38
Cardiac index by thermodilution† (L/min/m <sup>2</sup> ) (n=32)	2.16 (0.42)	2.17 (0.66)	0.98
Pulmonary arterial oxygen saturation, % (n=23)	59.92 (10.59)	61.78 (9.18)	0.66
Pulmonary vascular resistance‡, WU (n=31)	8.33 (4.92)	10.2 (5.75)	0.55
Positive vasodilator testing, n (%) (n=23)	1 (5.88%)	1 (16.67%)	0.46

All values are presented as mean (SD) or median (IQR) for continuous variable, and number (percentage) for categorical variables

\*Pulmonary Artery Pulsatility Index (PAPi): calculated as (sPAP – dPAP)/mrap, where sPAP is systolic pulmonary artery pressure, dPAP is diastolic pulmonary artery pressure and mrap is mean right atrial pressure.

†Cardiac index by thermodilution: calculated as cardiac output/body surface area.

‡Pulmonary vascular resistance (PVR): calculated as (mPAP – pcwp)/CO, where mPAP is mean pulmonary artery pressure, pcwp is pulmonary capillary wedge pressure and CO is cardiac output.  
WU, Wood unit.

pronounced female predominance. Data from Health Care and Utilization Project database<sup>16</sup> showed that hospitalised MA users have 2.6 increased risk of having an ICD-coded PAH diagnosis compared with non-users. The finding appeared more prominent in female users with a RR of 3.32; 95% CI 2.56 to 4.29,  $p < 0.001$ ), compared with male users (RR 2.16; 95% CI 1.6 to 2.9;  $P, 0.001$ ).<sup>16</sup> Another study<sup>31</sup> found that the only risk factor associated with MA-PAH is the female sex. Similarly, gender disparity in the right ventricle changes associated with MA have been reported in animal models of MA-PAH.<sup>32</sup>

In line with prior studies above,<sup>16 19</sup> our observations echo the pattern of a predominantly female distribution in MA-PAH. However, the proportion of females in the MA-PAH group was not as high as in IPAH. We also found that males exhibited more severe symptoms compared with females. This was evident from the lower per cent predicted 6MWD and the higher prevalence of participants with WHO functional class 3 and 4 among male participants. Interestingly, there were no significant differences in haemodynamic findings between the sexes.

The disparity in functional capacity or per cent predicted 6MWD between males and females could potentially be attributed to variations in MA exposure or the route of MA administration between the sexes. Additionally, we noticed a slightly higher prevalence of BMPR2 mutation carriers among female patients with MA-PAH in comparison to their male counterparts. This may suggest a potential sex-specific risk factor for the development of MA-PAH. However, it is crucial to conduct further studies to investigate this possibility and determine the underlying mechanisms involved.

Our study has several limitations. First, the diagnosis and classification of PAH were obtained from physicians

at enrolling centres which may introduce potential misclassification bias. This is particularly relevant since approximately 0.03% of the IPAH group had a history of amphetamine or cocaine use, both of which are categorised as having a ‘possible association’ with PAH, raising the possibility of these individuals being misclassified as having IPAH, rather than drug and toxin-associated PAH. Another limitation of our study is the relatively small sample size of participants with MA-PAH leading to a lower MA-PAH prevalence rate in our cohort compared with previous studies. This constrained sample size could also explain why many of our study’s findings did not achieve statistical significance, primarily due to a reduction in statistical power. Moreover, the route of administration and amount of MA exposure was not known. Both factors could result in variability among each centre in determination of the sufficient amount of MA needed to develop MA-PAH. As there were no data on the dose and duration of exposure to MA in the database, our study could not close the knowledge gap on the diagnostic criteria for MA-PAH which should be addressed in future studies. Similarly, the lack of echocardiography data in the PAH biobank database hindered our ability to investigate the impact of MA on cardiac function. Additionally, there might be a potential selection bias in the Biobank registry, as patients were required to provide consent for participation, which could have led to the exclusion of a disproportionate number of patients with MA-PAH who did not consent to the study.

## CONCLUSION

In conclusion, MA is a commonly abused drug with a high addiction potential known to cause toxicity in multiple

organ systems. Our study supports previous studies demonstrating unfavourable haemodynamics in patients with MA-PAH and provides insight into the differences between male and female patients with MA-PAH. As the incidence of MA use continues to rise globally, understanding the pathophysiology of MA-PAH is crucial to develop effective prevention and treatment strategies for this condition. However, our study has limitations, including possible misclassification and selection bias, small sample size, and the lack of data on the amount and duration of MA exposure. Future research should address these limitations to further advance our knowledge of MA-PAH.

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**Contributors** PC: original draft writing, formal analysis, review and editing. ND, KM, NG, NH and CK: review and editing. MANB: formal analysis. RW: conceptualisation, supervision, original draft writing, review and editing. PC is a guarantor for this paper, accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

**Funding** Samples and/or data from the National Biological Sample and Data Repository for PAH, which receives government support under an investigator-initiated grant (R24 HL105333) awarded by the National Heart Lung and Blood Institute (NHLBI), were used in this study. We thank contributors, including the Pulmonary Hypertension Centers who collected samples used in this study, as well as patients and their families, whose help and participation made this work possible.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. The clinical dataset is from the PAH biobank registry (third party).

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