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Risks of psychosis in methamphetamine users: a cross-sectional study in Thailand

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ABSTRACT

Objective: To determine factors related to recent MAP among individuals recently using MA.

Design: Cross-sectional study carried out between July 2015 and June 2017.

Setting: Four mental health hospitals and one substance abuse treatment center in Thailand.

Participants: Individuals recruited onto the study included those aged 18 years or more, of both sexes, who reported MA use in the month prior to admission.

Measures: Any recent psychosis was confirmed using the Mini International Neuropsychiatric Interview – Plus, Psychotic Module. The Timeline Follow Back was used to determine days of MA use. The severity of MA dependence was assessed using the Severity of Dependence Scale (SDS). Quantitative hair analysis was carried out to confirm recent use of MA and measure the amount of MA use. We compared several characteristics between those who had recently experienced psychosis and those who had not.

Results: This study included 120 participants who had not experienced psychosis and 113 participants who had. The mean age was 28 years and mean abstinence was 17 days. The levels of MA concentration in hair were not significantly different between groups (p =0.115). Based on the final logistic regression model, the independent factors associated with MAP (odds ratio, 95% confidence interval) included being male (OR 4.02, 95% CI 1.67-10.90), ≥16 days of MA use in the past month (OR 2.33, 95% CI 21.23-4.52), MA dependence (OR 9.34, 95% CI 2.44-61.84), hospitalization history related to substance abuse (OR 3.68, 95% CI 2.00-7.00).

Conclusions: Health professionals should closely monitor the development of MAP in MA-dependent men who frequently use MA and have a history of hospitalization for substance abuse. The measure of MA concentration levels in the hair may add no benefit for the prediction of the development of MAP.

Key words: amphetamine, stimulant, psychotic disorder, predictor, factor

ARTICLE SUMMARY

Strengths and limitations of this study

- To minimize the problems of inaccurate recalls on MA use and MAP experience, this study examined risks of recent MAP in a clinical sample in which there was recent use of MA.
- This is the first study using MA concentration levels in the hair to confirm recent MA use and determine the amount of MA use.
- Only few females, intravenous users, and those with a history of hospitalization for mental illnesses participated in this study.
- Some risks of MAP were not included in the study.
- This sample appeared to have mild cognitive impairment, which might affect the accuracy of reported data.

INTRODUCTION

Methamphetamine-associated psychosis (MAP) is an increasing health problem. Amphetamines are one of the most common drug use in East and Southeast Asia. In 2016, an estimated 34.2 million people worldwide used amphetamines in the past year [1]. In its class, methamphetamine (MA), a very potent amphetamine derivative, is the most frequently used substance [2]. Between 21 and 46% of MA users are likely to develop psychosis at least once in a lifetime [3]. Based on these estimations, MAP may currently affect millions of people around the world.

The symptoms of MAP are similar to those of schizophrenia and are associated with serious negative consequences. Its common symptoms include auditory hallucinations, visual hallucinations, strange or unusual beliefs, persecutory delusion, and negative psychotic symptoms, which cannot be distinguished from schizophrenic psychotic symptoms [4,5]. These psychotic symptoms usually cause anxiety, fear, terror, and decreased behavioral control. Case of severe psychosis can lead to unpredictable episodes of aggression and violence. Previous studies found that MA users with psychotic symptoms had a higher risk of violent behavior than MA users who had no psychotic symptoms [6]. Other than the more frequent utilization of health services and attempted suicide, MA users with MAP are more likely to have medical, employment, and legal problems than those without MAP [7]. The findings from long-term studies also suggested that 25-38% of individuals with MAP may develop primary or persistent psychosis some time in later life [8,9].

Because a subset of MA users may develop psychotic symptoms, important questions are raised about MA users who may have an increased risk of MAP. Previous studies suggest that MAP is associated with a number of MA use patterns and psychiatric comorbidities. In early Japanese studies, in which most users exclusively used MA (1955-1992), the investigators found an association between frequent and long-term use of MA and MAP [10]. Based on a recent review, replicated risks factors included early age MA use, frequent and long-term use of MA, MA dependence, alcohol and other drug use, major depressive disorders, and antisocial personality disorders [11].

Despite the increasing evidence around risk factors of MAP, there are some limitations in previous studies. Firstly, many studies were carried out using patients with a life-time history of MA use and/or MAP. The results of these studies may be less reliable because the

participants may not have been able to recall those experiences accurately. Secondly, some of them did not exclude individuals with primary psychotic disorders prior to MA use. Lastly, most studies did not use a valid method to confirm or measure the amount of MA use. For these reasons, we proposed to carry out a cross-sectional study to determine the risks of psychosis in Thai people who recently used MA and had recently experienced MAP. This studied population was chosen to minimize the problems of inaccurate recalls on MA use and MAP experience. We hypothesized that a number of patients' characteristics, including the amount of MA in hair of the users, should be used as predictors of MAP.

METHODS

This cross-sectional study was carried out in MA users admitted to four mental health hospitals and one substance abuse treatment center in Thailand. Suanprung Psychiatric Hospital and Thanyarak Chiang Mai Hospital are located in Northern Thailand. Nakhon Phanom Rajanagarindra Psychiatric Hospital is located in Northeastern Thailand. The Galyarajanagarindra Institute is located in Central Thailand. Songkhla Rajanagarindra Psychiatric Hospital is located in Southern Thailand. The Ethics Committee (EC) for Human Research of the Ministry of Public Health approved the study protocol for Thanyarak Chiang Mai Hospital, Nakhon Phanom Rajanagarindra Psychiatric Hospital, and Songkhla Rajanagarindra Psychiatric Hospital. Each EC for Human Research of Suanprung Psychiatric Hospital and Galyarajanagarindra Institute approved the study protocol at its site. All the participants provided written informed consent prior to participation in the studies. All methods used in the study were performed in accordance with the guidelines given and the regulation agreed with the ECs. This study carried out between July 2015 and June 2017

Participants

We assessed 120 MA users with MAP and 120 MA user without MAP. Participants included those aged 18 years or over, of both sexes, with self-reported MA use at least once in the month prior to admission. The primary reasons for their hospitalization were MAP and/or MA use disorders. The Mini International Neuropsychiatric Interview (MINI) - Plus, Psychotic Module, was used to confirm a recent diagnosis of substance-induced psychotic disorder [12]. Based on the data elicited from this module, participants who developed psychosis prior to substance use and due to a general medical condition were excluded from the study.

Assessment

All clinical assessments were completed in a single day. As a cross-sectional study, this study had no follow-up visit. We assessed the participants when they were less likely to harm themselves or others. Apart from socio-demographic data, we interviewed each participant to elicit the pattern and history of MA use. We assessed the severity of depression and MA withdrawal using the 9-item Patient Health Questionnaire (PHQ-9) and the Amphetamine Withdrawal Questionnaire [13,14]. The Timeline Follow Back was used to determine days of MA use [15]. The severity of MA dependence, current psychotic symptoms, and cognitive impairment were assessed using the Severity of Dependence Scale (SDS) [16], the 18-item Brief Psychiatric Rating Scale (BPRS) [17], and the Montreal Cognitive Assessment (MoCA) [18], respectively. We confirmed any diagnosis of alcohol and other substance use disorders and antisocial personality disorder using the MINI, alcohol use disorder, substance use disorders, and antisocial personality disorder modules, respectively [12]. In addition, the MINI, suicidality module was also used to assess the level of suicidal tendency.

Hair was collected from each participant during hospitalization. Scalp hair was cut close to the scalp from the vertex posterior region, with root ends marked, and kept in a clean plastic bag. The bag was then sealed with aluminum foil paper and shipped to the Department of Forensic Medicine, Chiang Mai University for quantitative hair analysis. The analysis for hair MA levels followed a previously published protocol involving solid-phase microextraction (SPME) in-line with gas-chromatography/mass-spectrometry (GC–MS) [19]. Derivatizing reagents for hair analysis were heptafluorobutyric chloride (HFBCl, 98% purity) and heptafluorobutyric anhydride (HFBA, 99% purity). Both reagents were purchased from Sigma–Aldrich (St. Louis, MO, USA). The limit of detection (LOD) and limit of quantitation (LOQ) for the present analysis were 0.10 and 0.15 ng/mg of hair, respectively.

MA concentration levels in the hair was the primary outcome measure. Other measures were considered as the secondary outcomes.

Statistical Analyses

Our sample size calculation was based on the number of events per variable (NEV) in logistic regression analysis. We hypothesized that a maximum of 10 variables might be included in the final model of logistic regression analysis. Peduzzi and colleagues (1996) have proposed that a logistic regression model with an NEV of 10 or more would be less biased [20]. In this

study, we planned to enroll at least 100 patients with MAP and 100 patients without MAP. To compensate for some participants with incomplete data, we decided to enroll 120 patients for each group.

All missing data were considered as not available data. We present each variable as percentage, mean, and/or standard deviation. The association between each potential factor and MAP was assessed using a univariate analysis, including the Chi-square (χ^2) test for categorical data for all cell sizes >5, the Fisher's Exact test for categorical data for a cell size ≤5, and the Student's *t*-test for continuous data. Manual backward elimination, binary logistic regression analysis was used to identify the independent risks that showed a significant correlation with MAP. The first regression model included all univariate variables significantly correlated with MAP ($p \leq 0.05$). The variable with the highest *p*-value of each regression model was then eliminated step by step. Only the risks significantly predicting MAP ($p < 0.05$) were included in the final regression model. Odds ratios (OR) with corresponding 95% confidence intervals (CIs) and β's were used to estimate the associations of nominal and continuous variables with MAP, respectively. The Hosmer and Lemeshow (H–L) test was applied, and its *p*-value of 0.05 or higher indicated that the model fitted well with the data. The variance inflation factors (VIFs) of each variable included in the final model were computed, and a VIF >10 indicated that multicollinearity of the corresponding variable was high [21]. A *p*-value of less than 0.05 indicated a significant prediction. All reported *p*-values are two-sided.

All statistical analyses were done using R 3.5.1 [22]. We used the Rcmdr 2.4-4 for univariate and multivariate analyses, the RcmdrPlugin.ROC 1.0-18 for testing the Hosmer and Lemeshow goodness of fit (GOF), and the rcompanion 1.13.2 for calculating the Nagelkerke R^2 [23–25].

Patient and public involvement

Participants were not directly involved in the design of the study. The main results will be communicated to health professionals, who may need some predictors of MAP in their clinical practice.

RESULTS

A total number of participants were 120 participants with MAP and 120 participants without MAP. Of 120 participants without MAP, 11of them were excluded because their hair tests were negative for MA.

The data of 233 participants were included in the analysis. The whole sample included 201 males and 32 females who had a mean age (SD) of 28.3 (7.2) years, a mean of days since last use (SD) of 16.80 (9.27), a mean PHQ-9 score (SD) of 6.8 (4.5), and a mean AWQ score (SD) of 7.3 (5.4).

Mean BPRS scores (SD) of the MAP group was 25.42 (6.47). Table 1 shows the demographic data and characteristics of both groups. Mean (SD) of MA concentration levels in the hair of the MAP group [13.68 ng/mg (25.95)] and that of the no MAP group [8.93 ng/mg (24.66)] were not significantly different (p=0.115). Mean (SD) MOCA scores of the MAP group [24.95 (2.96)] and no MAP groups [25.77 (3.23)] were significantly different (p = 0.046).

[Insert Table 1 Here]

The univariate analysis revealed the association of MA psychosis and seven factors, including: being male, MA dependence, antisocial personality disorder, history of hospitalization for mental illnesses, history of hospitalization for substance abuse, intravenous use in the past month, MA use ≥16 days in the past month, and younger age at first use (p's <0.05) (see Table 1). These seven factors were independent variables included in the first binary logistic regression analysis. After three steps of manual elimination of non-significant predictors, the final model included four risks that significantly predicted MA psychosis. These were being male, MA dependence, history of hospitalization for substance abuse, and MA use ≥16 days in the past month (p's <0.05) (see Table 2). The H-L goodness of fit (GOF) test indicated no evidence of poor fit (χ^2 = 1.39, df = 8, p = 0.99). The VIFs of all four predictors were between 1.02 and 1.05.

[Insert Table 2 Here]

DISCUSSION

This study examined risks of MAP in a clinical sample in which there was recent use of MA. The recent MA use and recent MAP were confirmed by using hair analysis and MINI-Plus, respectively. The low BPRS scores (mean=25.42) of the MAP group suggested that they were assessed after the recovery of psychosis. Risks of MA psychosis included being male, meeting the DSM-IV diagnosis of MA dependence, history of hospitalization for substance abuse, and using MA ≥16 days in the past month. However, the amount of MA use measured by hair analysis was not related with experience of MA psychosis.

Although there have been many studies on the risks of MAP, only a few of them were carried out in MA users with a recent history of psychosis [26–28]. Although the mean level of hair MA in the MAP group was higher, the differences of these levels were not significant between groups. This finding was in contrast with that of a previous study reporting the association of MA amount of use and lifetime diagnosis of MAP [29]. Similar to the findings from two previous studies [27,28], we did find a correlation between the frequency of recent MA use and the development of MAP. However, the previous and the present studies differ on at least two respects. While the previous studies assessed the association of self-reported MA use and lifetime MAP, our study examined the correlation between hair MA levels and recent MAP. If any future study confirms the present findings, that frequency but not amount of MA use predicts MAP, it would mean that frequency is more important than the amount of MA use in predicting MAP.

This study assessed MA dependence using two measures, the SDS and the DSM-IV diagnosis of MA dependence. Our finding that MA-dependent users had a higher risk of MAP than a MA abuser confirms a previous report [30]. In another study, the investigators found a correlation between MAP and MA dependence, defined by using a SDS score of 4 or more [28]. However, our study did not find a difference in SDS scores between groups. The discordance between the diagnosis of MA dependence and SDS scores may reflect that these two measures assess different aspects of MA dependence. The present finding that the history of hospitalization for substance use could predict MAP appears to be in concordance with the predictability of MA dependence.

Although a literature review did not find any correlation between sociodemographic characteristics and MAP [11], our and previous studies did find that male MA users were more likely to experience MAP [27]. As two diseases in the same continuum [31], the higher risk of

males for MAP appears to be in line with the findings that males are more likely than females to develop schizophrenia [32].

To our knowledge, this is the first study using hair analysis to confirm recent MA use and determine the amount of MA use. By using this objective test, we excluded the data of 11 participants with negative results of hair analysis. The amount of MA use measured by hair analysis in this study should be more accurate than that calculated based on self-reporting [29]. The recent MAP diagnosed in this study was also confirmed using the MINI-Plus, Psychotic Module, which is a structure clinical interview widely used for diagnosis. By using the logistic regression, the predictors found in this study had already been adjusted by multiple variables.

There were several limitations of this study. Firstly, only few females, intravenous users, and those with a history of hospitalization for mental illnesses participated in this study. The present findings, therefore, could not apply in these populations. Secondly, the Nagelkerke R^2 (Cragg and Uhler) of 0.26 suggested that these four variables could explain 26% of the variance, which implied that some risks of MAP were not included in the study. Examples of risks reported in previous studies but not included in the present study are: polydrug use [26]; history of conduct, depressive, and anxiety disorders [27]; pre-morbid schizoid/schizotypal personality trait [29]; family history of psychotic disorders [27]; family history of schizophrenia and bipolar disorder [33]. Finally, based on the MOCA scores, the participants in this sample appeared to have mild cognitive impairment, which might affect the accuracy of reported data. Although the MOCA scores of the MAP group were significantly lower than those of the no MAP group, we did not include this variable in the logistic regression model. This decision was made because the poorer cognition in the MAP group might not be a risk but be a consequence of MAP.

Health professionals should closely monitor the development of MAP in MA-dependent men who frequently use MA and have a history of hospitalization for substance abuse. The measure of MA concentration levels in the hair may add no benefit for the prediction of the development of MAP. Future studies on the correlation between the amount of MA use and the development of MAP are warranted.

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Contributors

WL conceived the idea of this work, collected the data, analyzed/interpreted the data, and drafted the article. KP, KI, AS, and NS conceived the idea of this work and collected the data. PS and AC conceived the idea of this work, collected the data, and drafted the article. MS conceived the idea of this work, analyzed/interpreted the data, and drafted the article. All authors critically revised the article and approved the final manuscript.

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Competing interests

M.S. has received speaker's honorarium from Lundbeck and Sumitomo Dainippon Pharma. WL, KP, DI, AS, NS, PK, PS, and AJ declare no competing interests.

Patient consent for publication

Not required

Ethics approvals

Approval for this study was obtained from the local medical ethics committee 'Nakhon Phanom Rajanagarindra Psychiatric Hospital' under the project number 102/2558 on June 25, 2015.

Provenance and peer review

Not commissioned, externally peer reviewed.

Data sharing statement

No additional data from this study are available from a repository. Data are available on request from the corresponding author.

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Table 1: Demographic and clinical characteristics of MA users with and without psychosis

	MA users without psychosis (N = 120)	MA users with psychosis (N=113)	Statistical analysis
	n (%)	n (%)	Chi-Square/Fisher's Exact test
Gender: Male	95 (79.2)	106 (93.8)	$\chi 2$=9.33 p=0.002
MA use disorder			
Abuse	18 (15.0)	2 (1.8)	OR=9.72 p<0.001
Dependence	102 (85)	111 (98.2)	
Co-morbid alcohol use disorder (including lifetime)	52 (43.3)	54 (47.8)	$\chi 2$=0.303 p=0.582
Co-morbid cannabis use disorder (including lifetime)	25 (20.8)	33 (29.2)	$\chi 2$=1.756 p=0.185
History of intravenous drug use	4 (3.3)	5 (4.4)	OR=1.34 p=0.743
History of suicide attempt	10 (8.3)	17 (15.0)	$\chi 2$=1.95 p=0.163
Antisocial personality disorder	13 (10.8)	27 (23.9)	$\chi 2$=6.09 p=0.014
History of hospitalization for mental illnesses	1 (0.8)	11 (9.7)	OR=12.73 p=0.002
History of hospitalization for substance abuse	24 (20)	52 (46)	$\chi 2$=16.76 p <0.001
Most common route of MA use in the past month			
Smoking	120 (100.0)	107 (94.7)	OR=0.0 p=0.012

	MA users without psychosis (N = 120)	MA users with psychosis (N=113)	Statistical analysis
Intravenous use	0 (0.0)	6 (5.3)	
≥16 days of MA use in the past month	23 (19.2)	41 (36.3)	$\chi 2$=7.72 p=0.005
	Mean (SD)	**Mean (SD)**	**Student *t*-test**
Age (years)	27.8 (7.72)	28.75 (6.65)	t=1.006, p=0.316
Age at first MA use (years)	19.04 (5.83)	17.65 (4.31)	t=2.068, p=0.040
Severity of dependence (SDS score)	4.70 (2.34)	5.08 (2.38)	t=1.227, p=0.221
Cognitive function (MoCA score)	25.77 (3.23)	24.95 (2.96)	t=2.01, p=0.046
MA concentration levels in hair (ng/mg)	18.93 (24.66)	13.68 (25.95)	t=1.582, p=0.115

MA: methamphetamine, SDS: Severity of Dependence Scale, MoCA: Montreal Cognitive Assessment

Table 2 Manual backward elimination and binary logistic regression analysis to determine the risks for MA psychosis

Risk factor	β	SE β	Odds ratio (95% confidence interval)
Intercept	-4.05***	0.91	0.02 (0.00-0.10)
Male (vs. female)	1.39**	0.48	4.03 (1.59-10.20)
MA dependence (vs. MA abuse)	2.24**	0.79	9.41 (2.01- 44.00)
History of hospitalization for substance abuse (vs. no history)	1.35***	0.33	3.85 (2.03-7.28)
≥16 days of MA use in the past month (vs. ≤15 days in the past month)	0.86*	0.33	2.35 (1.22-4.52)

MA: methamphetamine

***p <0.001; **p <0.01; *p <0.05.

Nagelkerke R^2 (Cragg and Uhler) = 0.26

Hosmer and Lemeshow goodness of fit (GOF) test: $\chi 2$= 1.39, df = 8, p-value = 0.99

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
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	5

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5
	#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. Give information separately for for exposed and unexposed groups if applicable.	6
Bias	#9	Describe any efforts to address potential sources of bias	5
Study size	#10	Explain how the study size was arrived at	6-7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	N/A
Statistical methods	#12e	Describe any sensitivity analyses	N/A
Results			
Participants	#13a	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. Give information separately for for exposed and unexposed groups if applicable.	8
Participants	#13b	Give reasons for non-participation at each stage	8
Participants	#13c	Consider use of a flow diagram	N/A

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	15
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	15
Main results	#16a	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	8, 16
Main results	#16b	Report category boundaries when continuous variables were categorized	8, 16
Main results	#16c	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—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	#18	Summarise key results with reference to study objectives	9
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.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	10
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	11

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Risks of psychosis in methamphetamine users: a cross-sectional study in Thailand

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Risks of psychosis in methamphetamine users: a cross-sectional study in Thailand

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ABSTRACT

Objective: To determine factors related to recent methamphetamine-associated psychosis (MAP) among individuals recently using methamphetamine (MA).

Design: Cross-sectional study carried out between July 2015 and June 2017.

Setting: Four mental health hospitals and one substance abuse treatment center in Thailand.

Participants: Individuals recruited onto the study included those aged 18 years or more, of both sexes, who reported MA use in the month prior to admission.

Measures: Any recent psychosis was confirmed using the Mini International Neuropsychiatric Interview – Plus, Psychotic Module. The Timeline Follow Back was used to determine days of MA use. The severity of MA dependence was assessed using the Severity of Dependence Scale (SDS). Quantitative hair analysis was carried out to confirm recent use of MA and measure the amount of MA use. We compared several characteristics between those who had recently experienced psychosis and those who had not.

Results: This study included 120 participants without MAP and 113 participants with MAP. The mean age was 28 years and mean abstinence was 17 days. The levels of MA concentration in hair were not significantly different between groups (p =0.115). Based on the final logistic regression model, the independent factors associated with MAP (odds ratio, 95% confidence interval) included being male (OR 4.03, 95% CI 1.59-10.20), ≥16 days of MA use in the past month (OR 2.35, 95% CI 1.22-4.52), MA dependence (OR 9.41, 95% CI 2.01-44.00), hospitalization history related to substance abuse (OR 3.85, 95% CI 2.03-7.28).

Conclusions: Health professionals should closely monitor the development of MAP in MA-dependent men who frequently use MA and have a history of hospitalization for substance abuse. The measure of MA concentration levels in the hair may add no benefit for the prediction of the development of MAP.

Key words: amphetamine, stimulant, psychotic disorder, predictor, factor

ARTICLE SUMMARY

Strengths and limitations of this study

- This study examined risks of recent methamphetamine-associated psychosis (MAP) in a clinical sample in which there was recent use of methamphetamine (MA).
- This study used MA concentration levels in the hair to confirm recent MA use and determine the amount of MA use.
- This study used a structure clinical interview for diagnosis to confirm a recent diagnosis of substance-induced psychotic disorder.
- This is a cross-sectional study.
- Some risks of MAP were not included in the study, e.g., polydrug use; history of conduct, depressive, and anxiety disorders; pre-morbid schizoid/schizotypal personality trait; family history of psychotic disorders; family history of schizophrenia and bipolar disorder.

INTRODUCTION

Methamphetamine-associated psychosis (MAP) is an increasing health problem. Amphetamines are one of the most common drug use in East and Southeast Asia. In 2016, an estimated 34.2 million people worldwide used amphetamines in the past year [1]. In its class, methamphetamine (MA), a very potent amphetamine derivative, is the most frequently used substance [2]. Between 21 and 46% of MA users are likely to develop psychosis at least once in a lifetime [3]. Based on these estimations, MAP may currently affect millions of people around the world.

The symptoms of MAP are similar to those of schizophrenia and are associated with serious negative consequences. Its common symptoms include auditory hallucinations, visual hallucinations, strange or unusual beliefs, persecutory delusion, and negative psychotic symptoms, which cannot be distinguished from schizophrenic psychotic symptoms [4,5]. These psychotic symptoms usually cause anxiety, fear, terror, and decreased behavioral control. Case of severe psychosis can lead to unpredictable episodes of aggression and violence. Previous studies found that MA users with psychotic symptoms had a higher risk of violent behavior than MA users who had no psychotic symptoms [6]. Other than the more frequent utilization of health services and attempted suicide, MA users with MAP are more likely to have medical, employment, and legal problems than those without MAP [7]. The findings from long-term studies also suggested that 25-38% of individuals with MAP may develop primary or persistent psychosis some time in later life [8,9].

Because a subset of MA users may develop psychotic symptoms, important questions are raised about MA users who may have an increased risk of MAP. Previous studies suggest that MAP is associated with a number of MA use patterns and psychiatric comorbidities. In early Japanese studies, in which most users exclusively used MA (1955-1992), the investigators found an association between frequent and long-term use of MA and MAP [10]. Based on a recent review, replicated risks factors included early age MA use, frequent and long-term use of MA, MA dependence, alcohol and other drug use, major depressive disorders, and antisocial personality disorders [11]. That review found no association between sociodemographic factors and MAP. In addition, some risk factors are not yet clear, e.g., other drug use, psychiatric co-morbidity, family history of psychiatric illness, childhood trauma.

Despite the increasing evidence around risk factors of MAP, there are some limitations in previous studies. Firstly, many studies were carried out using patients with a life-time history of MA use and/or MAP. The results of these studies may be less reliable because the participants may not have been able to recall those experiences accurately. Secondly, some of them did not exclude individuals with primary psychotic disorders prior to MA use. Lastly, most studies did not use a valid method to confirm or measure the amount of MA use. For these reasons, we proposed to carry out a cross-sectional study to determine the risks of psychosis in Thai people who recently used MA and had recently experienced MAP. This studied population was chosen to minimize the problems of inaccurate recalls on MA use and MAP experience. We hypothesized that a number of patients' characteristics, including the amount of MA in hair of the users, should be used as predictors of MAP.

METHODS

This cross-sectional study was carried out in MA users admitted to four mental health hospitals and one substance abuse treatment center in Thailand. Suanprung Psychiatric Hospital and Thanyarak Chiang Mai Hospital are located in Northern Thailand. Nakhon Phanom Rajanagarindra Psychiatric Hospital is located in Northeastern Thailand. The Galyarajanagarindra Institute is located in Central Thailand. Songkhla Rajanagarindra Psychiatric Hospital is located in Southern Thailand. The Ethics Committee (EC) for Human Research of the Ministry of Public Health approved the study protocol for Thanyarak Chiang Mai Hospital, Nakhon Phanom Rajanagarindra Psychiatric Hospital, and Songkhla Rajanagarindra Psychiatric Hospital. Each EC for Human Research of Suanprung Psychiatric Hospital and Galyarajanagarindra Institute approved the study protocol at its site. All the participants provided written informed consent prior to participation in the studies. All methods used in the study were performed in accordance with the guidelines given and the regulation agreed with the ECs. This study carried out between July 2015 and June 2017

Participants

We assessed 120 MA users with MAP and 120 MA user without MAP. Participants included those aged 18 years or over, of both sexes, with self-reported MA use at least once in the month prior to admission. The primary reasons for their hospitalization were MAP and/or MA use disorders. The Mini International Neuropsychiatric Interview (MINI) - Plus, Psychotic Module, was used to confirm a recent diagnosis of substance-induced psychotic disorder [12]. Based on the data elicited from this module, participants who developed

psychosis prior to substance use and due to a general medical condition were excluded from the study.

Assessment

All clinical assessments were completed in a single day. As a cross-sectional study, this study had no follow-up visit. We assessed the participants when they were less likely to harm themselves or others. Apart from socio-demographic data, we interviewed each participant to elicit the pattern and history of MA use. We assessed the severity of depression and MA withdrawal using the 9-item Patient Health Questionnaire (PHQ-9) and the Amphetamine Withdrawal Questionnaire [13,14]. The Timeline Follow Back was used to determine days of MA use [15]. The severity of MA dependence, current psychotic symptoms, and cognitive impairment were assessed using the Severity of Dependence Scale (SDS) [16], the 18-item Brief Psychiatric Rating Scale (BPRS) [17], and the Montreal Cognitive Assessment (MoCA) [18], respectively. We confirmed any diagnosis of alcohol and other substance use disorders and antisocial personality disorder using the MINI, alcohol use disorder, substance use disorders, and antisocial personality disorder modules, respectively [12]. In addition, the MINI, suicidality module was also used to assess the level of suicidal tendency.

Hair was collected from each participant during hospitalization. Scalp hair was cut close to the scalp from the vertex posterior region, with root ends marked, and kept in a clean plastic bag. The bag was then sealed with aluminum foil paper and shipped to the Department of Forensic Medicine, Chiang Mai University for quantitative hair analysis. The analysis for hair MA levels followed a previously published protocol involving solid-phase microextraction (SPME) in-line with gas-chromatography/mass-spectrometry (GC–MS) [19]. Derivatizing reagents for hair analysis were heptafluorobutyric chloride (HFBCl, 98% purity) and heptafluorobutyric anhydride (HFBA, 99% purity). Both reagents were purchased from Sigma–Aldrich (St. Louis, MO, USA). The limit of detection (LOD) and limit of quantitation (LOQ) for the present analysis were 0.10 and 0.15 ng/mg of hair, respectively.

MA concentration levels in the hair was the primary outcome measure. Other measures were considered as the secondary outcomes.

Statistical Analyses

Our sample size calculation was based on the number of events per variable (NEV) in logistic regression analysis. We hypothesized that a maximum of 10 variables might be included in the final model of logistic regression analysis. Peduzzi and colleagues (1996) have proposed that a logistic regression model with an NEV of 10 or more would be less biased [20]. In this study, we planned to enroll at least 100 patients with MAP and 100 patients without MAP. To compensate for some participants with incomplete data, we decided to enroll 120 patients for each group.

All missing data were considered as not available data. We present each variable as percentage, mean, and/or standard deviation. The association between each potential factor and MAP was assessed using a univariate analysis, including the Chi-square (χ^2) test for categorical data for all cell sizes >5, the Fisher's Exact test for categorical data for a cell size ≤5, and the Student's *t*-test for continuous data. Manual backward elimination, binary logistic regression analysis was used to identify the independent risks that showed a significant correlation with MAP. The first regression model included all univariate variables significantly correlated with MAP ($p \leq 0.05$). The variable with the highest *p*-value of each regression model was then eliminated step by step. Only the risks significantly predicting MAP ($p < 0.05$) were included in the final regression model. Odds ratios (OR) with corresponding 95% confidence intervals (CIs) and β's were used to estimate the associations of nominal and continuous variables with MAP, respectively. The Hosmer and Lemeshow (H–L) test was applied, and its *p*-value of 0.05 or higher indicated that the model fitted well with the data. The variance inflation factors (VIFs) of each variable included in the final model were computed, and a VIF >10 indicated that multicollinearity of the corresponding variable was high [21]. A *p*-value of less than 0.05 indicated a significant prediction. All reported *p*-values are two-sided.

All statistical analyses were done using R 3.5.1 [22]. We used the Rcmdr 2.4-4 for univariate and multivariate analyses, the RcmdrPlugin.ROC 1.0-18 for testing the Hosmer and Lemeshow goodness of fit (GOF), and the rcompanion 1.13.2 for calculating the Nagelkerke R^2 [23–25].

Patient and public involvement

Participants were not directly involved in the design of the study. The main results will be communicated to health professionals, who may need some predictors of MAP in their clinical practice.

RESULTS

A total number of participants were 120 participants with MAP and 120 participants without MAP. Of 120 participants with MAP, 7 of them were excluded because their hair tests were negative for MA.

The data of 233 participants were included in the analysis. The whole sample included 201 males and 32 females who had a mean age (SD) of 28.3 (7.2) years, a mean of days since last use (SD) of 16.80 (9.27), a mean PHQ-9 score (SD) of 6.8 (4.5), and a mean AWQ score (SD) of 7.3 (5.4).

Mean BPRS scores (SD) of the MAP group was 25.42 (6.47). Table 1 shows the demographic data and characteristics of both groups. Mean (SD) of MA concentration levels in the hair of the MAP group [13.68 ng/mg (25.95)] and that of the no MAP group [8.93 ng/mg (24.66)] were not significantly different (p=0.115). The MA concentration levels in the hair and the BPRS scores were not significantly correlated in both MAP group (Spearman's Rho = 0.160, p = 0.091) and no MAP group (Spearman's Rho = 0.031, p = 0.736). Mean (SD) MOCA scores of the MAP group [24.95 (2.96)] and no MAP groups [25.77 (3.23)] were significantly different (p = 0.046).

[Insert Table 1 Here]

The univariate analysis revealed the association of MA psychosis and eight factors, including: being male, MA dependence, antisocial personality disorder, history of hospitalization for mental illnesses, history of hospitalization for substance abuse, intravenous use in the past month, MA use ≥16 days in the past month, and younger age at first use (p's <0.05) (see Table 1). These eight factors were independent variables included in the first binary logistic regression analysis. After four steps of manual elimination of non-significant predictors, the final model included four risks that significantly predicted MA psychosis. These were being male, MA dependence, history of hospitalization for substance abuse, and MA use ≥16 days in the past month (p's <0.05) (see Table 2). The H-L goodness

of fit (GOF) test indicated no evidence of poor fit ($\chi^2 = 1.39$, $df = 8$, $p = 0.99$). The VIFs of all four predictors were between 1.02 and 1.05.

[Insert Table 2 Here]

DISCUSSION

This study examined risks of MAP in a clinical sample in which there was recent use of MA. The recent MA use and recent MAP were confirmed by using hair analysis and MINI-Plus, respectively. The low BPRS scores (mean=25.42) of the MAP group suggested that they were assessed after the recovery of psychosis. Risks of MA psychosis included being male, meeting the DSM-IV diagnosis of MA dependence, history of hospitalization for substance abuse, and using MA ≥16 days in the past month. However, the amount of MA use measured by hair analysis was not related with experience of MA psychosis.

Although there have been many studies on the risks of MAP, only a few of them were carried out in MA users with a recent history of psychosis [26–28]. Although the mean level of hair MA in the MAP group was higher, the differences of these levels were not significant between groups. This finding was in contrast with that of a previous study reporting the association of MA amount of use and lifetime diagnosis of MAP [29]. Similar to the findings from two previous studies [27,28], we did find a correlation between the frequency of recent MA use and the development of MAP. However, the previous and the present studies differ on at least two respects. While the previous studies assessed the association of self-reported MA use and lifetime MAP, our study examined the correlation between hair MA levels and recent MAP. If any future study confirms the present findings, that frequency but not amount of MA use predicts MAP, it would mean that frequency is more important than the amount of MA use in predicting MAP.

This study assessed MA dependence using two measures, the SDS and the DSM-IV diagnosis of MA dependence. Our finding that MA-dependent users had a higher risk of MAP than a MA abuser confirms a previous report [30]. In another study, the investigators found a correlation between MAP and MA dependence, defined by using a SDS score of 4 or more [28]. However, our study did not find a difference in SDS scores between groups. The discordance between the diagnosis of MA dependence and SDS scores may reflect that these two

measures assess different aspects of MA dependence. The present finding that the history of hospitalization for substance use could predict MAP appears to be in concordance with the predictability of MA dependence. Taken together, the SDS should be used with caution in future clinical studies of MAP.

Although a literature review did not find any correlation between sociodemographic characteristics and MAP [11], our and previous studies did find that male MA users were more likely to experience MAP [27]. As two diseases in the same continuum [31], the higher risk of males for MAP appears to be in line with the findings that males are more likely than females to develop schizophrenia [32].

To our knowledge, this is the first study using hair analysis to confirm recent MA use and determine the amount of MA use. By using this objective test, we excluded the data of 11 participants with negative results of hair analysis. The amount of MA use measured by hair analysis in this study should be more accurate than that calculated based on self-reporting [29]. The recent MAP diagnosed in this study was also confirmed using the MINI-Plus, Psychotic Module, which is a structure clinical interview widely used for diagnosis. By using the logistic regression, the predictors found in this study had already been adjusted by multiple variables.

There were several limitations of this study. Firstly, only few females, intravenous users, and those with a history of hospitalization for mental illnesses participated in this study. The present findings, therefore, could not apply in these populations. Secondly, the Nagelkerke R^2 (Cragg and Uhler) of 0.26 suggested that these four variables could explain 26% of the variance, which implied that some risks of MAP were not included in the study. Examples of risks reported in previous studies but not included in the present study are: polydrug use [26]; history of conduct, depressive, and anxiety disorders [27]; pre-morbid schizoid/schizotypal personality trait [29]; *family history of psychotic disorders [27]; family history of schizophrenia and bipolar disorder [33]*. Not only the transient MAP, relatives of persistent patients with MAP also had a higher prevalence rate of schizophrenia compared to relatives of patients with transient MAP [34]. Thirdly, as a cross-sectional study, we could not confirm that the group without MAP would not develop a psychotic illness at a later point of time. Fourthly, the group without MAP participated in this study was MA users who were hospitalized due to MA use disorder. As heavy users of MA, this comparison group, therefore, might not be

much different from the MAP group. Fifthly, some important data were not recorded, e.g., the frequency of hospitalizations, the period of time between last MA use and the hair collection. Finally, based on the MOCA scores, the participants in this sample appeared to have mild cognitive impairment, which might affect the accuracy of reported data. Although the MOCA scores of the MAP group were significantly lower than those of the no MAP group, we did not include this variable in the logistic regression model. This decision was made because the poorer cognition in the MAP group might not be a risk but be a consequence of MAP.

Health professionals should closely monitor the development of MAP in MA-dependent men who frequently use MA and have a history of hospitalization for substance abuse. The measure of MA concentration levels in the hair may add no benefit for the prediction of the development of MAP. *Future studies on the correlation between the amount of MA use and the development of MAP are warranted.*

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Contributors

WL conceived the idea of this work, collected the data, analyzed/interpreted the data, and drafted the article. KP, DI, AS, and NS conceived the idea of this work and collected the data. PK, PS and AJ conceived the idea of this work, collected the data, and drafted the article. MS conceived the idea of this work, analyzed/interpreted the data, and drafted the article. All authors critically revised the article and approved the final manuscript.

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Competing interests

M.S. has received speaker's honorarium from Lundbeck and Sumitomo Dainippon Pharma. WL, KP, DI, AS, NS, PK, PS, and AJ declare no competing interests.

Patient consent for publication

Not required

Ethics approvals

Approval for this study was obtained from the local medical ethics committee 'Nakhon Phanom Rajanagarindra Psychiatric Hospital' under the project number 102/2558 on June 25, 2015.

Provenance and peer review

Not commissioned, externally peer reviewed.

Data sharing statement

No additional data from this study are available from a repository. Data are available on request from the corresponding author.

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Table 1: Demographic and clinical characteristics of MA users with and without psychosis

	MA users without psychosis (N = 120)	MA users with psychosis (N=113)	Statistical analysis
	n (%)	n (%)	Chi-Square/Fisher's Exact test
Gender: Male	95 (79.2)	106 (93.8)	$\chi 2$=9.33 p=0.002
MA use disorder			
Abuse	18 (15.0)	2 (1.8)	OR=9.72 p<0.001
Dependence	102 (85)	111 (98.2)	
Co-morbid alcohol use disorder (including lifetime)	52 (43.3)	54 (47.8)	$\chi 2$=0.303 p=0.582
Co-morbid cannabis use disorder (including lifetime)	25 (20.8)	33 (29.2)	$\chi 2$=1.756 p=0.185
History of intravenous drug use	4 (3.3)	5 (4.4)	OR=1.34 p=0.743
History of suicide attempt	10 (8.3)	17 (15.0)	$\chi 2$=1.95 p=0.163
Antisocial personality disorder	13 (10.8)	27 (23.9)	$\chi 2$=6.09 p=0.014
History of hospitalization for mental illnesses	1 (0.8)	11 (9.7)	OR=12.73 p=0.002
History of hospitalization for substance abuse	24 (20)	52 (46)	$\chi 2$=16.76 p <0.001
Most common route of MA use in the past month			
Smoking	120 (100.0)	107 (94.7)	OR=0.0 p=0.012

	MA users without psychosis (N = 120)	MA users with psychosis (N=113)	Statistical analysis
Intravenous use	0 (0.0)	6 (5.3)	
≥16 days of MA use in the past month	23 (19.2)	41 (36.3)	$\chi 2$=7.72 p=0.005
	Mean (SD)	**Mean (SD)**	**Student *t*-test**
Age (years)	27.8 (7.72)	28.75 (6.65)	t=1.006, p=0.316
Age at first MA use (years)	19.04 (5.83)	17.65 (4.31)	t=2.068, p=0.040
Severity of dependence (SDS score)	4.70 (2.34)	5.08 (2.38)	t=1.227, p=0.221
Cognitive function (MoCA score)	25.77 (3.23)	24.95 (2.96)	t=2.01, p=0.046
MA concentration levels in hair (ng/mg)	18.93 (24.66)	13.68 (25.95)	t=1.582, p=0.115

MA: methamphetamine, SDS: Severity of Dependence Scale, MoCA: Montreal Cognitive Assessment

Table 2 Manual backward elimination and binary logistic regression analysis to determine the risks for MA psychosis

Risk factor	β	SE β	Odds ratio (95% confidence interval)
Intercept	-4.05***	0.91	0.02 (0.00-0.10)
Male (vs. female)	1.39**	0.48	4.03 (1.59-10.20)
MA dependence (vs. MA abuse)	2.24**	0.79	9.41 (2.01- 44.00)
History of hospitalization for substance abuse (vs. no history)	1.35***	0.33	3.85 (2.03-7.28)
≥16 days of MA use in the past month (vs. ≤15 days in the past month)	0.86*	0.33	2.35 (1.22-4.52)

MA: methamphetamine

***p <0.001; **p <0.01; *p <0.05.

Nagelkerke R^2 (Cragg and Uhler) = 0.26

Hosmer and Lemeshow goodness of fit (GOF) test: $\chi 2$= 1.39, df = 8, p-value = 0.99

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	*Page Number*
Title and abstract			
Title	*#1a*	*Indicate the study's design with a commonly used term in the title or the abstract*	*1*
Abstract	*#1b*	*Provide in the abstract an informative and balanced summary of what was done and what was found*	*2*
Introduction			
Background / rationale	*#2*	*Explain the scientific background and rationale for the investigation being reported*	*4-5*
Objectives	*#3*	*State specific objectives, including any prespecified hypotheses*	*5*
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*
Eligibility criteria	*#6a*	*Give the eligibility criteria, and the sources and methods of selection of participants.*	*5*
	#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. Give information separately for for exposed and unexposed groups if applicable.*	*6*

Bias	*#9*	*Describe any efforts to address potential sources of bias*	*5*
Study size	*#10*	*Explain how the study size was arrived at*	*7*
Quantitative variables	*#11*	*Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why*	*7*
Statistical methods	*#12a*	*Describe all statistical methods, including those used to control for confounding*	*7*
Statistical methods	*#12b*	*Describe any methods used to examine subgroups and interactions*	*7*
Statistical methods	*#12c*	*Explain how missing data were addressed*	*7*
Statistical methods	*#12d*	*If applicable, describe analytical methods taking account of sampling strategy*	*N/A*
Statistical methods	*#12e*	*Describe any sensitivity analyses*	*N/A*
Results			
Participants	*#13a*	*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. Give information separately for for exposed and unexposed groups if applicable.*	*8*
Participants	*#13b*	*Give reasons for non-participation at each stage*	*8*
Participants	*#13c*	*Consider use of a flow diagram*	*N/A*
Descriptive data	*#14a*	*Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.*	*8, 16*
Descriptive data	*#14b*	*Indicate number of participants with missing data for each variable of interest*	*8*
Outcome data	*#15*	*Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.*	*15*
Main results	*#16a*	*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*	*8, 16*
Main results	*#16b*	*Report category boundaries when continuous variables were categorized*	*8, 16*
Main results	*#16c*	*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—e.g., analyses of subgroups and interactions, and sensitivity analyses*	*8*
Discussion			
Key results	*#18*	*Summarise key results with reference to study objectives*	*9*

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.*	*10-11*
Interpretation	*#20*	*Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.*	*10-11*
Generalisability	*#21*	*Discuss the generalisability (external validity) of the study results*	*11*
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*	*12*