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The Prevalence of Metabolic Syndrome in Alcohol Use Disorders: A Systematic Review and Meta-analysis

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Abstract

Aims: People with alcohol use disorders (AUDs) have a double increased risk for cardiovascular diseases (CVD) and associated premature mortality. Metabolic syndrome (MetS) and its components are highly predictive of CVD. The primary aim of this meta-analysis was to describe pooled rates of MetS and its components in people with AUDs taking into account variations in demographic and clinical variables.

Methods: Medline, Embase and CINAHL were searched until 03/2016 for cross-sectional and baseline data of longitudinal studies in adults with AUDs. Two independent reviewers extracted data. Random effects meta-analysis with a relative risk, subgroups and meta-regression analyses were employed.

Results: The pooled MetS prevalence after adjusting for publication bias was 21.8% (95% CI = 19.1%–24.8%; *N* studies = 5; *n* participants = 865; age range = 34.8–51.1 years). Abdominal obesity was observed in 38.3% (*N* = 4, *n* = 389; 95%CI = 30.2%–47.0%), hyperglycemia in 14.3% (*N* = 4, *n* = 389; 95% CI = 3.7%–42.3%), hypertriglyceridemia in 43.9% (*N* = 4, *n* = 389; 95% CI = 31.7%–56.8%), low high-density lipoprotein cholesterol in 7.6% (*N* = 4, *n* = 389; 95% CI = 4.3%–13.2%) and hypertension in 46.5% (95% CI = 21.7%–73.1%). The MetS prevalence was similar across settings. A separate meta-regression analysis revealed that a higher MetS frequency was moderated by a higher percentage of psychiatric co-morbidity (coefficient = 3.651; standard error = 1.10, 95% CI = 1.50 to 5.80, $z = 3.3$, $P < 0.001$),

Conclusions: Routine screening and multidisciplinary management of metabolic abnormalities in people with AUD is needed. Special attention should be given to people with AUDs with psychiatric co-morbidities. Future research should focus on how cardio-metabolic outcomes are moderated by clinical characteristics.

Short summary: The metabolic syndrome (MetS) and its components are highly predictive of cardiovascular diseases. Our meta-analysis demonstrates that more than 1 in 5 persons with alcohol use disorder (AUDs) has the MetS. Routine screening and multidisciplinary management of metabolic abnormalities should be an integral part of the multidisciplinary treatment of AUDs.

INTRODUCTION

Alcohol use disorders (AUDs) are among the most common and undertreated mental disorders (Rehm *et al.*, 2014). Applying Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) diagnostic criteria (American Psychiatric Association, 2013), in 2012–2013 36.0% of male and 22.7% of female adults in the United States met the criteria for AUDs at some time in their lives, and 17.6% of men and 10.4% of women did so in the past year (Grant *et al.*, 2015). In general population surveys people with AUDs experience an excess mortality rate two times higher than those without AUDs (Roerecke and Rehm, 2013). Compared with the general population, people with AUDs in treatment have a more than 10-fold risk of mortality from liver cirrhosis and mental disorders, a 7-fold risk for injury fatalities and a 2-fold risk for cardiovascular and cancer deaths (Roerecke and Rehm, 2014).

In addition to excessive alcohol consumption, risk factors predisposing people with AUDs to an increased risk for CVD include associated unhealthy lifestyle behaviors such as lack of sufficient physical activity (Smothers and Bertolucci, 2001) and co-morbid substance abuse (McKee *et al.*, 2007), in particular smoking (Goodwin *et al.*, 2013), and an impaired cardiorespiratory fitness (Herbsleb *et al.*, 2013). To assist clinicians in identifying and treating patients at an increased risk of CVDs, the concept of the metabolic syndrome (MetS) has been introduced. MetS is defined by a combination of central obesity, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides and hyperglycemia. In the general population, these clustered risk factors have been associated with the development of CVDs and excess mortality (Galassi *et al.*, 2006; Gami *et al.*, 2007; Mottillo *et al.*, 2010). Current definitions for MetS are aimed at being easy to use in clinical settings and share similar diagnostic thresholds. However, the role of abdominal obesity is central to the International Diabetes Federation (IDF) definition (Alberti *et al.*, 2005), with provision of ethnic specific thresholds for waist circumference, while central obesity is not a mandatory National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) MetS criterion (Expert Panel on Detection, 2001; Grundy *et al.*, 2005). As a prevalent condition and predictor of CVDs across racial, gender and age groups, MetS provides the opportunity to identify high-risk populations and prevent the progression of CVD morbidity and premature mortality (Alberti *et al.*, 2009).

Pooling data in people with AUDs allows for investigation of the effect of demographic variables (e.g. age, gender, illness duration) and clinical variables (e.g. % psychiatric co-morbidity, % physical co-morbidity, % smoking) on MetS. If risk stratification is observed, this could potentially help guide clinicians in monitoring and treating high-risk persons.

We conducted a systematic review and meta-analysis to describe the pooled prevalence of MetS and its components in people with AUDs taking into account variations in demographic and clinical variables. Our secondary aim was to compare the MetS prevalence in studies directly comparing persons with AUD with those without AUDs.

METHODS

This systematic review was conducted in accordance with the MOOSE guidelines (Stroup *et al.*, 2000) and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (Moher *et al.*, 2009).

Inclusion and exclusion criteria

We included observational studies (cross-sectional, retrospective and prospective studies) in adults that fulfilled the following criteria: (a) a primary diagnosis of alcohol use disorder, alcohol dependence, harmful alcohol use, alcohol abuse as diagnosed by the DSM-IV (American Psychiatric Association, 1994), DSM-5 (American Psychiatric Association, 2013) or the International Classification of Disease (WHO, 1993), irrespective of clinical setting (inpatient, outpatient or mixed); and (b) a MetS diagnosis according to ATP-III (Expert Panel on Detection, 2001), ATP-III-adapted (ATP-III-A) (Grundy *et al.*, 2005), International Diabetes Federation (Alberti *et al.*, 2005) standards. For a randomized control trial, we extracted the variables of interest at baseline. There were no language restrictions or time restrictions. For estimation of the prevalence of MetS, we excluded studies with: (a) non-standardized diagnoses, (b) non-standardized definitions of MetS, (c) insufficient data for extraction of MetS rates, (d) restriction to patients at risk for or without cardiovascular diseases and (e) restriction to children and/or adolescents. In the case of multiple publications from the same study, only the most recent paper or article with the longest follow-up was included. When required, we contacted the primary/corresponding authors of potential studies up to two times in a 3-week period to (a) confirm eligibility, and (b) acquire the variables of interest if they were not available in the publication.

Search criteria, study selection and critical appraisal

Two independent authors (DV, BS) searched Medline, Embase and CINAHL from database inception to 1 March 2016. Key words used were 'metabolic' OR 'blood pressure' OR 'glucose' or 'lipid' AND 'alcohol dependence' OR 'alcohol abuse' OR 'alcohol misuse' OR 'harmful alcohol use' OR 'alcohol use disorders' in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from recovered articles. After the removal of duplicates, reviewers screened the titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full text articles was developed through consensus. The two reviewers then considered the full texts of these articles and the final list of included articles was reached through consensus. A third reviewer (MDH) was available for mediation throughout this process. Methodological appraisal was performed according to PRISMA standards (Moher *et al.*, 2009), including evaluation of bias (confounding, overlapping data, publication bias). Publication bias was tested using the Egger's regression method (Egger *et al.*, 1997) and Begg-Mazumdar test (Begg and Mazumdar, 1994) , with a P value < 0.05 suggesting the presence of bias.

Statistical analyses

We pooled individual study data using the Der Simonian-Laird proportion method with Stats Direct (DerSimonian and Laird, 1986). The trim-and-fill approach (Duval and Tweedie, 2000) was used to adjust the overall estimate for funnel plot asymmetry. Due to anticipated heterogeneity, a random effects meta-analysis was employed. Heterogeneity was measured with the Q statistic, yielding a chi-square P value with $P < 0.05$, indicating significant heterogeneity of the pooled results (which is always presented at the end of the description of the results as a second and last P value). If available, we compared the prevalence of MetS between people with AUDs and general population control groups with AUD that were matched on age and sex, also only using data from studies in which they

were directly compared. Furthermore, in the entire dataset, we conducted subgroup analyses (including χ^2 tests, t-tests, odds ratios) to investigate gender differences, diagnostic DSM-IV (American Psychiatric Association, 1994) subgroup differences (alcohol abuse versus alcohol dependence) and differences across settings (inpatients, outpatients or community patients, mixed) and geographical regions. In order to reduce heterogeneity, we did not calculate diagnostic and gender differences across studies, but pooled only data of studies that compared these differences on a patient level. Further, we conducted meta-regression analyses to investigate potential moderators [age, percentage male, illness duration, smoking (%), physical inactivity (%), employment status (% employed), marital status (%single), % psychiatric co-morbidity (DSM or ICD), % physical co-morbidity (ICD)] with Comprehensive Meta-Analysis (version 3).

RESULTS

Search results and included participants

Our search yielded 5214 publications of which 5 studies (Jarvis *et al.*, 2007; Teixeira and Rocha, 2007; Kahl *et al.*, 2010; Glaus *et al.*, 2013; Mattoo *et al.*, 2013) including 7 unique MetS prevalence rates, met inclusion criteria (see Fig. 1 and Table 1). The list of excluded studies (with reasons) is available upon request. The final sample comprised 865 unique persons with AUDs. Sample sizes ranged from 39 (Teixeira and Rocha, 2007) to 264 (Glaus *et al.*, 2013) participants with a mean sample size of 124. Mean age was 44.0 years (range = 34.8–51.1 years), and mean illness duration when reported (N = 2, n = 146) was 8.3 years. Three studies (n = 192) reported smoking frequencies and 80.7% (n = 155) smoked. 73.4% were employed (N = 3, n = 192), 35.9% were single (N = 3, n = 192), 14.0% had a physical and 21.5% a psychiatric co-morbidity (N = 4, n = 382). Three studies (n = 282) were executed in inpatient settings, four (n = 583) in outpatient or community settings. Five studies (n = 562) included patients diagnosed with alcohol dependence, one study included 264 patients with alcohol abuse and one study (n = 39) did include both alcohol dependence and abuse populations.

Prevalence of metabolic syndrome

The estimated weighted mean prevalence of MetS was 19.3% (95% CI = 14.3%–25.6%; Q = 21.9, P < 0.001, n = 865). The Begg-Mazumdar (Kendall's tau b = 0.384, P = 0.22) and Egger test (bias = −2.73 (95% CI = −6.28 to 0.80; P = 0.10) indicated there was no strong evidence for publication bias. However, the trim-and-fill method demonstrated that adjusting for any publication bias increased the pooled MetS estimate slightly (21.8%, 95% CI = 19.1%–24.8%, Q = 21.9, n = 865). Two studies reported on obesity frequency defined as waist circumference (>102 cm in males and >88 cm in females (ATP-III or ATP-III-A), while two other studies reported the obesity frequency following the ethnicity-specific IDF-criteria. Overall, the proportion of patients with abdominal obesity was 38.3% (n = 389; 95% CI = 30.2%–47.0%; Q = 7.6, P = 0.054). Of studies reporting on hyperglycemia (≥110 mg/dl for ATP-III or ≥100 mg/dl for ATP-III-A and IDF), the frequency was 14.3% (N = 4, n = 389; 95% CI = 3.7%–42.3%; Q = 56.0,

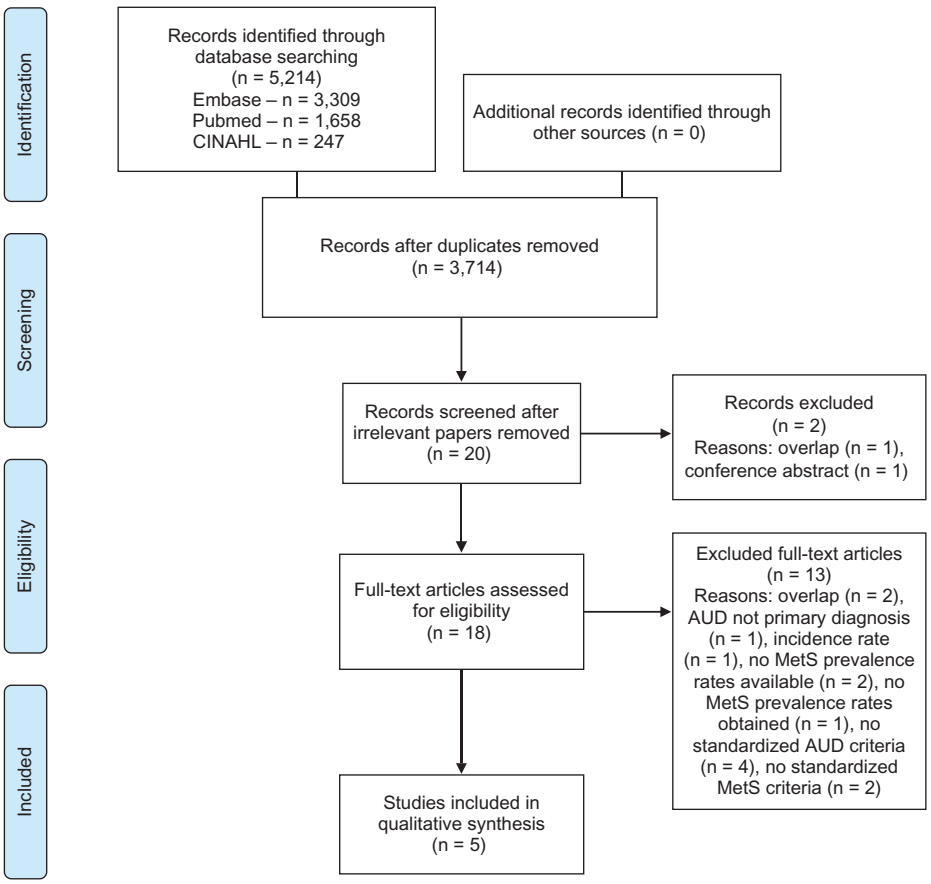

Fig. 1. PRISMA flow diagram.

Table 1. Details of the included studies

First author (year)	Country	Participants	MetS criterion	Mets prevalence	Prevalence MetS criteria	MetS prevalence controls[a]
Jarvis (2007)	USA	46 (18♀) alcohol and nicotine-dependent (100% smoking) inpatients; 34.8 ± 1.4years; DSM-IV; 46% employed; 39.0% single; 61.0% physically inactive	ATP III	22.0%	WC = 37.0%; BP = 47.0%; HDL = 13.0%; TG = 35.0%; FG = 13.0%	/
Teixeira (2007)	Brazil	39♂ inpatients; 49.7 ± 8.7years; ICD-10; no other formal psychiatric co-morbidity	NCEP	5.1%	/	/
Kahl (2010)	Germany	197 (64♀) alcohol-dependent inpatients; 47.2 ± 8.2years; DSM-IV; 32.5% psychiatric co-morbidity	AHA/NHBLI	30.9%	WC = 33.5%; BP = 78.7%; HDL = 4.0%; TG = 33.5%; FG = 47.2%	/
Glaus (2013)	Switzerland	264 (42♀) community patients with DSM-IV alcohol abuse; 50.1 ± 8.7 years	ATP III	18.2%	/	/
		173 (46♀) community patients with DSM-IV alcohol dependence; 51.1 ± 8.2 years;	ATP III	19.6%		
		97♂ alcohol-dependent; 40.3 ± 9.5 years; 12.4% single; 88.7% employed; 9.6% psychiatric co-morbidity; 14% physical co-morbidity: 68% smoking	IDF	21.6%	WC = 49.5%; BP = 43.3%; HDL = 9.3%; TG = 55.7%; FG = 9.3%	30%[b]
Mattoo (2013)	India	49♂ alcohol- and opioid-dependent; 35.1 ± 10.8 years; 75.5% single; 69.4% employed; 9.6% psychiatric co-morbidity; 14% physical co-morbidity; 87.8% smoking	IDF	8.2%	WC = 32.7%; BP = 16.3%; HDL = 8.2%; TG = 49.0%; FG = 4.1%	

WC = waist circumference, BP = blood pressure, HDL = high-density lipoprotein cholesterol, TG = triglycerides, FG = fasting glucose; ATP III = Adult Treatment Panel III; AHA/NHBLI = American Heart Association/National Heart, Lung and Blood Institute; NCEP = National Cholesterol Education Program; IDF = International Diabetes Federation.

[a]Only if age- and gender-matched

[b]Extended analysis of Aneja *et al.* (2013).

$P < 0.001$). Hypertriglyceridemia was present in 43.9% ($N = 4$, $n = 389$; 95% CI = 31.7%–56.8%; Q = 16.4, $P < 0.001$), low high-density lipoprotein (HDL) cholesterol was present in 7.6% ($N = 4$, $n = 389$; 95% CI = 4.3%–13.2%; Q = 6.6, $P = 0.084$) and hypertension was present in 46.5% ($N = 4$; $n = 389$; 95% CI = 21.7%–73.1%; Q = 67.8, $P < 0.001$) (ATP-III, ATP-III-A and IDF).

Demographic and clinical predictors for the MetS prevalence

Pooled MetS prevalences per setting, geographical region, alcohol status and Mets criteria used can be found in Table 2. There were no differences in MetS prevalence between inpatients and out/community patients ($P = 0.36$), between people with alcohol abuse and those with alcohol dependence ($P = 0.15$) and between different MetS criteria used ($P = 0.13$). A lower MetS compared to European studies was observed in the study from South America ($P = 0.04$). Separate meta-regression analyses revealed that higher MetS frequencies were moderated by a lower percentage of male inclusions (coefficient = −1.306; standard error = 0.348, 95% CI = −1.99 to -0.62, $z = -3.76$, $P < 0.001$) and a higher percentage of psychiatric co-morbidity (coefficient = 3.651; standard error = 1.10, 95% CI = 1.50 to 5.80, $z = 3.3$, $P < 0.001$), but not by age (coefficient = 0.009; standard error = 0.026, 95% CI = −0.043 to 0.061, $z = 0.35$, $P = 0.72$).

Relative risk (RR) of MetS and metabolic abnormalities in persons with AUD compared with general population controls without AUD

There were insufficient data to compare the MetS and metabolic abnormalities in persons with AUD compared with general population controls without AUD.

DISCUSSION

General findings

To the authors' knowledge, this is the first meta-analysis of MetS and its components in people with AUDs. Approximately 1 in 5 people with an AUD, or 21.8% (95% CI = 19.1%–24.8%, Q = 21.9, $n = 865$) (range = 34.8 –51.1 years) were found to have MetS. Prevalence of individual diagnostic criteria ranged from 7.6% ($N = 4$, $n = 389$; 95% CI = 4.3%–13.2%) for too low levels of HDL-cholesterol to 46.5% ($N = 4$; $n = 389$; 95% CI = 21.7%–73.1%) for hypertension. Due to the lack of data we were not able to compare these rates with age- and gender-matched healthy controls. An extended analysis (Aneja *et al.*, 2013) of the cross-sectional Indian study of Mattoo *et al.* (2013), comparing the MetS prevalence in 100 men (mean age = 43.2years) with and 50 (mean age = 40.8years) without AUDs, concluded that those with AUDs had a comparable MetS risk to those without AUDs (27% versus 30%). In the study of Kahl *et al.* (2010), the MetS prevalence in the alcohol-dependent

Table 2. Meta-analytic results of the prevalence of metabolic syndrome (MetS) in people with alcohol use disorder

Analysis	N studies	N participants	Meta-analysis		I^2	*P*
			Mets (%)	95%CI		
Setting					72.6	0.36
Inpatients	3	282	23.0%	14.8%–33.9%		
Out / community patients	4	562	17.9%	12.5%–24.7%		
Region					72.6	0.23
Europe	3	634	22.5%	15.1%–32.2%		
North America	1	46	21.7%	8.8%–44.3%		
South America	1	39	5.1%	1.0%–21.5%		
Asia	2	146	15.8%	8.2%–28.5%		
Alcohol status					72.6	0.15
Alcohol dependence	5	562	21.3%	15.3%–28.9%		
Alcohol abuse	1	264	18.2%	9.2%–32.8%		
MetS criteria					72.6	0.13
ATP III	3	476	18.8%	13.6%–25.6%		
ATP III A	2	243	28.0%	20.0%–37.8%		
IDF	2	146	17.1%	10.6%–26.6%		

ATP = Adult Treatment Panel, ATP A = Adult Treatment Panel Adapted, IDF = International Diabetes Federation criteria.

group was almost twice as high as that in an age-, but not gender matched primary care control group (31% and 17%, respectively).

Knowledge of factors associated with the highest MetS risk can help identify individuals at greatest need for monitoring and intervention. In contrast with population data (Ford *et al.*, 2002) and earlier work in people with severe mental illness (SMI) (Vancampfort *et al.*, 2015), we encountered a higher MetS prevalence in studies with a lower percentage of males with AUDs. More research is needed to clarify this gender difference. Also in contrast with data in the general population (Ford *et al.*, 2002) and in people with SMI (Vancampfort *et al.*, 2015), increasing age was not a key predictor of MetS. A possible reason might however be the limited age range we observed in the current dataset.

The current meta-analysis demonstrates that in particular the presence of psychiatric comorbidity may have a pivotal role when considering metabolic abnormalities in people with AUDs. At study level the variability in percentage of people with AUDs with psychiatric co-morbidity explained the variability in MetS prevalence. Previous research has demonstrated that people with major depressive disorder (Vancampfort *et al.*, 2014), bipolar disorder (Vancampfort *et al.*, 2013) and posttraumatic stress disorder (Rosenbaum *et al.*, 2015), all highly prevalent in AUD, are at an increased risk for MetS. The high co-occurrence between psychiatric comorbidity and MetS suggests a possible pathophysiological overlap. Although the precise mechanisms mediating the pathophysiological overlap between MetS and psychiatric co-morbidity in AUD have not yet been elucidated, elevated cortisol secretion due to hyperactivity of the hypothalamic–pituitary–adrenal axis, (pro)-inflammatory processes involving interleukin-6 and C-reactive protein, oxidative stress, autonomic nervous system dysregulation including an increase in sympathetic and decrease in parasympathetic activity, and insulin resistance are all interacting biological mechanisms that may mediate the association between AUD, psychiatric co-morbidity and MetS. Although biological processes might be important, poor background lifestyle and socioeconomic factors associated with AUD and mental health problems are probably equally relevant. Finally, also metabolic side effects of psychotropic medication (Vancampfort *et al.*, 2015) might play a pivotal role.

Our meta-analyses also highlighted geographical differences in MetS with the lowest rate observed in South-America (i.e. Brazil; *N* comparisons = 1) and the highest in Europe (*N* = 3), which indicates as well that the possible influence of lifestyle and environmental factors with or without genetic risk differences should be considered. These geographical differences should however be considered with caution due to the limited studies available. Considering the current meta-analytic data, it appears that a cumulative long-term effect of psychiatric co-morbidities and poor health behaviors places people with AUD at the greatest risk for cardio-metabolic disorders. People with AUD are more likely than the general population to have unhealthy lifestyle behaviors, such as being sedentary (Smothers and Bertolucci, 2001) and smoking (McKee *et al.*, 2007) placing them at risk for MetS and CVD. Thus, considering the cardio-metabolic risks observed, screening for and trying to minimize risk factors (including adverse lifestyle factors) should be a key priority in the multidisciplinary treatment of people with AUDs.

Limitations

Whilst this is the most comprehensive and thorough meta-analysis of MetS in people with AUD conducted to date, we acknowledge several limitations that are largely reflected by factors in the primary data. First, because our study findings were based on cross-sectional rather than longitudinal data, directionality of the association between for example the presence of psychiatric co-morbidity and observed metabolic parameters cannot be deduced with certainty; that is, it is possible that those with inherently higher metabolic risk factors may be more likely to have psychiatric co-morbidity. Second, variables such as concomitant somatic and psychotropic medication use, smoking rates, physical inactivity, marital and employment status were not reported or were insufficiently reported or controlled for in most available studies. Third, a threat to the validity of any meta-analysis is publication bias and heterogeneity, which we encountered in several of our analyses. However, although the main findings were heterogeneous, they were also highly robust and there was no strong evidence for publication bias. Fourth, we may have experienced some inclusion bias. In particular, we adopted strict inclusion criteria in order to ensure that we only included high quality studies with clearly outlined AUD and defined MetS, which may have inadvertently introduced this potential bias. Fifth, rigorous data comparing the risk for MetS and/or its individual criteria in

people with AUDs with age- and gender-matched healthy controls in large-scale studies are currently missing. Despite the abovementioned caveats, this is the largest study of MetS risk and its moderators in people with AUDs.

Future research

First, the pathophysiology underlying the association between AUD and MetS is complex and not well understood, requiring further investigation. Previous studies exploring the associations between alcohol use and cardiovascular risk factors have resulted in inconsistent associations (Fernández-Solà, 2015). This is however due probably to the fact that the dose–response relationship between alcohol and metabolic health follows a J- or U-shaped curve, pointing to lower all-cause mortality among light to moderate drinkers compared to heavy drinkers (Fernández-Solà, 2015). Any potentially beneficial effect is apparent only at low to modest use (Mostofsky *et al.*, 2016). However, this epidemiological evidence has also been criticized due to misclassification and confounding (Chikritzhs *et al.*, 2015). Using Mendelian randomization analysis of 56 epidemiological studies (n = 261,991), it was reported recently that reductions in alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health (Holmes *et al.*, 2014). In order to better understand the MetS risk in people with AUD more cross-sectional and longitudinal studies are therefore needed to compare the risk with well-matched healthy controls. Second, future research should explore the role of psychotropic medication which might be used as an adjunctive treatment for co-morbid psychiatric comorbidity. Third, research should comprehensively assess MetS risk factors following, at the very least, recommended monitoring guidelines and evaluate the optimal monitoring regimen and interventions. Finally, long-term follow-up is required to accurately document the emergence of more distal outcomes, such as diabetes, ischemic heart disease, medical costs and premature mortality.

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CONFLICT OF INTEREST STATEMENT

None declared.

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