Metabolic syndrome and substance use: A narrative review

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1. Introduction

Metabolic syndrome (MS), also known as syndrome X is a constellation of cardiac and glycaemic derangements such as hypertension, hyperglycaemia, dyslipidaemia, abdominal obesity and hyperinsulinemia. Modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, World Health Organisation (WHO), European Group for the Study of Insulin Resistance (EGIR) criteria, American Association of Clinical Endocrinologists criteria, and International Diabetes Federation (IDF) criteria are the criteria used to define MS. EGIR and WHO criteria mandates presence of insulin resistance in comparison to IDF criterion which requires presence of obesity (Huang, 2009). Similarly, the Japanese criteria for MS also requires visceral obesity as an essential criteria apart from two of the other metabolic derangements (Matsuzawa, 2005). Despite variations in the definitions, increasing trend of MS has been noted globally (Ranasinghe et al., 2017; Setayeshgar et al., 2012).

Comorbid MS with substance use is of paramount importance as Diabetes Mellitus (DM), Hypertension, and substance use disorders (SUD) figure among the top causes of global burden of disease (Mathers, 2008). Further, DM, Hypertension, SUD being non communicable chronic disorders (NCCD) and NCCDs increasingly becoming the primary contributors to the burden of disease in Asia, it becomes all the more imperative to study association between MS and SUD (Vos et al., 2017). A bidirectional relationship is proposed between MS and SUD. Nutritional deficiencies, genetic vulnerability along with substance use is hypothesized to increase risk of MS (Virmani et al., 2006; Virmani et al., 2007). Patients with MS have a higher occurrence of psychiatric comorbidity such as depression. Psychiatric medication used for treatment itself can lead to development of MS. Further, psychoactive substances are often used by patients with depression in order to "self-medicate" themselves to feel better (Nousen et al., 2013; Bolton et al., 2009).

Though a number of systematic reviews and meta-analyses have been published on MS and substance use, they have focused on a single psychoactive substance such as alcoholornicotine (Vancompfort et al., 2016; Sun et al., 2014; Alkerwi et al., 2009; Sun et al., 2012). These

meta analyses have primarily reported about prevalence (Vancampfort et al., 2016) and the risk of developing MS based on consumption of substance (Sun et al., 2014; Alkerwi et al., 2009; Sun et al., 2012). There is paucity of published literature which has critically reviewed the epidemiology of MS among substance users and association of various substances of abuse with MS with regard to important socio-demographic and clinical variables which could enhance our understanding of MS among substance users.With this background the current narrative review aimed to provide a comprehensive overview of prevalence and attributes of MS associated with various substances of abuse. This critically reviews the methodology of the studies and discusses the implications with the research questions being:

1 Does epidemiology of MS vary across substance users?
2 What are the substance and patient related attributes of MS?

2. Material and methods

2.1. Search strategy

A preliminary literature search was done using combination of terms "Metabolic Syndrome," and "Substance Use ", "Alcohol", "Nicotine", "Smoking", "Smokeless tobacco", "Cannabis", "Heroin", "Opioids", "Stimulants" using electronic database of MEDLINE through PubMed from inception till January 2019. This yielded 6905 results. Further, a Boolean search using MeSH terms of "Metabolic syndrome X" with "alcohol abuse"; "alcohol drinking"; "Nicotine"; "Smoking"; "Cannabis"; "Marijuana"; "Opioid dependence" was carried out. This search yielded 1155 results. Forward and backward search was done for the cross references of the articles. Google Scholar, MedInd and MedKnow were also used for supplementing the search.

2.2. Study selection

The articles were further screened by going through the titles and abstract and relevant articles were selected based on the following selection criteria. Peer – reviewed original studies published in English

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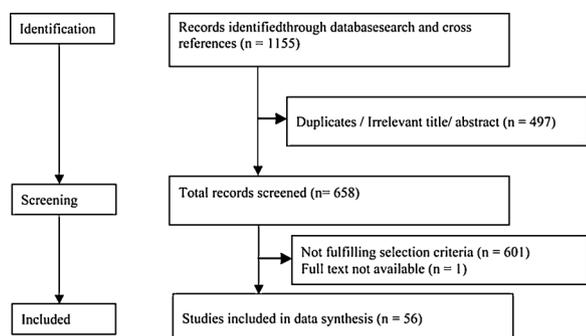bharadwaj.balaji@gmail.com (B. Bharadwaj).

Fig. 1. Flow chart of selection.

language journals were screened for inclusion in the review by two authors, KPP and AV. The articles which addressed the research question by reporting on any of the following areas were considered for inclusion in review (1) Prevalence of MS among population who were "substance users" from the community setting, 2) Prevalence of MS among subjectswho were diagnosed with "substance dependence"/ "substance use disorder" from the hospital setting (3) Assessing patient related attributes of MS by studying relationship between components of MS and patient characteristics (4) Assessing substance related attributes of MS by studying relationship between components of MS and characteristics of substance.Studies including subjects with psychiatric or physical comorbidity were not excluded from the review. Conference proceedings were excluded from the review. In case of discrepancy, the studies were included into the review based on consensus by all the authors. The flow chart of study selection has been depicted in Fig. 1.

2.3. Data synthesis and extraction

Extraction of data was done by PPK and AV independently. The data was then abstracted based on criteria of author, year, place of research, study methodology, subject characteristics including sample size, type of substance, and the chief findings. This was further organized into appropriate sections synthesizing the literature on MS.

3. Results

A total of 56 studies have been included. The studies have been presented under the tables of studies in hospital setting (n = 15) (Table 1), cross sectional studies in community setting (n = 25) (Table 2) and cohort studies in community setting (n = 16)(Table 3). The majority of the data comes from large scale community based household surveys. The studies from hospital setting have largely focused on reporting prevalence of MS.

Majority of the literature from the hospital as well as community setting included subjects with alcohol use. There were seven studies reporting about MS in opioid users. Two studies assessed MS in subjects of Methamphetamine dependence.There was a single study on cannabis from the community setting.Inconsistent findings have been noted with regard to the association of MS with gender, quantity, pattern and type of substance in studies conducted in community setting.

4. Discussion

4.1. Does epidemiology of MS vary across substance users?

The prevalence of MS varied as per study setting as well as type of substance. The prevalence of MS in hospital setting with substance dependence/ substance use disorders ranged from 5.1 to 30.6% (Jarvis et al., 2007; Kahl et al., 2010; Nebhinani et al., 2013; Mattoo et al., 2013; Lv et al., 2016; Zhang et al., 2017; Balhara et al., 2018; Kang and Song, 2015). The prevalence of MS among substance users in the

community setting ranged from 1.7% to 71.1% (Freiberg et al., 2004; Villegas et al., 2004; Urashima et al., 2005; Kang and Song, 2015; Park and Kim, 2015; Slagter et al., 2014). These figures are in stark contrast with data obtained from the general population, which has prevalence rates ranging from 20%-25% (Moreira et al., 2014).

It is important to note that half of the studies on in-patients (Jarvis et al., 2007; Kahl et al., 2010; Mattoo et al., 2011; Aneja et al., 2013; Nebhinani et al., 2013; Mattoo et al., 2013; Balhara et al., 2018) and four of the 22 community based studies reported prevalence of MS in subjects with alcohol use which ranged from 9.9% to 30.6% and 5.3% to 25% respectively.However, a meta-analyses of seven studies (five hospital and two community based) reported prevalence of pooled prevalence of 21.8% among subjects with alcohol use disorders with no significant difference across settings. (Vancampfort et al., 2016)

The prevalence of MS in Opioid dependent patients ranged from 5.1% (Balhara et al., 2018) to 29.6% (Vallecillo et al., 2018). There was a single study on cannabis conducted in community setting which reported prevalence of MS as 13.8% and 17.5% in current marijuana users and past marijuana users respectively (Vidot et al., 2016). It is important to note that majority of these patients had comorbid nicotine use as well. There are no studies which exclusively studied prevalence of MS among subjects with only nicotine use disorder. However, the prevalence of smoking among subjects with MS was found to range from 3% to 71% across countries (Balhara, 2012).

Patients with Methamphetamine use disorder had lower body mass index (BMI) and other components of Metabolic syndrome but the prevalence of Metabolic syndrome was not reported in these studies (Lv et al., 2016; Zhang et al., 2017).

These prevalence rates have to be interpreted with caution considering differences in criteria used. Highest prevalence of MS among patients in hospital setting, about 30.6% was found when diagnosed by AHA guidelinesand lowest prevalence, of 5.1% was with IDF criteria (Balhara et al., 2018). Further, methodological differences across studies could also lead to variations in prevalence of MS, which are discussed in 4.3.

4.2. What are the substance and patient related attributes of MS?

Most of the studies reviewed had explored the association of quantity, pattern of alcoholuse and genderwith MS. With regard to nicotine, association between pattern of nicotine use and MShad been studied. There is paucity of literature onpatient and substance related attributes of MS in patients with cannabis use, opioid and methamphetamine dependence as the extent literature has largely focused on reporting prevalence. (Pereska et al., 2011; Pereska et al., 2012; Nebhinani et al., 2013; Mattoo et al., 2013; Vidot et al., 2016; Zhnag et al., 2017; Vallecilo et al., 2018; Balhara et al., 2018) Hence, the discussion on substance and patient related attributes of MS is limited to alcohol and nicotine in the reviewed studies.

4.2.1. Substance and patient related attributes of MS in alcohol users
4.2.1.1. Pattern and quantity of alcohol. Patterns like binge drinking, problem drinking, hazardous drinking have been significantly associated with greater risk of MS. Higher risk of abdominal obesity, hypertension, hyperglycemia and dyslipidemia have been noted in problem drinkers as well as binge drinkers (Fan et al., 2008; Kim et al., 2011). Specifically, weekly binge drinkers had significantly higher blood pressure compared to monthly binge drinkers (Wellman et al., 2016).

Occasional heavy drinkers had higher risk for large waist circumference and hyperglycemia as well as had higher prevalence of MS compared to regular drinkers (Wakabayashi, 2014). In contrast, another study reported that MS was significantly higher in ex-drinkers compared to occasional drinkers (Villegas et al., 2004). However, it needs to be carefully assessed if suffering from MS or its components lead to subjects quitting alcohol, leading to apparent increase of MS in ex-drinkers.

Table 1

Studies on substance dependent subjects in hospital setting.

S.No	Author	Study characteristics Measures/Criteria for MS/ SUD	Chief findings
	(Jarvis et al., 2007) USA	N = 46 ADS & NDS: DSM IV TR criteria MS : Modified NCEP-ATP III	Prevalence of MS = 22% Dyslipidemia = 74% Overweight/obese = 54% Hypertension = 61% High homocysteine = 54% Elevated high-sensitivity C-reactive protein = 28%
	(Teixeira 2007) Brazil	N = 39 ADS : ICD-10 MS : NCEP	Prevalence of MS = 5.1%
	(Kahl et al., 2010) Germany	197 inpatient cases of ADS 1158 healthy controls AHA/NHLBI criteria ADS: DSM IV TR	Frequency of MS (30.6%) was higher compared to controls (17.0%). FBS and BP was higher in both genders TGs was greater in women only HDL was higher in men and women
	(Mattoo et al., 2011) Chandigarh	N = 110 Substance dependence : ICD 10 criteria MS : IDF	Prevalence of the MS -alcohol group = 24.6 % -opioid group = 29.3% MS in opioid dependent patients was significantly associated with age and BMI
	(Pereska et al., 2011) Macedonia	N = 66 opioid dependent (Heroin) Group 1 - with decreased HDL-C Group 2 - with normal HDL-C	Frequency of Low HDL = 58.8% Decreased apoA-I = 50.9% Increased TG = 35.9% Increased apoB/apoA-I = 3.8% Patients with lower HDL-C had significantly higher TGL and higher apoB/apoA-I compared to those with normal HDL-C ApoB/apoA-I index was significantly better predictor than HDL for increased TG/Low HDL
	(Perevska et al., 2012) Macedonia	Opioid dependent patients (Heroin) = 78 Divided into 2 groups: Group 1 : Duration of Dependence < / = 3 years Group 2: Duration of dependence > 3 years. Healthy controls = 32	Patients with longer dependence duration had significantly higher HOMA IR compared to healthy controls Patients with longer dependence duration had significantly lower HOMA IR compared with the group with the shorter dependence duration In patients with prolonged duration of dependence, reduction in HOMA- IR was significantly associated with decrease in β-cell function and waist circumference
	(Aneja et al., 2013) India	Cases = 100 cases of ADS Controls = 50 MS : IDF and NCEP ATP III criteria ADS : ICD 10	Prevalence of MS: IDF = 27% NCEP ATP- III = 18 Prevalence of MS was significantly lower compared to healthy controls (30% and 20%) Most common components of MS were WC > 90 cm and raised TG
	(Nebhinani et al., 2013) India	N = 256 MS : IDF and NCEP ATP III criteria Substance dependence : ICD 10	One year prevalence: IDF = 9.4% Modified NCEP ATP III criteria = 10.9% Highest prevalence of MS was found in patients with ADS + ODS (26.7%) followed by ADS (13.1%) and ODS (9.6%)
	(Mattoo et al., 2013) India	N = 250 Substance dependence : ICD 10 criteria MS : IDF	Prevalence of MS was 13.6% Prevalence of MS was highest in alcohol group (21.6%) Increased TGs were most common abnormality (54%) Age, body weight and BMI were the significant predictors of MS
	(Tsai et al., 2015) Taiwan	Cases = 41 Controls (no smokers) = 47 Atleast moderate dependence (5 or more on FTND)	Plasma ZAG levels of smokers were significantly higher than those of controls ZAG was found to be both an independent risk factor for MS as well as interacted with smoking for MS
	(Lv et al., 2016) China	N = 1019 cases with MA dependence and 1019 controls	Patients with MA-dependence had significantly : Lower BMI Lower FBS Higher SBP Duration of MA use was significantly inversely associated with BMI
	(Bathla et al., 2017) India	Cross sectional study N = 50 inpatients with substance dependence 46% - Alcohol 26% - Opioids MS: WHO criteria Substance dependence : ICD-10	Prevalence of MS was 20%
	(Vallecillo et al., 2018) Spain	N = 122 patients with ODS Modified NCEP ATP III	Prevalence of MS was 29.5% Significant association was found between methadone exposure and MS
	(Zhang et al., 2017) China	Cases = 938 with MA dependence Controls = 985	Levels of TC, TG, FBS, and BMI were significantly decreased in MA-dependent patients compared to controls Daily dose of MA was significantly associated with higher risk of lower TC Duration of MA use was significantly independently related to BMI

Table 1 (*continued*)

S.No	Author	Study characteristics Measures/Criteria for MS/ SUD	Chief findings
	(Balhara et al., 2018) India	N = 250 Patients with ADS = 101 Patients with ODS = 59 Dependence = DSM-IV TR MS : IDF, NCEP ATP III criteria	Prevalence of MS in subjects of ADS: IDF = 9.9% NCEP ATP- III = 20.8% Prevalence of MS in subjects of ODS: IDF = 5.1% NCEP ATP- III = 20.3%

ADS = Alcohol Dependence Syndrome; BMI = Body Mass Index; DSM = Diagnostic and Statistical Manual; FBS = Fasting blood sugar; FTND = Fagerstrom Test for Nicotine Dependence; HDL = High Density Lipoprotein; HOMA-IR = Homeostasis Model Assessment for Insulin Resistance ; HOMA-B% = Homeostasis Model Assessment for Insulin Resistance β-cell function ; ICD = International Classification of Diseases; IDF = International Diabetes Federation ; MA = Methamphetamine; MS = Metabolic syndrome; NCEP-ATP III = National Cholesterol Education Program's Adult Treatment Panel ;NDS = Nicotine Dependence Syndrome; SBP = Systolic Blood Pressure; SUD = Substance use disorder; TC = Total cholesterol; TG = Triglyceride; USA = United States of America; WHO = World Health Organisation; ZAG = Zinc α2-glycoprotein

Large community based cross sectional as well as longitudinal studies from Japan, Korea and Mediterranean region have found that the risk of MS increases with alcohol consumption, with heavy consumption having the highest risk (Yoon et al., 2004; Urashima et al., 2005; Kim et al., 2012; Barrio-Lopez et al., 2013). However, similar community based cross sectional studies from U.S, Sweden and Canada found that moderate alcohol consumption is beneficial against MS compared to mild or heavy consumption (Lidfeldt et al., 2003; Rosell et al., 2003; Freiberg et al., 2004; Carnethon et al., 2004; Gigleux et al., 2006). Very light alcohol consumption was found to be associated with lower prevalence of MS (Kim et al., 2017). A cohort from US found association of MS with all levels of alcohol consumption in obese or overweight individuals (Slagter et al., 2014). A cohort from Korea found significantly higher rate of MS in those with heavy drinking with no difference among very light, light and moderate drinkers (Buja et al., 2010).

Hence, several cross sectional as well as longitudinal studies have demonstrated higher risk of MS with heavy drinking. The association between quantities of alcohol consumption, especially moderate amount and MS remains controversial. This variation needs to be explored further in terms of socio-cultural differences, differences in study design as well as definitions of types of quantities of alcohol consumption. The beneficial effect of alcohol on MS is thought to be due to increase in HDL, insulin sensitivity and decrease of blood pressure and LDL. A J shaped relationship has been described between alcohol consumption and cardiovascular risk (Vernay et al., 2004; Kiechl et al., 1996).

4.2.1.2. Type of alcohol. Inconsistent findings have been noted regarding the metabolic friendly profile of beer or wine compared to liquor or spirits. Subjects consuming moderate amount of wine as well as mixed group (wine, spirits, and beer) had significantly lower prevalence of MS as well as lower insulin, fibrinogen and higher HDL compared with spirits (Rosell et al., 2003). Mild-moderate consumption of beer or wine was associated with lesser prevalence of MS as well as better lipid profileandlesser waist circumference (Freiberg et al., 2004). However, one Mediterranean cohort reported that mild-moderate beer consumption has been found to be associated with higher risk of MS, hypertriglyceridemia and lesser risk of having lower HDL (Barrio-Lopez et al., 2013).

These variations could be due to effect of several factors such as associated dietary profile, smoking, and differences in gender as well as quantity of alcohol consumption. Individuals consuming wine were found to consume higher amounts of vegetables and fish and less likely to be smokers. In contrast, those consuming spirits were found to consume higher carbohydrate containing food such as bacon, potatoes and smoke (Rosell et al., 2003; Tjønneland et al., 1999).

4.2.1.3. Gender mediated effects. The gender based effect of alcohol on MS is found to be variable across studies. Heavy drinking was associated with higher odds of developing MS in men compared to women (Zhu et al., 2004). In contrast, higher alcohol consumption was found to be associated with higher prevalence of MS in women with no significant increase of MS with alcohol consumption in men in Venezuela (Bermúdez et al., 2015). Heavy alcohol consumption has been consistently associated with increased risk of hypertension in men across studies. A J shaped relationship was observed between alcohol consumption and hypertension in women (Briasoulis et al., 2012).

Moderate alcohol consumption has been inversely associated with MS in men as well as women (Lidfeldt et al., 2003; Rosell et al., 2003; Gigleux et al., 2006). Further, moderate alcohol consumption was associated with higher HDL, decreased insulin and fibrinogen in men (Gigleux et al., 2006). Women consuming moderate amount of wine had significantly lower insulin, fibrinogen and higher HDL in comparison to those consuming spirits (Rosell et al., 2003).

In men, MS was found to be more commonly associated with lower HDL, abdominal obesity and hypertension. In women, MS was more commonly associated with hypertriglyceridemia and hyperglycemia. However in a geriatric Italian cohort, this association did not hold true for women (Park and Kim, 2015; Buja et al., 2010). This is in contrast to expected hyperglycemia, deranged lipid profile in post-menopausal women.

In contrast to the concept of "Telescoping" in women, some of the studies demonstrated that the effect of alcohol consumption (e.g., heavy drinking) on MS is greater or at least equal in men compared to women. (Rosell et al., 2003; Zhu et al., 2004; Kim et al., 2012; Wakabayashi et al., 2010; Lee et al., 2011, 2012) The discrepant findings could be primarily due to methodological differences. Further, it is important to interpret these findings in the context of effect of gender specific factors such as hormonal variation, differences in metabolism of alcohol, adipocyte size and distribution (Pradhan, 2014).

4.2.2. Substance and patient related attributes of MS in nicotine users
Smoking and MS has been an area of debate in the background of "smoking paradox". Both positive and negative associations have been found between quantity of smoking and MS (Santos et al., 2007; Nakanishi et al., 2005). A meta-analysis of 13 prospective studies found that active smokers have higher prevalence of MS compared to ex-smokers and light smokers (Sun et al., 2012). The variation in the findings could probably be explained by the following reasons.

Firstly, the criteria for assessing MS must be taken into account. For example, the odds ratio of developing MS was similar among recent and ex-smokers as per Japan MS criteria. However as per modified NCEP ATP criteria, the risk was greater among recent smokers compared to ex-smokers in the same study (Fan et al., 2006). This differential prevalence found as per the two criteria needs to be carefully interpreted.

Table 2

Cross sectional studies on substance using subjects from community setting.

S.No	Author	Sample characteristics	Results
Alcohol			
1	(Lidfeldt et al., 2003) Sweden	N = 10766 middle aged women WHILA study	One or more components of MS were negatively associated with low and moderate amount of alcohol consumption No significant difference was found amongst various categories of smoking
2	(Rosell et al., 2003) Sweden	3704 elderly patients EGIR criteria	In women, Moderate wine drinkers had significantly lower MS compared to low alcohol drinkers No alcohol drinkers had significantly higher MS compared to low alcohol drinkers No difference in MS was seen amongst the categories and type in men
3	(Freiberg et al., 2004) USA	N = 8,125 Modified NCEP ATP III	Prevalence of MS was slightly higher in women (22.7%) than men (21.9%) Significant negative association was found between alcohol consumption and MS in men and women Subjects consuming ≥ 20 drinks per month specially beer or wine had significantly lower prevalence of MS compared to current nondrinkers
4	(Villegas et al., 2004) Ireland	N = 1018 middle − aged men and women WHO criteria	Prevalence = 21.0% Prevalence was higher in : Men (24.61%) compared to women (17.8%) Ex drinkers compared to occasional and never drinkers Significant negative association was found between physical activity and MS
5	(Yoon et al., 2004) South Korea	KNHNES study N = 7962 Korean adults Modified NCEP ATP III	Risk of MS progressively increased with alcohol consumption Alcohol was inversely associated with low HDL in all alcohol groups
6	(Zhu et al., 2004) USA	N = 11,239 Modified NCEP ATP III criteria	Moderate alcohol intake was significantly associated with lower risk of MS in women only Subjects who were current smokers had significantly higher risk for MS compared to non smokers
7	(Urashima et al., 2005) Japan	N = 22,892 72% males Japan-specific MS (J-MS) and Modified NCEP ATP III (U-MS)	Prevalence : J-MS criteria: 8.4% U-MS criteria: 5.3% As per both criteria : Moderate and high alcohol consumption were significantly associated with MS compared to low consumption MS significantly higher in both current and ex-smokers compared with non smokers
8	(Fan et al., 2006) USA	The Western New York Health Study N = 28 Modified NCEP ATP III	Prevalence of MS increased with increasing quartiles of intensity Number of drinks per day and frequency of drinking emerged as significant predictors of higher FBS, HyperTG, High BP, and MS Lower HDL in all patients and abdominal obesity in women was significantly inversely associated with total drinking days
9	(Santos et al., 2007) Portugal	N = 2164 > 50% female Modified NCEP ATP III	MS was significantly lower in women who were light smokers compared to other groups No statistically significant association was found between alcohol and MS in both women and men amongst all groups
10	(Fan et al., 2008) China	N = 3953 Modified NCEP ATP III	Current alcohol consumption was significantly associated with : Higher SBP, HDL, FBS and lower LDL
11	(Wakabayashi, 2010) Japan	N = 11187 women and 19398 men Modified NCEP ATP III criteria	The odds ratio for MS was significantly lower and higher for light drinkers and heavy drinkers compared to non drinkers respectively in men The odds ratio for MS was significantly lower for light drinkers compared to non drinkers in women J- and V-shaped relationship was noted between log-converted TG and alcohol intake in men and women, respectively.
12	(Bessembinders et al., 2011) Netherlands	N = 300 with hyper TG (TG > 11.3 mmol/l)	TG levels were significantly higher in excessive drinkers and patients with acute pancreatitis
13	(Kim et al., 2011) South Korea	N = 714 KNHANES IV 2008 Modified NCEP ATP III	In problem group as well as hazardous group as defined as AUDIT, alcohol use was significantly associated with an increased risk of hypertension, fasting hyperglycemia, dyslipidemia, abdominal obesity and MS
	(Lee et al., 2011) South Korea	N = 1,768 Modified NCEP ATP III KNHNESSurvey	Significant association between "drinking frequency," "usual drinking quantity," "frequency of high-risk drinking," "frequency of inability to stop drinking," "frequency of feeling guilty after drinking," and "frequency of inability to remember after drinking" and MS was found in men. Significant relationships between MS and "usual drinking quantity," "frequency of feeling guilty after drinking," and "frequency of inability to stop drinking was found in women
	(Lee, 2012) South Korea	N = 3793 KNHNESSurvey IV	Prevalence of MS was significantly higher in those consuming 7 or more drinks (men) and > 3 drinks (women) compared to men and women who had 1 or 2 drinks per day Prevalence of MS was significantly higher in those with binge drinking pattern (more than 1 time/week for both sexes) compared to absence of binge drinking A dose dependent association was found between frequency of binge drinking with : High TG, high FBS, high blood pressure and abdominal obesity in men High FBS and high blood pressure in women.
	(Wakabayashi, 2012) Japan	2 groups: Older: aged ≥ 65 years Younger: aged ≥ 35 and < 45 Modified NCEP ATP III	OR for MS was significantly lower in light and heavy drinkers compared to non drinkers in the younger subjects However there no significant difference in risks for MS for all alcohol groups compared to non-drinker in older age group
	(Ni et al., 2013) Taiwan	TwSHHH 2002 study N = 6188 Modified NCEP ATP III	Cigarette smoking and betel-nut chewing were found to have mediating effects on SES and MS in males. No direct effect of SES on MS was found in males In females, SES was found to have a direct effect on MS

Table 2 (*continued*)

S.No	Author	Sample characteristics	Results
	(Wakabayashi, 2014) Japan	N = 7570 Modified NCEP ATP III, IDF	The association between heavy drinking and MS was greater in occasional drinkers compared to regular drinkers ORs for MS was significantly higher in occasional heavy drinkers and regular heavy drinkers compared to non drinkers OR for increased waist circumference was significantly greater in occasional heavy drinkers compared to regular heavy drinkers OR for hyperglycemia was significantly lower in regular heavy drinkers compared to occasional heavy drinkers
	(Kang and Song, 2015) South Korea	N = 11,559 KNHNES study2008–2010 Modified NCEP ATP III	Prevalence of MS was slightly higher in men (28.2%) compared to women (24.6%) In male smokers, increased risk of high TGs, low HDL, and decreased risk of high BP compared with nonsmokers Women smokers had a higher risk of abdominal obesity and high TGs compared with nonsmokers.
	(Park and Kim, 2015) South Korea	KNHANES study N = 5760 adults	Prevalence of MS was almost 25% Heavy drinking was associated with MS in both men and women Significant association was found between MS and increasing age Prevalence of MS was significantly higher in men compared to women, who belonged to young and middle aged group However, prevalence of MS was significantly lower in men compared to women, who belonged to older age group (aged 60 or more)
	(Bermúdez et al. (2015)) Venezuela	N = 2230 MMSP study Diagnosis of MS: IDF/AHA/NHLBI-2009 consensus statement	In females: The prevalence of MS as well as TG was found to significantly increase with alcohol consumption In males: No signification difference was found in prevalence of MS or TG levels with alcohol consumption
	(Vieira et al., 2016) Brazil	Brazilian Longitudinal Study of Adult Health N = 14375	The odds ratio of developing MS was significantly lower in those with light consumption of alcohol during meals ((≤ 4 drinks/week; 4-7 drinks/week)compared to those abstinent or occasional drinkers The odds ratio of developing MS was significantly higher in those with heavier consumption of alcohol (7 to 14 drinks/week; > 14 drinks/week) outside of meals
Cannabis			
1	Vidot et al., 2016 US	n = 8478 2005-2010 National Health and Nutrition Examination Surveys N = 8478	Prevalence of MS: Current marijuana users (1 day in the last 30 days) = 13.8% Past marijuana users (used previously but not within the last 30 days) = 17.5%

AHA = American Heart Association; AUDIT = Alcohol use disorder identification test; EGIR = European Group for the Study of Insulin Resistance; FBS = Fasting blood sugar; HDL = High Density Lipoprotein; IDF = International Diabetes Federation ; KNHNES study = Korean National Health and Nutrition Examination Survey ; LDL = Low density Lipoprotein; MA = Methamphetamine; MMMS = Maracaibo city metabolic syndrome prevalence; MS = Metabolic syndrome; NCEP-ATP III = National Cholesterol Education Program's Adult Treatment Panel ;NDS = Nicotine Dependence Syndrome; NHLBI = National Heart Lung and Blood institute; OR = Odds ratio; SBP = Systolic Blood Pressure; SES = Socioeconomic status; TC = Total cholesterol; TG = Triglyceride; TwSHHH = Taiwanese Survey on Prevalence of Hypertension, Hyperglycemia, and Hyperlipidemia; USA = United States of America; WHILA = Women's health in the Lund area; WHO = World Health Organisation

Visceral obesity (high waist circumference) is an essential criteria in the Japanese Criteria for MS, but not in the NCEP-ATP criteria.

Secondly, contradictory findings have been noted with regard to weight and smoking. Literature exists that smoking cessation has been found to be associated with weight gain (Tian et al., 2015). However, weight loss with smoking has been associated with decrease in lean mass rather than body fat (Chen et al., 2012). Hence, it needs to be evaluated if the weight gain post smoking cessation is due to increase in body fat or lean mass.

4.3. Methodological considerations

The discrepant findings noted could be due to effect of various factors such as age, gender, ethnicity, comorbid substance use, diet and physical activity, differences in operational definitions, reference group and study design. The findings of studies which exclusively studied a particular gender or age group cannot be generalizable (Lidfeldt et al., 2003; Rosell et al., 2003). Majority of studies have been done in community setting which might not be extrapolatable to patients with SUD from hospital setting. Most of the studies available are reported from U.S, U.K, Korea, and Japan (Urashima et al., 2005; Kim et al., 2012; Barrio-Lopez et al., 2013; Stoutenberg et al., 2013). This could have led to variation in the results due to different ethnic groups. Further, in

many of the studies on alcohol, the subjects also had comorbid nicotine use which could have altered the metabolic parameters. Physical activity and diet are important factors which have effects on metabolic syndrome. MS has been found to be significantly lower in individuals who are non-smokers, physically active, non obese, with lower carbohydrate intake and moderate alcohol consumption (Zhu et al., 2004; Wilsgaard and Jacobsen, 2007). In many of the studies, physical activity and diet were not addressed. Physical illness and psychiatric comorbidity are other important confounding variables which can lead to inflated rates of prevalence of MS as some of studieshad psychiatric and physical comorbidity as high as 41% (Vallecilo et al., 2018) and 38.3% (Nebhinani et al., 2013)

There have been varying definitions for mild, moderate and heavy or excessive consumption of alcohol (Lidfeldt et al., 2003; Rosell et al., 2003; Zhu et al., 2004; Urashima et al., 2005; Baik and Shin, 2008; Barrio-Lopez et al., 2013). A range of reference groups have been taken such as current users versus ex-users; chronic ex-users versus occasional users; heavy users versus non users etc. which makes the comparison among results of various studies difficult to perform (Wakabayashi, 2014; Wannamethee et al., 2006; Nakanishi et al., 2005; Lee et al., 2005). Since many of the studies have relied on self-report regarding substance use, recall bias cannot be ruled out. The only two published articles on methamphetamine dependence appear to be derived from a

Table 3

Cohort studies on substance using subjectsin community setting

S.No	Author	Study characteristics Criteria for MS	Results
	(Carnethon et al., 2004) USA	N = 4192 CARDIA study Follow up period = 16 years Modified NCEP ATP III	Increased risk of MS was associated with: Increasing Age Higher baseline BMI at baseline No alcohol consumption Weight gain Decreased physical activity
	(Gigleux et al., 2006) Canada	N = 4635 French Canadian men Quebec Cardiovascular Study Follow-up = 13 years Modified NCEP ATP III	Subjects consuming 5.2 g of alcohol/d (4th quartile) had significantly higher HDL, lower insulin and fibrinogen than those consuming 1.3 g of alcohol/d (1 st quartile) Consumption of ≤ 15.2 g/d was significantly associated with a 39% decrease of IHD Consumption of > 15.2 g/d was increase with risk of IHD only in patients with MS
	(Wannamethee et al., 2006) UK	Cross-sectional and longitudinal analyses of cohort study N = 3051 elderly men Modified NCEP ATP III	Current smokers had significantly higher risk of MS compared to never smokers Risk of MS was similar for long-term ex-smokers and never smokers No significant difference between categories of alcohol consumption and MS
	(Athyros et al., 2007) Greece	Cross sectional analysis of cohort study N = 4153	Moderate and heavy alcohol consumption were significantly associated with lesser and higher prevalence of MS respectively compared to non drinkers
	(Onat et al., 2007) Turkey	N = 3385 Mean follow up = 5.9 years	Heavy smoking (11 or more cigarettes/day) was found to be significantly protective for developing MS and Diabetes Mellitus in women
	(Wilsgaard and Jacobsen, 2007) Norway	TROMSO study 1979-2001 N = 17,014 men and women Modified NCEP ATP III criteria	Risk of MS was significantly higher in those smoking more than 20 cigarettes/day compared to non-smokers. Low or no alcohol consumption was associated with increased risk of MS in women only
	(Baik and Shin, 2008) Korea	N = 3833 Follow up = 4 years Modified NCEP ATP III and IDF criteria	Relative risk of MS was significantly higher in heavy drinkers compared to non drinkers All components of MS were significantly associated with heavy drinking
	(Buja et al., 2010) Italy	N = 2443 elderly subjects Mean follow up = 3.5 years Modified NCEP ATP III	No significant difference in prevalence as well as incidence of MS among all categories in men as well as women SBG, FBS and WC was significantly associated with alcohol consumption in men only
	(Zhu et al., 2004) China	N = 693 men Follow up = 2.9-5.5 years Modified NCEP ATP III JCDCG criteria	There was significantly higher dose dependent increase in association of MS in smokers as per NCEP-ATP III criteria Smokers who had quit smoking ≥13 years had significantly lower risk of developing MS as per JCDCG criteria
	(Kim et al., 2012) South Korea	N = 4505 men Hospital based study Average follow up = 3 years World Health Organization-West Pacific Region guideline	Continuous moderate and heavy drinking had higher rate of MS compared to other groups at the end of follow up
	(Barrio-Lopez et al., 2013) Spain	N = 8103 Follow up ≥ 6 years Harmonizing criteria of the IDF and AHA/ NHLBI criteria	Consumption of ≥ 7 drinks per week was associated with: Higher rate of MS, hyperTG, higher FBS compared to non drinkers Beer was associated with higher risk of hyperTG, MS and lower HDL
	(Stoutenberg et al., 2013) USA	N = 7483 men Study period: 1979-2005 Modified NCEP ATP III	Inverse association was found between incidence of MS and alcohol consumption among all categories
	(Slagter et al., 2014) Netherlands	N = 64,046 categorised as normal weight, overweight and obese Study period = 6 years Modified NCEP ATP III criteria	Prevalence range of MS was as follows: Normal weight: 1.7%–8.2% Overweight: 13.0%–32.1% Obese: 39.8%–71.1% The highest BMI was found in obese subjects who were heavy smokers and had more than 1-2 drinks per day Subjects with consumption of both alcohol (> 1 drink/day) and tobacco had higher TG Consumption of > 2 drinks/day was associated with higher BP blood pressure, especially in heavy smokers.
	(Kim et al., 2015) USA	N = 589 ASPIRE study Primary health care setting	No significant association was found between frequency and severity of drug use with inadequate BP control or BG control When compared with cannabis, Cocaine use was associated with inadequate BG control
	(Wellman et al., 2016) Canada	N = 756	SBP at 24 years of age was significantly higher among: Current monthly bingers compared to non binge drinkers Current weekly bingers compared to non binge drinkers SBP at age 24 years of age was higher among monthly bingers as well as weekly bingers (pattern at 20 years of age) compared to non bingers
	(Kim et al., 2017) South Korea	N = 10037 NCEP-ATP criteria	Lower alcohol consumption (0.1-5 g/day) was significantly associated with lower prevalence of MS in males as well as females No significant association was found between heavy alcohol consumption and MS.

AHA = American Heart Association; ASPIRE = Assessing Screening Plus brief Intervention's Resulting Efficacy to stop drug use; BMI = Body Mass Index; CARDIA = Coronary Artery Risk Development in Young Adults ; FBS = Fasting blood sugar; HDL = High Density Lipoprotein; IDF = International Diabetes Federation ; IHD = Ischemic Heart Disease; JCDCG = Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults;MS = Metabolic Syndrome; NCEP-ATP = National Cholesterol Education Programme Adult Treatment Panel; NHLBI = National Heart, Lung, and Blood Institute; SBP = Systolic Blood Pressure; TC = Total cholesterol; TG = Triglyceride; USA = United States of America; WC = Waist Circumference.

single group of patients (Lv et al., 2016; Zhang et al., 2017). Finally, there were paucity of prospective studies in comparison to the numerous cross sectional studies.

4.4. Implications

4.4.1. Role of screening

Considering the prevalence rates of MS among substance users in hospital and community setting, there is need for regular screening for MS among substance users. There must be implementation of effective primary as well as secondary preventive strategies against MSamongst substance users, preferably which are cost effective, especially in the resource deficit setting. These strategies aim to decrease the morbidity and mortality due to the combined burden of MS and SUD. However, considering the varying prevalence rates across settings, there is need for generating meta analyses for determining pooled prevalence for various substances of abuse..

4.4.2. Should low-moderate alcohol consumption be prescribed?

Studies seem to suggest that low daily consumption of alcohol of less than 10 g/day (1 Unit/ day) may not be associated with an increased risk of MS. However, there is consistent evidence that heavy use (> 30 g/day or > 3 Units/ day), even if taken intermittently, is associated with a higher risk of hypertension, dyslipidemia and MS. Studies suggest that there may be a lower risk of MS with moderate consumption of alcohol. However, there are several caveats that need to be discussed.

First, many of the studies reporting beneficial effect of moderate consumption of alcohol have been done in the Western setting with varying operational definitions of moderate use which limit its generalizability. Secondly, difficulty in controlling level of use is one of characteristics of substance use disorders. Even with low levels of use, the risk to progression to heavy drinking and alcohol dependence is always present due to the addictive nature of alcohol. Thus there is no scientific merit in prescription of alcohol use for health.

Third, alcohol use in moderate amounts is associated with hepatic impairment such as fatty changes, impaired fatty acid metabolism and raised triglycerides. Similarly, there is risk of hypertension in those who drink in high amounts even intermittently (such as over weekends). These risks may outweigh the benefits. Fourth, in overweight and obese subjects, these risks are even more, along with increased carcinogenic potential specially in women, teratogenic potential and cognitive impairment (Corrao et al., 2004; Cao et al., 2015).

Finally, alcohol use is usually accompanied by intake of fat and carbohydrate rich food as well as nicotine use which might indirectly contribute to cardio-metabolic derangements. Further, the sociocultural milieu also plays a significant role in ascertaining if moderate consumption of alcohol should actually be "recommended" at all. In contrast to the developed countries in the Western setting, alcohol consumption is considered as a taboo and social evil in some parts of the World. It has been shown that in countries that follow a "dry culture" pattern of drinking, there may be more abstainers, but those who consume alcohol often do it in heavy amounts, often in hazardous, problematic or even dependent patterns of use (Kim et al., 2012; World Health Organisation, 2011; Bloomfield et al., 2003). As shown in our review, such patterns are more likely to cause harm. Also, alcohol is definitely not advisable to certain groups in particular such as those with family history of breast cancer, cardiovascular illness, those recently abstinent from alcohol, pregnant and lactating mothers, elderly and geriatric population.

4.5. Conclusion

The prevalence of MS varied as per study setting as well as type of substance. The prevalence of MS ranged from 5.1 to 30.6% and 1.7% to 71.1% in hospital and community setting respectively. Alcohol and

nicotine have been largely studied followed by opioids with limited literature on methamphetamine and cannabis. Discrepant findings have been noted with regard to the effect of quantity, patterns and type of consumption of alcohol and nicotine on MS. It is important to interpret the inconsistent findings in light of several methodological issues. The effect of heavy drinking on MS is greater or at least equal in men compared to women, in contrast to the expected pattern of "Telescoping". The findings of lower risk of cardiovascular disease or MS found with low levels of alcohol consumption are found in a few studies and the apparent protective role is not found in many other studies.

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