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Abstract: Background: Nutrition is a prerequisite for health; yet, there is no special nutritional assessment or guidance for drug and alcohol dependent individuals, despite the fact that their food consumption is often very limited, risking malnutrition. Further, the premise is examined that malnutrition may promote drug seeking and impede recovery from substance use disorders (SUD).

Method: A narrative review addressed the relationship between substance use disorders and nutrition, including evidence for malnutrition, as well as their impact on metabolism and appetite regulation. The implications of the biopsychology of addiction and appetite for understanding the role of nutrition in SUD were also considered.

Results: The literature overwhelmingly finds that subjects with alcohol use disorder (AUD) and drug use disorder (DUD) typically suffer from nutrient deficiencies. These nutrient deficiencies may be complicit in the alcoholic myopathy, osteopenia and osteoporosis, and mood disorders including anxiety and depression, observed in AUD and DUD. These same individuals have also been found to have altered body composition and altered hormonal metabolic regulators. Additionally, brain processes fundamental for survival are stimulated both by food, particularly sweet foods, and by substances of abuse, with evidence supporting confusion (addiction transfer) when recovering from SUD between cravings for a substance and craving for food.

Conclusion: Poor nutritional status in AUD and DUD severely impacts their physical and psychological health, which may impede their ability to resist substances of abuse and recover their health. This review contributes to a better understanding of interventions that could best support individuals with substance use disorders.

The importance of nutrition in aiding recovery from substance use disorders: a review

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1. Introduction

Alcohol and drug dependency are not merely matters of addiction and substance misuse, but are accompanied by serious comorbidities. It is estimated that every year worldwide, 3.3 million people die from harmful alcohol consumption and that 15.3 million people use drugs in a way that is harmful (World Health Organisation, 2017). In England, there are estimated to be 1.6 million people suffering from alcohol dependence (Fenton and Newton, 2016), and approximately 1.5 million adults take illegal drugs at least monthly (Lader, 2015). In 2014-15, just over 141,000 new clients accessed drug and/or alcohol recovery services in England for a total of just under 300,000 in all services (Public Health England, 2015b). Of those, 130,000 left treatment during the same period, with approximately 52% or 68,000 recorded as having completed treatment (Public Health England, 2015b): thus, 48% of those who left treatment were still substance dependent.

Substance use disorders increase the long term risk of serious health complications (Hossain et al., 2007; Nazrul Islam et al., 2001; Quintero-Platt et al., 2015) and are linked to increased mortality (Quintero-Platt et al., 2015). Liver disease, cirrhosis, cardiovascular disease (Quintero-Platt et al., 2015; Zhang et al., 2008), diabetes, pulmonary disease (Zhang et al., 2008), poor wound healing (Guo and Dipietro, 2010), lowered immune function (Housova et al., 2005; Quintero-Platt et al., 2015) and depression (Tolliver and Anton, 2015) have all been linked to substance use disorders, as have the spread of HIV and hepatitis through illegal drug use (Nabipour et al., 2014). Drug use, not including alcohol, costs the UK National Health Service (NHS) almost £500 million every year; the cost of drug related crime alone is estimated to be £13.9 billion per year, with every £1 spent on drug treatment estimated to save £2.50 in health and criminal justice costs (NHS National Treatment Agency for Substance Misuse, 2016). Not only does recovery save public money, but society also benefits from the recovery of these individuals who are themselves, children, parents, neighbours, employees, employers and friends: successful treatment is important.

Supporting the nutritional status of individuals with alcohol use disorder (AUD) and drug use disorder (DUD) is often neglected or only a very small part of the recovery support offered by outpatient services. This is the case despite the fact that substance use disorders, in many cases, can lead to malnutrition, metabolic disorders that compromise nutrition (Nabipour et

al., 2014), altered body composition (Tang et al., 2010) and poor mental health (Tolliver and Anton, 2015). Thus, nutrition should be an important part of the treatment of substance use disorders; however, it is not given much consideration in treatment guidelines, despite evidence that recovery outcomes can be improved by nutrition therapy and well balanced nutrient intake (Biery et al., 1991; Grant et al., 2004). In the extensive UK National Institute for Health and Care Excellence (NICE) guidelines for alcohol use disorders, there is no mention of nutrition as a factor that needs to be specifically assessed or addressed (NICE, 2011). There are only three places in the guidelines where nutrition might be incorporated: the brief triage assessment category (NICE, 2011; Section 1.2.2.5) which specifies that ‘presence of any comorbidities or other factors’ be assessed and referred, the comprehensive assessment category (section 1.2.2.6) which instructs that ‘physical health problems’ be assessed, and, the very last entry in the intervention guidelines (section 1.3.8.5) which covers Wernicke-Korsakoff Syndrome (WKS) (NICE, 2011). It suggests thiamine supplementation for those at risk of Wernicke’s Encephalopathy (WE), and for those who are entering inpatient services or prison *and* are at risk of malnutrition or who are already suffering from malnutrition (NICE, 2011). In April 2015, NICE did not see a need to update the guidelines. The drug use disorders guidelines by NICE do not mention nutrition (NICE, 2012), nor do the relevant Department of Health guidelines (Department of Health, 2007); they only mention physical health. Thus, this review examines the evidence for the nutritional status of subjects with alcohol and drug use disorders, and considers the implications of malnutrition for treatment of these disorders.

2. Malnutrition in substance use disorders

Malnutrition, as will be discussed herein, has been eloquently defined as, “disturbance of form or function arising from the deficiency of one or more nutrients” (Schenker, 2003, p.91). Diagnostic criteria for malnutrition are inexact; therefore, it can be difficult to diagnose. The standard assessment takes into account an individual’s body mass index (BMI) and the possibility of unintentional weight loss of between 5-10% of total body weight in the last 3-6 months (British Association for Parenteral and Enteral Nutrition, 2016; BAPEN). Symptoms of low mood, fatigue, muscle weakness and increased infection and/or illness can also be indicative of malnutrition (BAPEN, 2016). One thing that makes diagnosis difficult is the link to weight; it is possible to be overweight and malnourished

(Gastelurrutia et al., 2011). Furthermore, individuals' behavioural symptoms related to malnutrition may be masked by drug and alcohol misuse.

It has been estimated that, of the British population, approximately 3 million are malnourished (BAPEN, 2016). This may be a result of a diet that is deficient in key macro- and micronutrients, insufficient intake, and/or poor nutrient digestion and absorption (BAPEN, 2016). Malnutrition can also result from a lack of: money, available outlets to purchase nutrient dense food, access to cooking facilities, knowledge about cooking, confidence in cooking, motivation/desire to eat and/or education about the importance of food, (Himmelgreen et al., 1998; Neale et al., 2012; Schenker, 2003). People suffering from substance use disorders may be particularly susceptible to compromised nutritional status and body composition. Substance use disorders have been shown to decrease appetite and taste for food (Neale et al., 2012) and physically impair the body's ability to access nutrients (Egerer et al., 2005). It is also possible that subjects with AUD and DUD were already nutrient deficient prior to chronic substance intake, as Schroeder and Higgins (2016) found that poor micronutrient status increased the likelihood of substance use disorders.

3. Alcohol use disorder and nutrition

3.1 Nutritional intake and absorption

Individuals with chronic AUD are generally malnourished (Chopra and Tiwari, 2012; Clugston and Blaner, 2012; Nair et al., 2015; Ross et al., 2012). Alcohol both inhibits the absorption of many nutrients directly (Badawy, 2014) and, with chronic alcohol intake, can also severely impact the health of the entire gastrointestinal (GI) tract. Chronic alcohol consumption has been linked to widespread physical injury and dysfunction including: mucosal damage in the mouth, oesophagus, and stomach, delayed gastric emptying, increased intestinal permeability and membrane damage, bacterial overgrowth and cancer (Egerer et al., 2005). This severely affects the digestion and absorption of essential nutrients (Chopra and Tiwari, 2012; Ross et al., 2012). As a result, nutrient deficiencies are prevalent in this population (Chopra and Tiwari, 2012; Stroehle et al., 2012). Research has shown that subjects with AUD are deficient in or have inadequate intake of most nutrients, including: thiamine (Dastur et al., 1975; de la Monte and Kril, 2014; Boyd et al., 1981; Stroehle et al.,

2012), riboflavin, niacin (Chopra and Tiwari, 2012; Dastur et al., 1975), B₅ (Nabipour et al., 2014), pyridoxine (Dastur et al., 1975; de la Monte and Kril, 2014; Stroehle et al., 2012), folic acid (de la Monte and Kril, 2014; Stroehle et al., 2012; Wu et al., 1975), vitamin A (Clugston et al., 2015; Ross et al., 2012), vitamin C (Boyd et al., 1981), vitamin D (Boyd et al., 1981; Quintero-Platt et al., 2015; Santolaria et al., 2000a; Wijnia et al., 2013; Wilkens Knudsen et al., 2014) vitamin E (Chopra and Tiwari, 2012; Tanner et al., 1986), vitamin K (Iber et al., 1986), magnesium (Dingwall et al., 2015; McLean and Manchip, 1999; Wilkens Knudsen et al., 2014) selenium (Tanner et al., 1986) and zinc, (de la Monte and Kril, 2014; Stroehle et al., 2012; Wilkens Knudsen et al., 2014) (Table 1). Vitamin B₁₂ may also be deficient; however, circulating levels may not accurately reflect the stores available for use (Kanazawa and Herbert, 1985). AUD subjects are also likely to become lactose intolerant because of a downregulation in lactase (Egerer et al., 2005). AD subjects also have altered eating patterns (Santolaria et al., 2000b).

3.2 Effects of alcohol on nutrients

Alcohol inhibits thiamine uptake by reducing the transcription factors for the two transporters that absorb thiamine in the brush border cells (Kiela, 2010). In addition, alcohol limits the production of thiamine pyrophosphokinase, an enzyme that converts thiamine to thiamine pyrophosphate (TPP) which is a coenzyme for metabolic functions (Kiela, 2010). Thiamine deficiency has long been associated with cognitive dysfunction (de la Monte and Kril, 2014) and established as the primary cause of Wernicke's encephalopathy (WE) (Kiela, 2010; Rees and Gowing, 2013; Ross et al., 2012; Sechi and Serra, 2007), which affects mood, coordination, and ocular movement (Sechi and Serra, 2007). Korsakoff Syndrome (KS), often paired with WE (WKS) because it develops in some of these patients, limits working memory (Sechi and Serra, 2007). Thiamine deficiency has been shown to cause neurodegeneration (Yang et al., 2011), and supplementation has been shown to improve symptoms especially in WE (Kiela, 2010; Sechi and Serra, 2007).

Magnesium is depleted by alcohol consumption (McLean and Manchip, 1999) and deficiency levels have been found in subjects with AUD but prevalence varies between 13% and approximately 50% (Dingwall et al., 2015; Wilkens Knudsen et al., 2014). This deficiency has been found to play a particular role in WE and WKS. Magnesium is a cofactor in the

conversion of thiamine to thiamine pyrophosphate (Bishai and Bozzetti, 1986). Some WE or WKS patients supplemented with thiamine alone did not improve (Bishai and Bozzetti, 1986) or improvement plateaued. In some of these cases, adding supplemental magnesium lead to an improvement in cognition (Bishai and Bozzetti, 1986; Dingwall et al., 2015). Among WKS patients, magnesium levels have also been shown to be correlated with cognitive function tests results (Dingwall et al., 2015). While thiamine and magnesium have been shown to improve WE symptoms, there has been little evidence of improvement in KS (Saad et al., 2010; Sechi and Serra, 2007).

Other mineral levels are also impacted by alcohol intake: alcohol induces zinc deficiency (Badawy, 2014) by increasing excretion (Ghorbani et al., 2016). Wilkens Knudsen et al. (2014) found insufficient zinc levels in 38% of subjects. Iron was also found to be deficient in the majority of cases of AUD and DUD that were investigated (Lieb et al., 2011; Ross et al., 2012); however, there is evidence that a small percentage of this population absorb the nutrient in excessive amounts (Egerer et al., 2005; Lieb et al., 2011), and similarly plasma levels of copper are typically reported to be raised in alcoholics (Cook et al., 1992).

Vitamin levels are also affected by alcohol intake. There is a high prevalence of low Vitamin D levels in AUD subjects (Ghorbani et al., 2016; Quintero-Platt et al., 2015; Santolaria et al., 2000a; Wijnia et al., 2013; Wilkens Knudsen et al., 2014). Wilkens Knudsen et al. (2014) found Vitamin D levels were deficient in over 50% of the study population while Quintero-Platt et al. (2015) estimated that 86% of subjects had vitamin D levels below normal. They also found that low vitamin D levels were correlated with lower lean mass, BMI and increased mortality (Quintero-Platt et al., 2015).

Antioxidant vitamin levels are low in populations with AUD. Liver stores of vitamin A appear to be impacted by alcohol dependence (Clugston et al., 2015; Guo and Dipietro, 2010; Nair et al., 2015; Ross et al., 2012); however, extrahepatic tissue levels appear to be increased (Clugston et al., 2015). The conversions of ethanol and retinol to acetic acid and retinoic acid, respectively, compete for a metabolic pathway (Clugston et al., 2015; Nair et al., 2015). This may explain the deficiency of metabolically active retinoic acid in subjects with AUD (Nair et al., 2015) and toxicity of supplemental vitamin A. For vitamin C, Ross et al. (2012) reported evidence of subclinical scurvy in some subjects despite their receiving a

multivitamin upon admission. Vitamin E levels have also been found to be low in subjects with AUD (Guo and Dipietro, 2010).

B vitamins have an interconnected relationship and therefore deficiency in one may affect the status of others (Shibata et al., 2015). Deficiency in niacin, which results in pellagra, has been documented in subjects with AUD (Badawy, 2014). They may be particularly vulnerable to this disease for several reasons. The level of protein and amino acid, specifically tryptophan, intake may be low, absorption in the GI tract may be compromised, conversion of tryptophan to niacin in the liver may be inhibited, and/or other cofactors including thiamine, riboflavin, pyridoxine and zinc, that are required for conversion and use, may be unavailable (Badawy, 2014). Moreover, pyridoxine deficiency is precipitated by alcohol ingestion (Ghorbani et al., 2016).

3.3 Body composition

There are several indications of anomalies in the body composition of subjects with AUD. Lower body mass index (BMI) and fat mass (FM) have been found in individuals with a high alcohol intake (Addolorato et al., 1998; Addolorato et al., 2000; Santolària et al., 2000a). Up to an unknown level of alcohol consumption, energy from alcohol increases BMI and FM of the subject, but after the tipping point, the increased alcohol consumption is inversely related to BMI and FM (de Timary et al., 2012; Liangpunsakul et al., 2010). de Timary et al. (2012) found that subjects consuming more than 12.5 kcal/kg/day (125 g/day for a 70-kg adult) had a lower BMI and FM than those consuming less, while Liangpunsakul et al. (2010) used a lower cut off of >70 g of alcohol per day. The exact tipping point is unknown, and may vary considerably among individuals. Even a normal BMI among subjects with AUD does not mean they are healthy. Waist-to-hip ratio may be higher in these individuals (Addolorato et al., 2000) but may not differ significantly from the general population (Wilkens Knudsen et al., 2014). Their FM percentage may also be relatively high (Martin-Gonzalez et al., 2011).

There are several possible explanations for the paradox of increased energy intake in subjects with AUD and lower than expected BMI and FM. Increased microsomal detoxification found in alcoholics (Addolorato et al., 1998) may require more energy. Preferential sources of energy may shift from glucose to acetate (Jequier, 1999) particularly in the brain (Volkow

et al., 2015). There is also some evidence of an increased use of lipids as a preferential energy source (Addolorato et al., 2006; Levine et al., 2000; Volkow et al., 2015), but this is not supported by all research (Jequier, 1999). Lower FM also may be the result of reduced lipogenesis during intoxication (Levine et al., 2000). There is some evidence of increased thermogenesis with increased alcohol intake (Haas, 2005; Levine et al., 2000), but other studies have indicated that alcohol does not affect metabolic rate (Liangpunsakul et al., 2010). It is likely to be a combination of these factors. Levine et al. (2000) found that it took 4 days for energy expenditure to decrease. This reduction in energy expenditure is in line with evidence that subjects with AUD gain weight in recovery (Krahn et al., 2006).

3.4 Alcoholic myopathy (AM)

Loss of lean mass has been linked with the probability of premature death (Martin-Gonzalez et al., 2011). Alcohol myopathy manifests as a loss of lean tissue and strength in subjects with AUD (de la Monte and Kril, 2014; Lang et al., 2005; Martin-Gonzalez et al., 2011; Sacanella et al., 1995; Steiner and Lang, 2015) and levels of degeneration are strongly correlated with lifetime alcohol intake levels (de la Monte and Kril, 2014; Lang et al., 2005; Sacanella et al., 1995). AM may have several causes; chronic alcohol intake impairs protein metabolism (Lang et al., 2005; Steiner and Lang, 2015; Wijnia et al., 2013), subjects with AUD may have a diet with a negative protein balance (Wijnia et al., 2013), and chronic alcohol consumption depletes liver reserves of protein, using them for energy (Chopra and Tiwari, 2012). Women seem to be at greater risk of AM than men (Steiner and Lang, 2015).

AM symptoms include: symmetrical pain of the shoulder, pelvis (Sacanella et al., 1995) ribs, lower back and legs, and over all muscle weakness (Wijnia et al., 2013). Research investigates hand grip strength (HGS) as a proxy to measure muscle mass. Wilkens Knudsen et al. (2014) found that subjects with AUD that showed reduced HGS were also nutrient deficient. Vitamin D is important for muscle strength and for development of skeletal muscle, so good vitamin D status may therefore be protective against myopathy; however, Vitamin D status has been shown to be deficient in subjects with AUD (Quintero-Platt et al., 2015; Santolaria et al., 2000a; Wijnia et al., 2013; Wilkens Knudsen et al., 2014). Deficiencies in B vitamins (de la Monte and Kril, 2014), magnesium, potassium, calcium and phosphate (Wijnia et al., 2013) may also contribute to this myopathy.

3.5 Osteoporosis and osteopaenia

Compromised bone density has been found in subjects with AUD (Santolaria et al., 2000a; Wilkens Knudsen et al., 2014) due to the deficiency of osteocalcin caused by alcohol intake and deficiency in vitamin D and insulin like growth factor-1 (Ghorbani et al., 2016). Santolaria et al. (2000a) reported an overall correlation between BMI and bone mineral density (BMD) and bone mineral content (BMC) and noted that over 40% of subjects with irregular eating had low BMC. Wilkens Knudsen et al. (2014) found evidence of osteopaenia in 52% and osteoporosis in 7% of their subjects with AUD. A recent meta-analysis (Bang et al., 2015) indicated an increased incidence of bone fracture among patients with alcoholic liver disease who did not have low BMD.

4. Drug use disorders and nutrition

4.1 Malnutrition in drug dependency

Malnutrition is also prevalent among subjects with DUD (Cunningham, 2016; el-Nakah et al., 1979; Hossain et al., 2007; Housova et al., 2005; Nabipour et al., 2014; Neale et al., 2012; Sukop et al., 2016; Tang et al., 2011). This may be the result of inadequate intake, poor food security (Himmelgreen et al., 1998; Housova et al., 2005; Tang et al., 2011; Tang et al., 2010), compromised liver storage and/or altered metabolism (Tang et al., 2010). Decreased appetite (Hossain et al., 2007; Nazrul Islam et al., 2001), inhibited gastric motility (Mysels and Sullivan, 2010) and increased excretion (Tang et al., 2010) may also play a role.

4.2 Effects of drugs on nutrients

Essential nutrients are depleted among drug users (Table 1). Intake of protein, thiamine, riboflavin, niacin, vitamin C, vitamin D, magnesium, calcium, copper (Saeland et al., 2011) and iron have been reported to be below reference intake levels in subjects with DUD (Hossain et al., 2007; Saeland et al., 2011). Nazrul Islam et al. (2001) also found low antioxidant levels of Vitamins A, C and E among subjects with DUD and noted an inverse

relationship between length of DUD and nutrient levels. Specifically, in heroin dependent subjects, levels of protein, folate, thiamine, riboflavin, B₆ and vitamin E were the most common deficiencies (el-Nakah et al., 1979; Varela et al., 1997), and Sukop et al. (2016) observed WE in crack-cocaine addicts.

Copper levels have been reported to be elevated (Hossain et al., 2007; Saeland et al., 2011); however, this may be due to increased inflammation, stress and infection (Hossain et al., 2007). Hossain et al. (2007) also found levels of serum zinc to be higher than controls and suggested that this may be a secondary effect of malnutrition.

4.3 Body composition

Individuals with DUD have generally been found to have lower BMI and FM percentage, and higher fat free mass (FFM), than healthy controls (Ersche et al., 2013; Himmelgreen et al., 1998; Mysels and Sullivan, 2010; Quach et al., 2008; Tang et al., 2011; Tang et al., 2010), although some have BMIs in the overweight and obese categories (Fenn et al., 2015). Tang et al. (2011) found that 50% of HIV-negative subjects with DUD had an underweight BMI, and McIlwraith et al. (2014) found that injecting drug users, specifically heroin users, were particularly at risk of having a BMI in the underweight range. They also found that amphetamine users were more likely to be obese than both heroin and morphine users (McIlwraith et al., 2014). This is counterintuitive since amphetamines have been used to support weight loss since the 1950's (Haslam, 2016), but may be more a reflection of the lifestyle choices of these populations than the effects of the drugs themselves. On the other hand, another study found that over 80% of male and nearly 50% of female subjects with DUD had a normal BMI, with only 3% and 10%, respectively, underweight (Saeland et al., 2011).

Similar to subjects with AUD, there appears to be an altered metabolism among subjects with DUD (McIlwraith et al., 2014; Quach et al., 2008; Tang et al., 2010). Nutrient intake has not been found to be associated with BMI in subjects with DUD subjects (Quach et al., 2008). Repeated cocaine use reduces body fat storage (Ersche et al., 2013) and leads to significantly lower BMI (Quach et al., 2008) than that maintained by non-drug users. Relatively high levels of fat intake were not associated with fat deposition (Billing and Ersche, 2015; Ersche

et al., 2013). Billing and Ersche (2015) proposed that cocaine mediated fat intake does not increase body fat possibly because it mobilizes the neuropeptide cocaine and amphetamine regulated transcript (CART) which not only affects appetite but alters the metabolism of fat so that it is not deposited but rather oxidized (Billing and Ersche, 2015). Cocaine simultaneously upregulates glucocorticoid production (Billing and Ersche, 2015). Together these factors increase thermogenesis and reduce fat deposition, while potentially promoting appetite for fat-rich foods (Billing and Ersche, 2015). This may partially explain the altered metabolism, at least in cocaine use.

Subjects with DUD report weight gain in recovery (Varela et al., 1997, Neale et al., 2012); this could be due to increased food intake as well as normalization of metabolism. Fenn et al. (2015) studied patients in the first six months of methadone treatment and found that despite already having a normal to overweight BMI, subjects continued to gain weight through recovery. This was especially true of the female population who increased their body weight by an average of 17.5% whereas males' weight increased approximately 6.4%. Mysels and Sullivan (2010) found evidence that more methadone patients are overweight or obese than controls.

4.4 Causes of undernutrition

The reasons for poor nutritional status in subjects with DUD appear to be more primary in nature; choice of drugs over food being the main reason (Neale et al., 2012; Nabipour et al., 2014). However, other factors including suppressed appetite, changes in taste, lack of money, motivation and/or cooking facilities have also been noted (Varela et al., 1997; Neale et al., 2012). Unlike alcohol, drugs do not specifically compromise the structure of the GI tract; however, users do experience digestion and absorption difficulties, often through diarrhoea, constipation or vomiting (Neale et al., 2012). In addition, opioids reduce motility in the GI tract (White, 2010). Eating disorders are also prevalent among this population (Neale et al., 2012).

5. Relatedness of the physiology and psychology of nutrition and appetite to substance use disorders

There is considerable overlap in the biopsychological processes underlying substance abuse and eating behaviour: both behaviours share brain circuitry mediating reward, salience and motivation (Volkow et al., 2011); both are strongly influenced by emotional states and stress (Gibson, 2012; Martin et al., 2016; Vögele and Gibson, 2017); both involve consummatory and consumatory acts, and are ultimately expressions of appetite (Gibson and Desmond, 1999; Westwater et al., 2016). Moreover, they both follow similar laws that govern such habitual appetitive behaviours, such as learned control via classical and operant conditioning, context- and state-dependency, and subconscious expression (Gibson and Brunstrom, 2007; Gibson and Desmond, 1999; Heinz et al., 2016; Martin et al., 2016; Rogers, 2017). Furthermore, there is substantial overlap in personality traits, or other ‘common liabilities’, associated with risk of SUDs and of disorders associated with overeating (Davis, 2013; Krug et al., 2008; Vanyukov et al., 2012; Vögele and Gibson, 2017; Volkow et al., 2012); for example, reward sensitivity is associated with greater alcohol and cigarette consumption, as well as intake of fat-rich foods, in a non-clinical population (Tapper et al., 2015).

A defining feature of drugs of abuse is that they strongly activate brain dopaminergic, noradrenergic, serotonergic, opioidergic and cannabinoid pathways involved in pleasure, reward and motivation (Higgins et al., 2013; Richard et al., 2013). These same pathways underlie hedonic and motivational responses to eating (Hill et al., 2014; Morganstern et al., 2011), and are particularly responsive when experiencing palatable, energy-rich food while hungry (Goldstone et al., 2009), as befits the appetitive impact of such foods. Energy is the primary reinforcing quality in food, and the brain is exquisitely sensitive to its supply (Gearhardt et al., 2016; Hetherington et al., 2013; Peters et al., 2007). Increasingly, animal models of bingeing on sweet palatable food show addictive-like behaviour that is evidenced to be mediated by dopamine and endogenous opioid neurotransmitters in these brain circuits (Avena et al., 2011), and invariably requires both stress and hunger to be present (Boggiano et al., 2005; Gibson, 2012). Both overconsumption of energy-rich foods in such animal models, and the pleasantness and intake of palatable foods in human beings are reduced by non-specific opioid antagonists such as naloxone and naltrexone, and selective mu-opioid antagonists (Giuliano et al., 2012; Yeomans and Gray 2002): conversely, bingeing on palatable food by stressed and food-restricted rats can be enhanced by opioid agonists (Boggiano et al., 2005). There is also some evidence to suggest that behaviour similar to drug withdrawal manifests when access to sweet palatable foods is restricted (Avena et al., 2011), and that ‘bingeing’ on fat-rich foods can alleviate opiate withdrawal in rats (Bocarsly

et al., 2011) and enhance motivation to consume alcohol in mice (Blanco-Gandia et al., 2017). Furthermore, it has been argued that some foods, particularly those high in sugar, may have ‘addictive potential’ for some people (Davis et al., 2011); however, a ‘food addiction’ model is by no means universally accepted, and may instead represent highly motivated appetitive behaviour induced by intermittent access to rewarding nutritional stimuli when nutritionally depleted (i.e. ‘eating addiction’; Hebebrand et al., 2014; Rogers, 2017; Westwater et al., 2016).

The question arises whether examining these similarities in the biopsychology of appetite and substance use disorder can help further our understanding of the causes of malnutrition in substance use disorders, as well as the implications of nutritional therapy for substance use outcomes. For example, given that many subjects with AUD and DUD are malnourished, it is not surprising that they experience cravings, but it may be difficult for them to differentiate between urges to consume addictive substances and those driven by a need for food, i.e. “addiction transfer” (Brunault et al., 2015). Craving or seeking relief of need is a survival behaviour under the influence of the reward pathways in the brain (Carr, 2007; Volkow et al., 2011), which are themselves altered by nutritional need (Hetherington et al., 2013). Thus, food deprivation lowers the threshold for activation of reward pathways, increasing sensitivity to drugs of abuse as well as food (Aitken et al., 2016; Carr, 2007; Volkow et al., 2011), potentially further reinforcing consumption of either; conversely, cocaine abstinence devalues sweet taste, mediated by accumbal dopamine (Carelli and West, 2014). Nutrient deficiencies may also contribute to cravings or at least encourage drug seeking (Gibson, 2001), as nutrient depleted animals seek novel reinforcing experiences, mediated by brain dopamine activation (Costa et al., 2014; Keller et al., 2014), drink more alcohol (Stiglick and Woodworth, 1984) and prefer alcohol-paired flavours (Deems et al., 1986). Moreover, bariatric surgery patients, particularly those who have lost greater weight after the Roux-en-Y gastric bypass procedure, are at enhanced risk of SUD (Reslan et al., 2014), perhaps representing another example of addiction transfer. Conversely, subjects with AUD given nutrition counselling, who may have chosen to eat more or more regularly, had less alcohol craving and more periods of abstinence (Biery et al., 1991). These interactions between dependency and nutritional status, and the potential for induction of a feed-forward loop, are schematically illustrated in Figure 1.

5.1 Appetite-regulating hormones and substance use disorder

Expressions of appetite such as hunger and cravings are regulated by anorexigenic and orexigenic peptide hormones. Given the overlap already described between appetite for drugs, alcohol and food, it can be expected that substance use disorders can affect, and be affected by, these hormones (Goncalves et al., 2015; Hillemecher, 2011; Mysels and Sullivan, 2010). These interactions are now considered for the peripherally released but centrally active hormones ghrelin, leptin and insulin; although numerous other neurohormones could be involved, data in human addicts are scarce (Leggio et al., 2010).

5.1.1 Ghrelin

Ghrelin is an orexigenic peptide hormone that is primarily released from cells in the gastric mucosa. Blood levels of ghrelin normally rise in association with increasing hunger prior to a meal, then fall during and after eating, in line with the known suppression of ghrelin by ingestion of macronutrients (Al Massadi et al., 2017). In animal studies, ghrelin has been shown to increase alcohol intake and likewise ghrelin antagonists reduce intake (Gomez et al., 2015). Conversely, alcohol suppresses ghrelin production (Badaoui et al., 2008; Leggio et al., 2011), and subjects with AUD have been shown to have significantly lower ghrelin levels than controls in most research (Addolorato et al., 2006; Badaoui et al., 2008; de Timary et al., 2012; Gomez et al., 2015; Leggio et al., 2011), but not all (Kraus et al., 2005). Badaoui et al. (2008) reported a weak inverse correlation between plasma ghrelin, its release from stomach, and levels of alcohol consumption. This may reflect impaired nutritional status, but even so level of alcohol craving was positively related to ghrelin levels (Addolorato et al., 2006). Leggio et al. (2012) and Koopmann et al. (2012) similarly found that higher active ghrelin was associated with greater craving, and moreover ghrelin levels rose during abstinence. In animal studies, ghrelin levels were found to rebound after 30 days of abstinence (Gomez et al., 2015). Although the impact of nutritional status in these studies was not clear, reduced ghrelin production may increase risk of malnutrition by contributing to suppressed appetite, whereas its increase during abstinence may contribute to relapse in alcoholics, and thus ghrelin antagonists have been proposed as a treatment for AUD (Addolorato et al., 2006; Egecioglu et al., 2011; Koopmann et al., 2012; Leggio et al., 2012) and other DUD (Jerlhag et al., 2010). Nevertheless, the overlap between ghrelin and alcohol or drug craving, the rise in ghrelin during abstinence, and nutritional status and appetite remains to be explored in

detail and can be confounded by habitual levels of alcohol intake and associated shifts in metabolism (de Timary et al., 2012).

5.1.2 Leptin

Leptin, a peptide hormone that in part provides an anorexigenic signal of adipose tissue energy storage, appears to be affected differently in subjects with AUD and DUD. Subjects with AUD that have low to moderate alcohol consumption have been found to have higher levels of leptin even adjusted for BMI compared to matched controls (de Timary et al., 2012); at high levels of alcohol intake, body fat is reduced due to increased lipolysis and leptin levels are lower. Cocaine users were found to have decreased leptin levels which were possibly the result of increased glucocorticoid levels and lower fat mass (Billing and Ersche, 2015). Leptin levels were also found to be low in subjects with DUD (heroin) versus controls until after methadone treatment (Housova et al., 2005). Leptin levels in subjects with DUD were correlated with BMI and FM (Ersche et al., 2013), but for some this was only the case after methadone treatment (Housova et al., 2005) and possible weight gain, indicating disruption of leptin regulation by chronic drug abuse. In rat studies, central administration of high levels of leptin reduced food intake and increased sensitivity to drugs of abuse (Carr, 2007); moreover, increased leptin has also been shown to reduce heroin relapse (Mysels and Sullivan, 2010). Leptin also regulates hypothalamic endocannabinoids that alter appetite (Di Marzo et al., 2001). These findings support a link between food restriction, satiety signalling and drug intake. Hetherington et al. (2013) further support this position in their theoretical account of appetite and satiety, which includes both reward-based motivation and hedonic pleasure seeking, and their satisfaction by food ingestion, i.e. satiety is linked to modulation of reward pathways via neuroendocrine signalling.

5.1.3 Insulin

Both drug and alcohol use have been shown to result in insulin dysregulation, probably interacting with effects on leptin (Amitani et al., 2013), leading to both high insulin fasting levels (Mysels and Sullivan, 2010; de Timary et al., 2012; Nabipour et al., 2014; Billing and Ersche, 2015) and slow postprandial response (Mysels and Sullivan, 2010). Disruption of insulin regulation and consequent adverse effects on glycaemia could lead to increased drug or alcohol craving (Biery et al., 1991) and poor control of appetite and satiety (Strachan et al., 2004).

5.2 Sweet preference and substance use disorder

Reinforcement of consumption of substances of abuse and of sweet foods share the same reward pathways in the brain (Avena et al., 2009; Colantuoni et al., 2001; Leggio et al., 2011; Mysels and Sullivan, 2010; Spangler et al., 2004); specifically, activation of mu-opioid receptors occurs following dopaminergic signals from the ventral tegmental area (VTA) to the nucleus accumbens (Avena et al., 2009; Bonacchi et al.; Housova et al., 2005; Leggio et al., 2011; Morganstern et al., 2011; Mysels and Sullivan, 2010; Spangler et al., 2004). Thus, it has been proposed that any food that substantially stimulates DA in the VTA may become ‘addictive’ (Avena et al., 2009) at least in the sense of reinforcing subsequent consummatory behaviour towards that food (but see Hebebrand et al., 2014, and Rogers, 2017, for critiques of ‘food addiction’). Intermittent and excessive sugar feeding has been shown to change neurochemical pathways in the same way that addictive drugs do (Colantuoni et al., 2001; Avena et al., 2009), and people with high reward sensitivity show a preference for sweet and fat foods as well as increased alcohol consumption, binge eating and other addictive behaviours (Davis, 2013; Tapper et al., 2015). In rats, the increase in motivation to consume sucrose induced by ghrelin is dependent on VTA-accumbal DA whereas ghrelin-induced increase in chow intake is not (Skibicka et al., 2013).

Overall, substantial evidence supports a reliable enhanced preference for sweet foods in both subjects with AUD and DUD (Fenn et al., 2015; Himmelgreen et al., 1998; Janowsky et al., 2003; Krahn et al., 2006; Leggio et al., 2011; Levine et al., 2003; Saeland et al., 2011; Stickel et al., 2016). For example, sweet preference increases with exposure to opioids (Mysels and Sullivan, 2010), heroin users have been found to seek convenient, sweet foods and eat more sporadically (Varela et al., 1997; Neale et al., 2012), and methadone subjects often report a craving for sugar (Fenn et al., 2015; Peles et al., 2016). Saeland et al. (2011) found that 30% of dietary energy intake among the study population of subjects with DUD was comprised of added sugar and Mysels and Sullivan’s (2010) review reported that methadone patients had an increased consumption of sugary foods where sugar, similarly, accounted for 31% of intake. By comparison, recent dietary guidelines recommend an upper limit of 5% of total energy intake as added sugar, and current intakes in the UK rarely exceed 15% even for children (Public Health England, 2015a). Stickel et al. (2016) found that cravings for

chocolate increased significantly in the month following abstinence in subjects with AUD. Contrary to this, some research into cocaine users has shown preferences for high fat and carbohydrate-rich foods, but not sugary foods (Ersche et al., 2013); however, Janowsky et al. (2003) reported that cocaine dependent subjects preferred the highest level of sweetness in taste tests. Furthermore, young children who had both a family history of AUD and self-reported depressive symptoms showed the strongest preference for sweetness (Mennella et al., 2010). This is in line with considerable evidence associating negative moods with substance use disorders, cravings for and consumption of sweet tasting energy-rich foods (Gibson, 2012; Krug et al., 2008; Leggio et al., 2011).

This preference for sweet taste is not an absolute, but may be a marker for addictive tendencies. For AUD, Kampov-Polevoy et al. (2003) found that men with a genetic link to alcohol use disorder had a greater sweet preference than men with AUD without a genetic link. Similarly, animal models associating preferences for sweetness and alcohol suggest strong genetic determinants (Kampov-Polevoy et al., 1999). Furthermore, a preference for sweetness combined with a novelty-seeking personality markedly increased the risk of suffering from AUD (Lange et al., 2010). Krahn et al. (2006) found that the sweet preference among subjects with AUD declined following periods of abstinence. Levine et al. (2003) reported that heroin users had a higher affinity and cravings for sweet foods before using heroin than after, whereas opiate antagonists decrease sweet preference (Mysels and Sullivan, 2010) and individuals with AUD that initially have a greater liking for sweetness respond better to treatment with opiate antagonists (Laaksonen et al., 2011). Moreover, there is considerable evidence in animal models that sugar may to some extent substitute for rewarding drugs when they are not available (Avena et al., 2009; Colantuoni et al., 2001; Levine et al., 2003). These drivers to consume large amounts of sugar will likely result in dilution of nutritional quality of the diet in SUD.

6. Mood and nutrition

Individuals suffering from substance use disorders often have co-morbidities of anxiety, depression and other mental health diagnoses that could contribute to resistance to recovery (Tolliver and Anton, 2015). Essential nutrients play an important role in brain regulation of mood (Du et al., 2016), and so another potential influence on DUD and AUD is the impact of nutritional deficiencies on mood. Amino acids including tryptophan, phenylalanine and

tyrosine are important for neurotransmitter production, including serotonin (Ormstad et al., 2016) dopamine (Jongkees et al., 2015; O'Hara et al., 2016) and noradrenaline (Jongkees et al., 2015). While controversies remain in evidence that increased supplementation of amino acids can effectively combat mood disorders (Markus and De Raedt, 2011; Ormstad et al., 2016; Parker and Brotchie, 2011), several short-term studies show potential benefits of supplementation with tryptophan-rich proteins (Capello and Markus, 2014; Gibson et al., 2014; Mohajeri et al., 2015), and a recent analysis of NHANES data found that lower levels of depression were associated with higher dietary tryptophan intake in an adjusted model in US adults (Lieberman et al., 2016), indicating that sufficient levels of nutrients may benefit mood. This includes the provision of cofactors: serotonin production requires pyridoxine, zinc and chromium (Muss et al., 2016). Additional micronutrient research has shown that deficiencies in magnesium (Eby and Eby, 2006; Mlyniec et al., 2014), zinc (Mlyniec et al., 2014; Tyszka-Czochara et al., 2014), chromium (Mlyniec et al., 2014), selenium (Pasco et al., 2012), folate and B12 (Almeida et al., 2015) are linked to depression, while deficiencies in zinc, magnesium, and lithium are linked to anxiety (Mlyniec et al., 2014). In addition, low n-3 polyunsaturated fat levels have also been found to impact mood negatively in subjects with AUD and DUD, and be associated with relapse (Barbadoro et al., 2013; Buydens-Branchey et al., 2009).

7. Conclusion

There appears to be a consensus in the research literature that subjects with AUD and DUD are often malnourished and nutrient deficient; that substance use disorders affect nutritional status and body composition through poor nutrient intake, absorption and altered metabolism; that the evolutionary mechanisms that regulate survival behaviour, such as novelty and goal seeking and a drive to explore the environment, are activated by nutritional deprivation and, being dependent on mesocorticolimbic dopamine (Costa et al., 2014), are also affected by addictive substances synergistically with nutritional state (Keller et al., 2014); that the production of hormones that affect hunger are dysregulated by these same substances; and finally that mood is adversely influenced by nutritional insufficiency.

There does not appear, however, to be much research dedicated to addressing malnutrition in subjects with AUD and DUD in recovery, yet which may have a very real impact on the

progress of recovery for these individuals, a point echoed by Cunningham (2016). This lack of cohesive research means that it is likely that people in recovery are not receiving sufficient nutritional intervention despite many being malnourished. Even subtle imbalances in nutrition can lead to low mood and reduced energy levels, by altering hormone and monoamine function (Kaye, 2008). All these factors can reduce an individual's ability to recover by reducing their ability to withstand pain, and increasing their drive to seek reward, while addictive substances provide apparent relief from their needs, impairing self-determined nutritional recovery (see Figure 1). Simple dietary advice, for example focussing on consumption of sweet food, is unlikely to be effective (Krahn et al., 2006). Instead, our synthesis of the evidence highlights that it is important that the services that support individuals with substance use disorders begin to use the nutritional and psychological knowledge that is available to support recovery, and that more research is done to understand what efficacious and effective nutrition-related interventions can be implemented. To date, only a few small-scale and specific nutritional interventions in substance use disorder have been reported, whether to ameliorate psychological (Buydens-Branchey et al., 2008) or physical consequences (McCarty, 2013). We would suggest that interventions in recovery include rigorous nutritional assessment, treatment and monitoring, and that this in turn should be linked to indicators of recovery. Where evidence of particular nutrient deficits is available, appropriate supplementation should be recommended: in the early stages of recovery, use of a palatable drink to deliver multiple nutrients in an easily accepted form may be a practicable first step.

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Figure 1 Caption

A schematic illustration of the proposed feed-forward addiction-enhancing effect of deficient nutritional status on AUD and DUD that follows from the negative impact of SUD on food choice and eating behaviour. Rounded rectangles are behavioural states, ellipses are environmental influences, squared rectangles are nutrition-related consequences and effects. Arrows represent enhancing influences; darker shaded arrows form the feed-forward loop of nutritional influence. More details are given in section 5; N. Acc. DA: nucleus accumbens dopamine.

Table 1: Summary of key studies showing evidence of nutrient deficiency or inadequate nutrient intake in participants with substance use disorders

	Measures	n	Reference
Alcohol studies			
Vitamin A	Blood sample; diet quality and appetite questionnaire	76	Ross et al., 2012
Thiamine	7-day dietary recall	73	Boyd et al., 1981
	Blood serum; cerebrospinal fluid	59	Dastur et al., 1975
Riboflavin	Blood serum; cerebrospinal fluid	59	Dastur et al., 1975
Niacin	Blood serum; cerebrospinal fluid	59	Dastur et al., 1975
Vitamin B6	Blood serum; cerebrospinal fluid	59	Dastur et al., 1975
Folate	Blood sample	84	Wu et al., 1975
Vitamin C	7-day dietary recall	73	Boyd et al., 1981
Vitamin D	Blood sample	128	Quintero-Platt et al., 2015
	7-day food diary; blood sample	80	Wilkens Knudsen, et al., 2014
	Blood sample	181	Santolaria et al., 2000a
	7-day dietary recall	73	Boyd et al., 1981
Vitamin E	Blood sample	32	Tanner et al., 1986
Vitamin K	Blood sample	20	Iber et al., 1986
Magnesium	Blood sample	105	Dingwall et al., 2015
	7-day food diary; blood sample	80	Wilkens Knudsen, et al., 2014
Selenium	Blood sample	32	Tanner et al., 1986
Zinc	7-day food diary; blood sample	80	Wilkens Knudsen, et al., 2014

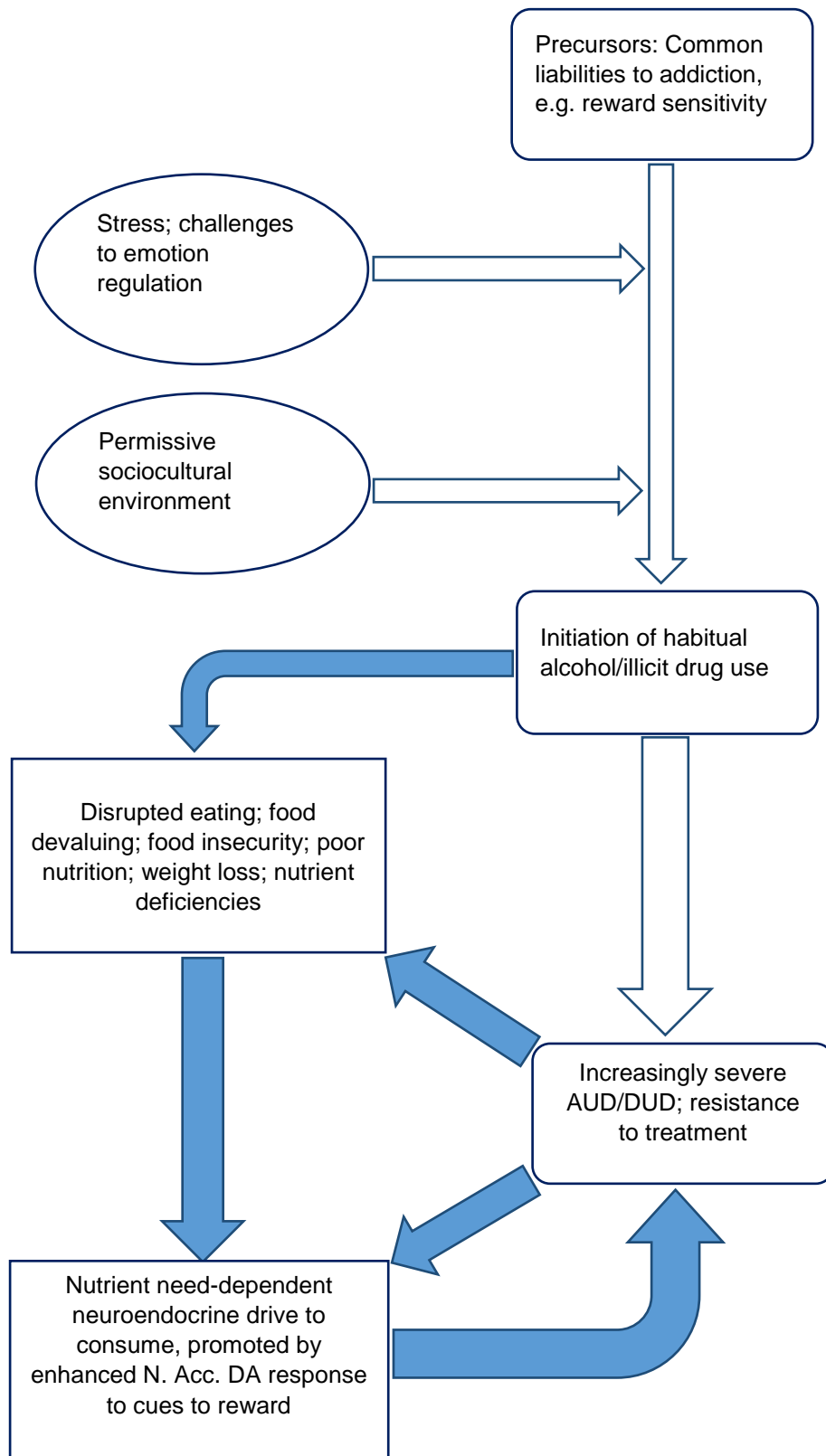
Table 1 continued**Drug studies**

Vitamin A	Blood sample; diet quality and appetite questionnaire	76	Ross et al., 2012
	Blood sample	253	Nazrul Islam et al., 2001
Thiamine	24-hour dietary recall; blood sample	195	Saeland et al., 2011
	Blood sample	149	el-Nakah, et al., 1979 *
Riboflavin	24-hour dietary recall; blood sample	195	Saeland et al., 2011
	Prospective food record questionnaire	62	Varela, et al., 2001
	Blood sample	149	el-Nakah, et al., 1979 *
Niacin	24-hour dietary recall; blood sample	195	Saeland et al., 2011
Vitamin B6	Prospective food record questionnaire	62	Varela, et al., 2001
	Blood sample	149	el-Nakah, et al., 1979 *
Folate	Prospective food record questionnaire	62	Varela, et al., 2001
	Blood sample	149	el-Nakah, et al., 1979 *
Vitamin B12	Blood sample	149	el-Nakah, et al., 1979 *
Vitamin C	24-hour dietary recall; blood sample	195	Saeland et al., 2011
	Blood sample	253	Nazrul Islam et al., 2001
Vitamin D	24-hour dietary recall; blood sample	195	Saeland et al., 2011
Vitamin E	Blood sample	253	Nazrul Islam et al., 2001
	Prospective food record questionnaire	62	Varela, et al., 2001

Calcium	24-hour dietary recall; blood sample	195	Saeland et al., 2011
Copper	24-hour dietary recall; blood sample	195	Saeland et al., 2011
Iron	Blood sample	253	Hossain et al 2007
Magnesium	24-hour dietary recall; blood sample	195	Saeland et al., 2011
	Prospective food record questionnaire	62	Varela, et al., 2001
Zinc	Prospective food record questionnaire	62	Varela, et al., 2001

Table compiled from key papers published in the last two decades as well as highly cited studies carried out earlier that provided unique evidence, with sample sizes of at least 20. * Study included heroin users only.

FIGURE 1:



Highlights:

- Malnutrition is prevalent among individuals with alcohol and drug use disorders.
- There is a lack of guidance on nutritional therapy for those recovering from substance use disorders.
- Addiction and appetite share underlying brain and behavioural processes so are likely to interact.
- Malnutrition in substance use disorders could promote drug-seeking and impede recovery.
- Effective treatments should incorporate nutritional assessment and therapy.

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KDJ led the review of impact of substance misuse on nutritional status and drafted the abstract and conclusion. ELG led the review of relevance of nutritional status to biopsychology of appetite and addiction. Both authors edited the complete manuscript (original submission and revision), and have approved the final version for submission.

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