An evaluation of different methodologies employed to investigate the effects of mixing alcohol with energy drink

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Published work and a critical commentary submitted in partial fulfilment of the requirements of the University of the West of England, Bristol for the degree of Doctor of Philosophy by publications (DPhil)

Section A: Commentary

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Firstly, I would like to thank my supervisors for their invaluable support and guidance. Associate Professor Chris Alford ignited my interest in Psychopharmacology and provided me with my first research experience, as well as the opportunity to embark on this journey. Without his unwavering support, expert knowledge and limitless patience this submission would not be possible. I would also like to thank Professor Joris Verster for his constant source of advice and encouragement to aim higher, and Dr Karina Stewart for always providing an impartial and detailed review of the research process.

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Lastly, this work is dedicated to the memory of Freddie and Monnie – forever in my heart!

Supervisory team

Director of Studies: Associate Professor Chris Alford

Second Supervisor 1: Dr Karina Stewart

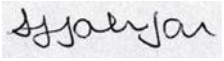
Second Supervisor 2: Professor Joris C Verster

Declaration of authorship and training

I confirm that all of the work presented in this doctoral thesis, including the selected publications and accompanying commentary (except where stated), is the original work of the author.

I confirm that none of the published body of work included within this portfolio of publications has been submitted for another academic award in this or any other institution.

I confirm that the necessary training requirements have been met (60-120 credits, of which at least 60 are at Level M – please see appendix 1).



Sean James Johnson, 2023

Abstract

The increase in popularity of AMED consumption among young people in the past decade has led to public health concerns regarding its use. It has been suggested that the stimulant effects of caffeine in energy drinks may counteract the sedative effects of alcohol, resulting in consumers feeling less impaired and less intoxicated than they actually are, and therefore more likely to consume further quantities of alcohol and engage in risker behaviour. However, the early research supporting this theory has several limitations.

To advance the scholarship of AMED research, the publications included in this thesis have provided sequential methodological improvements to better inform the safety of its use. The findings have been broadly consistent across the different methodologies employed. AMED consumers have been shown to differ from AO consumers across a range of characteristics, including higher alcohol intake and risk-taking behaviours. However, within-subject comparisons have indicated that among AMED consumers mixing alcohol with energy drinks does not significantly increase total alcohol consumption, subjective intoxication or negative alcohol-related consequences compared to consuming alcohol alone.

This thesis proposes that AMED consumption may be one of several manifestations of an underlying trait for greater alcohol consumption along with a cluster of other risky behaviours. Therefore, AMED use may be a valuable indicator for healthcare practitioners to identify individuals who may benefit the most from risk and harm reduction strategies for excessive alcohol consumption per se. However, the research findings to date do not justify the restriction of AMED over other forms of alcohol.

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Abbreviations

AHRG – Alcohol Hangover Research Group

AS – Professor Andrew Scholey

AT – Professor Alan Tapp

AMED – Alcohol Mixed with Energy Drinks

AMOB – Alcohol Mixed with Other non-alcoholic Beverages

AO – Alcohol-Only

BAC – Blood Alcohol Concentration

CA – Associate Professor Chris Alford

CTR – Centre for Trials Research

EMA – Ecological Momentary Assessment

KS – Dr Karina Stewart

JV – Professor Joris Verster

LTE – Letter to the Editor

NUS – National Union of Students

QAA – Quality Assurance Agency

RCT – Randomised controlled trial

SAE – Serious Adverse Event

SB – Dr Sarah Benson

StAR – Student and Alcohol Research group

UWE - University of the West of England

Chapter 1: Introduction

1.1 Requirements of the UWE Bristol DPhil by publication award

Qualification descriptors are used in Higher Education to describe the relative intellectual demands, complexity, depth and independent learning associated with a particular level of learning. The qualification descriptors for the DPhil by publication award at UWE Bristol are aligned with guidelines set out by the Quality Assurance Agency (QAA) for Higher Education (QAA, 2015). The award of a doctorate at UWE Bristol requires the postgraduate researcher to demonstrate that they:

- have conducted enquiry leading to the creation and interpretation of new knowledge through original research or other advanced scholarship, shown by satisfying scholarly review by accomplished and recognised scholars in the field.
- can demonstrate a critical understanding of the current state of knowledge in that field of theory and/or practice.
- show the ability to conceptualise, design and implement a project for the generation of new knowledge at the forefront of the discipline or field of practice including the capacity to adjust the project design in the light of emergent issues and understandings.
- can demonstrate a critical understanding of the methodology of enquiry.
- have developed independent judgement of issues and ideas in the field of research and / or practice and are able to communicate and justify that judgement to appropriate audiences.
- can critically reflect on their work and evaluate its strengths and weaknesses including understanding validation procedures.

The DPhil by publication is assessed as meeting the above criteria via the submission of a collection of published work together with a critical commentary setting out the nature and significance of the

collection as a whole in terms of its contribution to new knowledge within the subject field, and a viva voce (oral) examination.

1.2 DPhil objectives

The objective of this DPhil by publication is to evidence how my research has contributed new knowledge in the field of alcohol mixed with energy drinks, testing and building upon previous methodologies used and adding to the public health debate on the safety of its use. In order to demonstrate how my research has consistently met the UWE Bristol doctoral descriptors listed above, I will provide a critical commentary on a coherent collection of ten peer reviewed publications that have been generated from two systematic/critical reviews and meta-analyses and three sequential research studies. This critical commentary will include a synthesis of the evidence generated as well as an examination of the strengths and limitations of this published work and suggestions for future research. I will also reflect on my wider research achievements during and beyond my doctoral journal and how I have developed as an independent researcher.

Table 1. Citations of works submitted in support of DPhil by publication award

Publication number	**Citation**
1	Verster, J. C., Benson, S., **Johnson, S. J.,** Scholey, A., & Alford, C. (2016). Mixing alcohol with energy drink (AMED) and total alcohol consumption: a systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, 31(1), 2-10.
2	**Johnson, S. J.,** Alford, C., Stewart, K., & Verster, J. C. (2016). A UK student survey investigating the effects of consuming alcohol mixed with energy drinks on

	overall alcohol consumption and alcohol-related negative consequences. *Preventive Medicine Reports*, 4, 496-501.
3	**Johnson, S. J.,** Alford, C., Verster, J. C., & Stewart, K. (2016). Motives for mixing alcohol with energy drinks and other non-alcoholic beverages and its effects on overall alcohol consumption among UK students. *Appetite*, 96, 588-597.
4	**Johnson, S. J.,** Alford, C., Stewart, K., & Verster, J. C. (2018). Are energy drinks unique mixers in terms of their effects on alcohol consumption and negative alcohol-related consequences? *International journal of general medicine*, 11, 15.
5	Benson, S., **Johnson, S. J.,** Alford, C., Scholey, A., & Verster, J. C. (2021). A Cross-Cultural Comparison of the Effects of Alcohol Mixed with Energy Drink (AMED) Consumption on Overall Alcohol Consumption and Related Consequences. *International Journal of Environmental Research and Public Health*, 18(14), 7579.
6	**Johnson, S. J.,** Benson, S., Scholey, A., Alford, C., & Verster, J. C. (2021). Risk-taking behavior and the consumption of alcohol mixed with energy drink among Australian, Dutch and UK students. *International journal of environmental research and public health*, 18(10), 5315.
7	**Johnson, S. J.,** Verster, J. C., & Alford, C. (2022). An on-premise study to investigate the effects of mixing alcohol with caffeinated beverages. *Brain and behavior*, e2445.
8	**Johnson, S. J.,** Verster, J. C., & Alford, C. (2022). A Comparison Between Ecological Momentary Assessment and the Adapted-Quick Drinking Screen: Alcohol Mixed with Energy Drinks. *Alcohol and Alcoholism.*

9	Verster, J. C., Benson, S., **Johnson, S. J.,** Alford, C., Godefroy, S. B., & Scholey, A. (2018). Alcohol mixed with energy drink (AMED): A critical review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, 33(2), e2650.
10	Scholey, A., Benson, S., **Johnson, S.J.,** Alford, C., Godefroy, S. B., & Verster, J. C. (2018). Why meta is better: A reply to Linden-Carmichael et al. (2018). *Human Psychopharmacology*, 33(4).

Notes: Co-author signed statements of intellectual contributions to works submitted can be found in Appendix 2.

Chapter 2: An overview of career to date and development of research interests

This chapter provides an overview of my career to date and charts the chronological development of my research interests which have informed the content of this submission. In doing so, I demonstrate how I have developed as a researcher and become an active member of the research community, both within the topic of alcohol and energy drinks and further afield.

Whilst studying Psychology at A level I became fascinated by the human mind. I was interested in gaining knowledge of mental processes that allowed me to understand how we all think, act and feel. I was intrigued by what might cause someone to behave in a different way to others, or how their behaviour differed depending on the situation. This passion continued as I progressed to study a BSc Psychology degree at UWE Bristol in 2007, graduating with first class honours in 2010. It was during my final year that I was introduced to Psychopharmacology by Associate Professor Chris Alford (CA). Studying the effects of drugs on the brain allowed me to gain an understanding of how behaviours, feelings and cognition could be improved or impaired by different substances. My dissertation project investigated the actual and perceived effects of caffeine on mood and performance is sleep restricted states. This was my first experience of conducting independent research with the support of my supervisor. I learnt a lot during this process on research design, data collection, analysis and reporting. I presented the findings at the annual British Association of Psychopharmacology conference (Alford & Johnson, 2011) which provided a great opportunity to network with leading scholars in my field of interest. Following my degree, I was extremely fortunate to be offered the opportunity to continue contributing to CA's research group as a Research Assistant on studies investigating the effect of caffeine on human performance and mood.

This experience inspired me to pursue a career as a researcher, but opportunities were few and far between. I therefore began a related position working as a Pharmacovigilance Safety Officer at the Wales Cancer Trials Unit, Cardiff University in 2011. In this role I was responsible for recording, coding and reporting of Serious Adverse Event (SAE) data for clinical trials and assessing the

ongoing safety profile of the given treatment. I kept in regular contact with CA and in 2014 he informed me about a potential PhD studentship. I applied, and on route to my daughter's birth a few weeks later I received a phone call to say I had been successful. That car journey was life-changing in more ways than one!

The PhD studentship was sponsored by Red Bull GmbH and supervised by CA, alongside Dr Karina Stewart (KS) and Professor Joris Verster (JV). The initial aim of the studentship was to investigate caffeine consumption, safety, effects and benefits during popular consumption occasions. Based on emerging literature the consumption occasions of interest were when mixed with alcohol and for sports performance and were planned to be investigated using surveys, focus groups and laboratory studies.

As explained in more detail below and illustrated in the publications submitted as part of this DPhil, there was growing public interest and academic debate regarding the effects of mixing alcohol with energy drinks. Following my preliminary planned study which examined prevalence, motivations and consequences of mixing caffeine with alcohol via a UK-wide survey (project 2), I became immersed in this debate. I developed a personal desire to pursue this area of research further and was fortunate to be supported by both the sponsor and my supervisory team. The research became an iterative process with one study leading logically on to the next as the academic debate unfolded. Novel methodologies (projects 3 and 4) were applied to address the shortcomings of previous studies.

Within a few months of beginning my PhD studentship I was invited to provide teaching support in the Department of Health and Applied Sciences. This initially involved the facilitation of seminars, workshops and practical's but soon progressed to an Associate Lecturer position where I was responsible for lecture delivery and module leader duties. I taught to a wide range of levels, including foundation degree (People & Social Science), degree (Mind, Brain and Development, Psychopharmacology) and postgraduate (MSc Public Health). I also assisted in the supervision of students for their dissertation projects. I thoroughly enjoyed teaching and the challenges it presented.

I continued to progress my research and completed data collection (project 3 and 4) whilst balancing my teaching commitments. Given the competitive and dynamic area of research and the new methodological techniques employed in my research, myself and my supervisors felt that it was important to be quick with publishing research findings to keep a pace with the academic debate. We therefore decided to prioritise dissemination of findings, including international conferences, and switch from a standard PhD to a part-time DPhil.

This allowed me to continue teaching and also take up an additional position as the Alcohol Impact Research Lead for UWE Student Union in 2015. Alcohol Impact is an accreditation programme run by the National Union of Students (NUS) which aims to embed social norms of responsible drinking on campus, changing attitudes towards alcohol, and building healthier, safer, more productive student communities. I was responsible for developing collaborative research, interventions and initiatives between university and student union departments, as well as external stakeholders such as Bristol City Council and night-time entertainment venues. In collaboration with the NUS, I also took the lead in developing the Student Alcohol Research (StAR) group which brought together researchers across different universities to share ideas and best practice. I was involved in organising the first conference in the UK that focused on students' relationship with alcohol. This included assessing abstracts for suitability for presentation and approaching guest speakers for presentations. The conference was a good opportunity for delegates to share and expand their knowledge, as well as deepen their understanding of Alcohol Impact and how they could possibly get involved.

Alongside the focused research that formed the publications included in this DPhil submission, I also developed an interest in alcohol hangover research. My supervisors, CA and JV, were founding members of the Alcohol Hangover Research Group (AHRG), so it was a natural progression for me to include alcohol hangover outcomes within my own research and also become involved in other hangover projects. As can be seen in my bibliography of published works and conference presentations (Appendix 3) I regularly presented my research findings at the annual AHRG conference and co-authored a number of papers on this topic. I also contributed to media reports on

alcohol hangovers which was a great learning opportunity in summarising research findings for lay audiences.

Some of the research I was involved in investigated the effects of alcohol hangover on next day driving performance. In conducting this research, I developed skills in collecting data using driving simulators, and passed this on to students to conduct their third-year dissertation projects.

At the end of 2017 I was approached by Professor Alan Tapp (AT) from UWE Business School, to see if I would be interested in a Research Fellow position on a road safety intervention that aimed to reduce collisions among young male drivers from deprived backgrounds. The intervention was called Wheels, Skills and Thrills (WST2) and was a development of a pilot study (WST) that showed promise that advanced driver training could reduce risky driving behaviour. I took up the position and was responsible for the overall trial management of the project, from protocol development, recruitment, data collection and analysis. A key outcome of the project was that I worked with industry to develop new in-vehicle telematics research methods and analysis techniques. The project was a collaboration with research partners including the Institute of Advance Motorists, Department for Transport, Road Safety Trust and Co-Investigators from the Transport Research Laboratory, University College London and Loughborough University. I was responsible for communicating project progress and outcomes including periodic reporting to trial management group, trial steering group, sponsors and Government departments. I also presented the research findings at a national conference (see Appendix 3).

In 2019 I left UWE Bristol to begin a new chapter in my research career as a Data Manager at Cardiff university. The position was based in the Centre for Trials Research (CTR) and my role involved working as part of a wider study team, including trial managers, statisticians, and chief investigators, to successfully deliver clinical trials, and other well-designed studies, from trial design through to publication, trial closure and archiving. I was specifically responsible for the planning and implementation of data management processes and systems across a diverse range of clinical trials, including blood cancer, learning disability and road safety. More recently (January 2022) I have

transitioned into a Data Analyst role, where I work closely with study statisticians on data cleaning and analysis for trial, reports, presentations and publications in high quality journals.

Since completing data collection in 2018 and the submission of this DPhil, time has been spent drafting manuscripts and negotiating the peer review process for the publications included herein, whilst also maintaining a full-time research position. I feel fortunate for the opportunities that have presented themselves during my doctoral journey and the flexibility to pursue interests as they emerged. Whilst I am relieved to have finally reached my goal in submitting this thesis, I am very much looking forward to expanding on my experiences and skills learnt thus far and continuing to develop my career as a researcher.

Chapter 3: Background

This chapter provides background and context for the subsequent critical commentary and demonstrates my *critical understanding of the current state of knowledge in this field of theory and/or practice*, the second doctoral descriptor.

3.1 Alcohol

Alcohol, also known as ethanol, is a psychoactive substance that has been consumed recreationally in in many cultures for centuries. Worldwide in 2016, 2.3 billion people identified as current drinkers, with alcohol being consumed by more than half of the population in three World Health Organization (WHO) regions – the Americas, Europe and Western Pacific (World Health Organization, 2019). In 2017, 57% of adults (16 years and older) in the UK reported drinking alcohol in the previous week, equating to approximately 29.2 million people (Office for National Statistics, 2018a). The average annual consumption of alcohol is 9.7 litres of pure alcohol per adult (15 years and older) in the UK, above the average per capita consumption of 25 other OECD countries (OECD, 2022). These statistics indicate that the majority of people in the UK drink alcohol, and for many it is associated with positive aspects of life, such as relaxing in the company of friends and family.

The consumption of alcohol has been shown to have some protective health benefits. For example, research has indicated a 25-40% reduced risk of heart attacks, ischemic stroke, peripheral vascular disease, and death from cardiovascular causes when alcohol is consumed light to moderately (Goldberg et al, 2001). Occurrence of gallstones (Grodstein et al, 1995; Leitzmann et al, 1999) and type 2 diabetes (Djoussé et al, 2007; Koppes et al, 2005) has also been shown to be less likely to occur in moderate compared to non-drinkers. However, a recent systematic analysis (Griswold et al, 2018) has concluded that the level of consumption that minimises health loss due to alcohol use is zero, with any potential health benefits from alcohol being outweighed by the negative effects. This has led to calls for countries to revisit their alcohol policies to lower population-level consumption.

This contention is supported by the alcohol consumption rates in the UK, which indicate that many people consume alcohol above the levels that have shown to have protective health effects. For example, 28% of men and 14% of women drink alcohol at increasing and higher risk levels (above 14 units per week) (NHS Digital, 2019) . Thus, common alcohol consumption practices among people in the UK are at a level of diminished return and increased risk, where the potential benefits are significantly outweighed by the negative consequences of consuming in excess.

Of particular concern is the prevalence of heavy episodic or binge drinking. The National Health Service (2019) defines this as consuming more than eight units of alcohol in one drinking occasion for men, and more than six units of alcohol for women. Research by the World Health Organisation (2014) found that Britain is one of the worst countries in the world for binge drinking, ranked 13th out of 196 countries, with 28% of Britons classed as having had an episode of heavy drinking in the previous month - twice the global average. Binge drinking is particularly prevalent among young people (16-24 year olds). Whilst young people are less likely to have consumed alcohol in the past week, they are more likely (37.3%) than any other age group to have "binged" on their heaviest drinking day (Office for National Statistics, 2017). These reported high rates of alcohol consumption present a serious social and public health problem that have wide ranging consequences.

In order to research alcohol consumption practices and their associated consequences it is important to understand alcohols pharmacokinetic and pharmacodynamic properties. Alcohol is consumed orally and as it is a small water soluble molecule it is absorbed from both the stomach (20%) and small intestine (80%) (Paton, 2005). There are a lot of factors that affect the rate of absorption, including gastrointestinal functioning, food intake, emotional state, exercise and type of drink consumed (Paton, 2005). Alcohol is metabolised in several stages involving the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Firstly, alcohol dehydrogenase and a co-factor, nicotinamide adenine dinucleotide (NAD), covert alcohol to acetaldehyde. This is then converted by aldehyde dehydrogenase into acetic acid, which is eventually broken down into carbon dioxide and water for easy elimination from the body. The bioavailability of alcohol is reduced by first pass metabolism (FPM), mainly via oxidation by ADH in the liver hepatocytes (Kent, 2012). The proportion of alcohol

that escapes FPM is rapidly distributed throughout the body tissues via the blood stream until an equilibrium between Blood Alcohol Concentration (BAC) and tissue concentration is reached, usually within 1 to 2 hours (Ferreira & Willoughby, 2008). The rate of metabolism and elimination is dependent on intra and inter-individual factors (Eckardt et al, 1998).

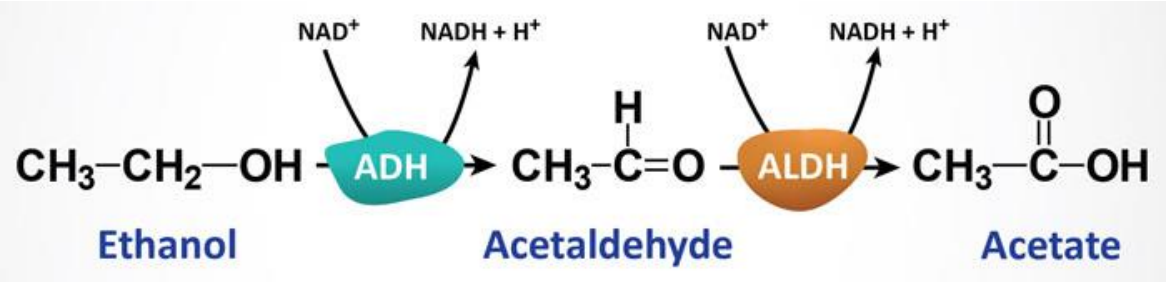

Figure 1. Visual summary of alcohol metabolism stages. Reproduced with the permission from thmedicalbiochemistrypage, LLC

The concentration of alcohol rises quickly within the central nervous system (CNS). This is because the brain receives a large proportion of total blood flow and alcohol readily crosses the blood-brain barrier. Alcohol has a wide spectrum of action within the CNS with different regions affected differently by dose (Rivers, 1994). It affects a large number of membrane proteins that participate in signalling pathways, including neurotransmitter receptors, enzymes and ion channels (Masters et al, 2009). The effects of alcohol have mainly focused on glutamate and gamma-aminobutyric acid (GABA), the main excitatory and inhibitory neurotransmitters in the CNS. Acute alcohol consumption inhibits functioning of excitatory glutamatergic neurotransmission by depressing the responsiveness of ion channels. In particular, acute alcohol inhibits the ability of glutamate to open the cation channel associated with N-methyl-D-aspartate (NMDA), a subtype of glutamate receptors. This action also reduces NMDA-induced release of other neurotransmitters, such as dopamine, norepinephrine and acetylcholine (Julien et al, 2011; Mukherjee et al, 2008a). These disruptions to normal functioning are implicated in many aspects of cognitive functioning, including “black-outs” or memory loss whilst under the influence of alcohol.

Acute alcohol consumption also has direct inhibitory effects. It increases GABA transmission by increasing chloride ion flow. This decreases the activity of the neuron resulting in behavioural change,

such as increases in sedation and muscle relaxation and decreases in cognitive, motor and attentional skills (Julien et al, 2011; Mukherjee et al, 2008b). Alcohol also interacts with the mesolimbic dopamine reward pathways and this mechanism of action has been suggested to contribute to the process of addiction (Lovinger, 2008).

Alcohol has biphasic effects on the subjective experience of stimulation and sedation across the BAC curve (Addicott et al, 2007). Initially, stimulant effects are reported during absorption as blood alcohol levels are rising, followed by depressant-like sedative effects as blood alcohol levels are falling (Holdstock & de Wit, 1998; Martin et al, 1993; Sutker et al, 1983). Peak BAC levels are dependent on a number of factors including processing rate, speed and type of alcohol consumed, food intake, tolerance and family history. The pharmacological effects of alcohol at the levels reported among UK students cause impairments in cognitive and psychomotor processes. This places alcohol consumers at increased risk of experiencing harm.

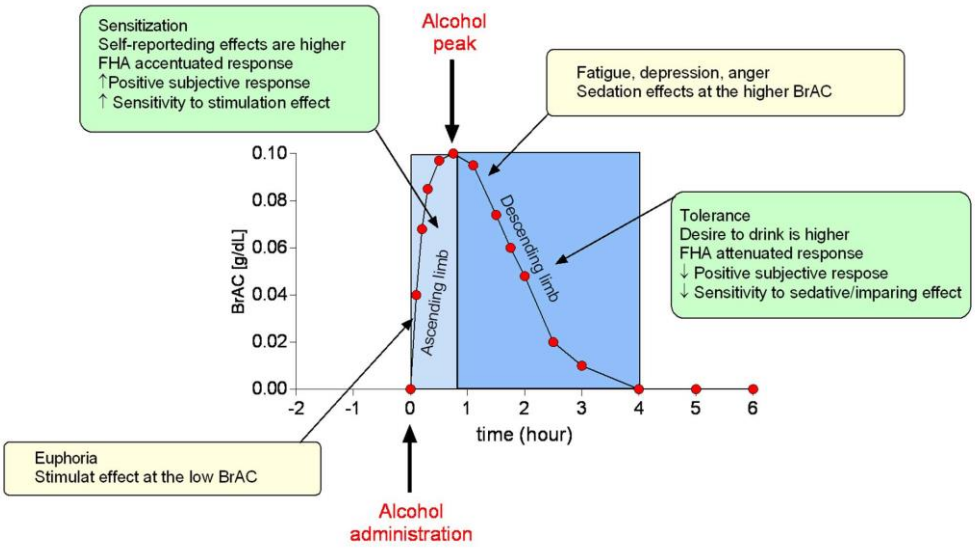

Figure 2. Alcohol-related biobehavioural and mood response within the biphasic effects of alcohol (Haass-Koffler & Perciballi, 2020)

Notes: Alcohol-related biobehavioral response (green boxes): ascending limb (greater positive subjective response and increased sensitivity to stimulating effects due to alcohol); descending limb

(lower negative subjective response and decreased sensitivity to sedative or impairing effects due to alcohol). Mood-related response (yellow boxes): euphoria with stimulation at the low BAC level; fatigue, depression, anger with sedation at the higher BAC level. Hypothetical BAC curve after one standard drink designed to reach to 0.1 g/dl, with peak reached between 30 and 90 min after alcohol administration.

Research has consistently demonstrated increased risk-taking following consumption of high levels of alcohol, including riskier driving (Holloway, 1995; Starmer, 1989; Verster et al, 2009), sexual risk-taking (Fromme et al, 1999), gambling (Barnes et al, 2002; Desai et al, 2006), drug use (Degenhardt et al, 2001), and aggressive and antisocial behaviours (Komro et al, 2000).

Increased risk-taking from excessive alcohol consumption has detrimental effects on society. Crime is frequently committed whilst under the influence of alcohol. In 2017, alcohol related crime accounted for 464,000 of the total 1.2 million 'violence against the person' offences recorded by police (Office for National Statistics, 2018c). In 2016/2017 in England and Wales, in 35.8% of sexual assault cases and 21.5% of hate crimes the victim believed the offender to be under the influence of alcohol (Office for National Statistics, 2018b). Crime is also commonly committed as a means to finance an alcohol addiction. For example, in 2017/2018 in England and Wales, in 24% (39,00 incidents) of robbery cases the victim believed the offender to be under the influence of alcohol (Office for National Statistics, 2020). Only a small minority of adults (18%) estimated to be in need of specialist treatment for alcohol dependency are receiving it (Public Health England, 2019). Despite this, alcohol dependency places a significant financial burden upon society with prescriptions to treat alcohol dependency costing £4.42 million a year, just under double the level 10 years ago (NHS Digital, 2018).

Problematic alcohol consumption can also lead to absenteeism. Alcohol-related sickness is estimated to cause 17 million lost working days each year in the UK (Human Resource Management, 2007). Alcohol consumption can also cause reduced productivity, performance and safety in the workplace, due to next day hangover effects, with a third of employees admitted to having been to work with a

hangover (MEPMIS, 2003). The total annual cost of alcohol to employers is estimated to be £7.3 billion a year (Lister et al, 2008).

Alcohol misuse can have a significant negative impact on health. It is the biggest risk factor attributable to early mortality, ill health and disability for those aged 15-49 years old in England (Forouzanfar et al, 2016). NHS Digital (2020) reported that in 2018/2019 there were almost 1.3 million estimated admissions where the primary reason for hospital admission or a secondary diagnosis was linked to alcohol. Of these, the main reason for admission to hospital was attributable to alcohol in 358,000 admissions. The biggest causes of these admissions were accidents and injuries, cancer, mental and behavioural disorders, cardiovascular disease and alcoholic liver disease respectively. There were 5,698 alcohol-specific deaths, with twice as many men than women. Thus, alcohol places a significant strain on the National Health Service (NHS).

In summary, whilst alcohol is consumed by the majority of the UK population, acute intoxication following excessive intake causes wide-ranging personal and social issues. It places a burden upon the UK economy with (Public Health England, 2016) estimating total cost of alcohol to be 1.3% of the gross domestic product (GDP), equivalent to £28.6 billion in 2021. Therefore, research which examines the factors that may contribute to this excessive consumption practice is necessary in order to improve the health, societal and economic consequences.

3.2 Energy drinks

Inspired by functional beverages in the Far East, energy drinks in their current form only became popular following the introduction of Red Bull® to the market in the late 1980's and the subsequent proliferation of brands. Energy drinks are non-alcoholic beverages designed to provide a boost of energy and enhance alertness and performance at times of fatigue. Since the turn of the century the consumption of energy drinks, particularly among young adults, has become popular worldwide. In 2019, UK sales of energy drinks grew by 3.9%, with a market worth over £2 billion (British Soft Drinks Association, 2019). The annual increase in energy drink sales in the UK indicate that energy drinks do not seem to be a transient trend in the soft drinks market. However, despite this growth,

energy drinks still represent only a small proportion of total beverage consumption, occupying just 5% of the total soft drinks market (British Soft Drinks Association, 2019).

Adolescents and young adults represent the majority of energy drink consumers (Heckman et al, 2010). The popularity amongst this cohort reflects the functional appeal of energy drinks matching their lifestyles and motivations (Attila & Çakir, 2011; Buxton & Hagan, 2012). The majority of research that has investigated the prevalence of energy drink use has focused on university students from the Unites States, Europe or Australia. These studies indicate a wide range of reported energy drink use amongst students, with past-month use ranging from 39% to 57% (Malinauskas et al, 2007; Miller, 2008; Oteri et al, 2007). The primary motivations for use have included to combat insufficient sleep, increase energy whilst studying, when driving long distances and to reduce alcohol hangover effects (Malinauskas et al, 2007).

Energy drink ingredient composition and quantity can vary according to brand preference and to the country's regulatory guidelines, but the main constituents include caffeine, taurine, guarana, sugar, sodium and vitamin B6 (Ishak et al, 2012). Some brands also include glucuronolactone, ginseng, ginkgo biloba, amongst other ingredients (Higgins et al, 2010).

Caffeine (1, 3, 7-trimethylxanthine) is the most commonly used behaviourally-active substance in the world (Giles et al, 2012). It is a naturally occurring chemical compound found in plant constituents such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut, and has a long history of human consumption. The reasons for caffeine's popularity lies in its psychostimulant properties which promote behavioural functions, such as vigilance, attention, mood and arousal (Fisone et al, 2004). Caffeine stimulates the central nervous system by acting as a non-selective adenosine receptor antagonist. Adenosine receptors modulate release of central nervous system neurotransmitters, generally exerting sedative, depressant, and anticonvulsant actions. Consequently, caffeine's function as a competitive inhibitor results in the release of norepinephrine, dopamine, and serotonin, producing a moderate stimulant and mood-enhancing effect. Blockade of the A_{2A} receptor by caffeine inhibits the sleep promoting effect with adenosine levels increasing across the hours of wakefulness, thus

increasing arousal and alertness at times of fatigue (Davis et al, 2003; Ferré, 2008; Huang et al, 2007; Landolt, 2008; Sturgess et al, 2010).

When consumed orally via energy drinks, caffeine is absorbed rapidly, reaching peak absorption 15 to 45 minutes after ingestion, with a plasma half-life of 5 to 6 hours (Smith, 2002). This can vary widely based on age, body weight, pregnancy status and medication use amongst other factors. Energy drinks come in different sizes with varying amounts of caffeine and other ingredients, but a typical energy drink contains 80mg of caffeine per 250ml. This is equivalent to the caffeine content of an espresso or two cans of cola, and less than a cup of filter coffee. Therefore, as can be seen in figure 3, the caffeine content of energy drinks does not vary widely from more traditionally consumed beverages.

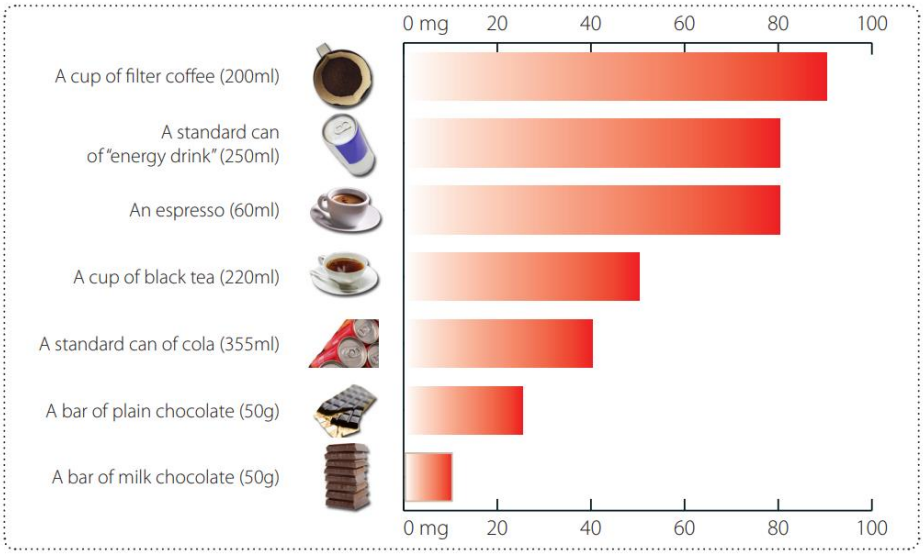

Figure 3. Caffeine content of commonly consumed beverages and food items (European Food Safety Authority, 2015)

Note: values provided are approximates as caffeine content and portion sizes vary within and between countries.

Research has consistently shown that moderate consumption of caffeine can have beneficial cognitive effects including improving attention (Lorist et al, 1994; Smith et al, 1994), information processing (Haskell et al, 2005; Lorist et al, 1994), working memory (Haskell et al, 2005) and vigilance (Brice & Smith, 2002; Childs & de Wit, 2006; Koelega, 1993). Caffeine has also been shown to decrease

subjective ratings of fatigue, and improve feelings of wellbeing, happiness, energy, alertness and sociability (Childs & de Wit, 2006; Haskell et al, 2008; Haskell et al, 2005; Yeomans et al, 2002). However, the beneficial effects of caffeine are dose dependent, with increasing amounts causing diminished improvements or even poorer performance (Attwood et al, 2007; Brice & Smith, 2002; Lorist & Tops, 2003). The state of caffeine withdrawal also has an effect on the performance enhancing benefits of caffeine (Rogers et al, 2005).

Some of the other main ingredients in energy drinks have also been shown to have beneficial effects. Energy drinks tend to contain high concentrations of sugars (glucose and sucrose) which are major sources of fuel required for the normal functioning of the central nervous system (Clauson et al, 2008). Research has shown that glucose can enhance cognitive performance on tasks of memory (Foster et al, 1998; Sünram-Lea et al, 2002), reaction time (Owens & Benton, 1994), rapid visual information processing (Benton et al, 1994; Donohoe & Benton, 1999), mental arithmetic (Kennedy & Scholey, 2000; Scholey et al, 2001) amongst other cognitive domains and practical tasks such as driving (Brice & Smith, 2001). This is particularly the case when performing demanding tasks where the processing load is high (Scholey et al, 2001).

Another widely used ingredient in energy drinks is taurine. Taurine is a nonessential sulphur-containing amino acid thought to play a role in metabolic processes. It is the most abundant amino acid and is associated with a variety of physiological functions including neuromodulation, neuroprotection, osmoregulation, cell membrane stability, and modulation of intracellular calcium levels (Heckman et al, 2010). The rationale for including amino acids in energy drinks is that, as the building blocks of proteins and the precursors of neurotransmitters, they will enhance protein synthesis and neurotransmitter reserve, thus influencing mood and performance (Childs, 2014). However, despite their widespread inclusion in energy drinks, the limited available research has concluded that there is no evidence of independent taurine effects on behavioural performance and mood (Giles et al, 2012; Peacock et al, 2013b). In fact, it has been suggested that taurine's primary role in energy drinks is to offer physiological therapeutic benefits via the synthesis of bile salts (European Food Safety Authority, 2009).

Experimental research that has examined the effects of energy drinks when consumed as a whole beverage have substantiated the claims made by the marketing companies that their products invigorate tired individuals (Childs & de Wit, 2008). The beneficial effects of energy drinks on mental and cognitive performance are widely acknowledged, with several studies showing that, compared to placebo, energy drinks increase mood, subjective alertness and performance on attention and memory tasks, as well as tests on executive function (Alford et al, 2001; Kennedy & Scholey, 2004; Scholey & Kennedy, 2004; Seidl et al, 2000; Smit et al, 2004; Warburton et al, 2001). Energy drinks have been shown to be particularly beneficial at counteracting sleepiness and impaired performance in those that are sleep deprived or restricted, including when driving (Horne & Reyner, 2001). Thus, energy drinks have been shown to have functional subjective and objective benefits when consumed at low to moderate doses (one to two 250ml cans of energy drinks).

Although what is not yet clear is whether the ingredients in energy drinks provide a synergistic net performance benefit when consumed as a whole beverage compared to their individual effect. To investigate this some experimental research has utilised placebo-controlled trials comparing the independent and combined effects of energy drink ingredients. The findings from the six studies that have compared caffeine and glucose, alone and in combination have shown mixed results on cognitive performance and mood (Adan & Serra-Grabulosa, 2010; Giles et al, 2012; Maridakis et al, 2009; Scholey & Kennedy, 2004; Serra-Grabulosa et al, 2010; Young & Benton, 2013). Three out of the six studies showed positive interaction effects on attention (Adan & Serra-Grabulosa, 2010; Scholey & Kennedy, 2004; Young & Benton, 2013), but no effects were found in other studies (Giles et al, 2012; Maridakis et al, 2009; Serra-Grabulosa et al, 2010). Two studies reported greater decreases in reaction time reflecting improved performance (Adan & Serra-Grabulosa, 2010; Scholey & Kennedy, 2004), whilst one study showed combined use attenuated caffeine induced decreases in choice reaction time (Young & Benton, 2013). Limited interactive effects were found on subjective states of mood, tiredness and fatigue.

There is currently limited research investigating the synergistic effects of caffeine and taurine. Of the two studies that are available, taurine has been shown to have no additional positive effect on

attention and memory (Giles et al, 2012), and attenuated caffeine-induced deceases in selective attention reaction time (Peacock et al, 2013b). Taurine also attenuated the stimulatory mood effects of caffeine and increased feelings of fatigue (Giles et al, 2012; Peacock et al, 2013b). The research to date therefore suggests that taurine counteracts the beneficial alerting effects of caffeine (Childs, 2014).

Other researchers have suggested explanations for the lack of evidence for a synergistic effect of energy drink ingredients, including that the levels of taurine in energy drinks being below therapeutic doses, and that the primary function of glucose is to enhance the taste of the beverage rather than to have an active pharmacological effect on cognitive performance and mood (Clauson et al, 2008). The available evidence has led researchers to generally claim caffeine as the core ingredient responsible for the stimulatory effect of energy drinks (Reissig et al, 2009).

3.3 Alcohol Mixed with Energy Drinks (AMED)

As energy drinks have gained increasing popularity within the past decade so too has the consumption trend of consuming alcohol mixed with energy drinks (AMED). The co-consumption of these beverages in the UK is often achieved by hand-mixing a standardised measure of spirits (25ml) with one can of energy drinks (250ml, 80mg caffeine), such as Vodka Red Bull®. These mixed drinks can also be purchased in larger quantities, such as jugs or cocktails, which are marketed as beverages to be shared with friends. Another popular method for consuming AMED is to drop a shot of alcohol into a portion of ED prior to drinking it quickly (Pennay & Lubman, 2012), such as when consuming Jager bombs. The consumption practice of ‘necking’ or ‘chugging’ the drink is often encouraged by friends and promoted by licence premises with reduced costs for increased purchases, such as 2 servings for £5. AMED can also include consuming alcohol and energy drinks separately during the same alcohol consumption occasion. This is usually defined as a period of two (de Haan et al, 2012b) to four hours (Woolsey, 2010), thus within a timeframe where both caffeine and alcohol are pharmacologically active.

Given the increasing popularity of AMED, and that caffeine is considered the principle ingredient for energy drinks purported functional effect, it is logical for questions to be raised regarding its interaction with alcohol (Alford et al, 2012). As the research outlined previously illustrates energy drinks have the ability to improve performance and increase alertness and stimulation, whereas alcohol typically impairs performance and increases sedation. As a consequence of the individual pharmacodynamic and behavioural effects of these beverages, it has been theorised that their combined use results in the stimulant effects of caffeine in energy drinks counteracting the sedative effects of alcohol, consequently reducing physiological and psychological sedation while increasing stimulation (Arria & O'Brien, 2011; Peacock et al, 2014). This state of intoxication has been termed 'wide-awake drunkenness' (Arria & O'Brien, 2011) reflecting that caffeine consumption might reduce sleepiness, but it does not alleviate alcohol-related impairment. This may lead consumers to underestimate their level of intoxication in comparison to if they had consumed the same amount of alcohol without energy drinks, an effect known as 'masking'. If consumers underestimate their level of intoxication, they may consume more alcohol and engage in more risk-taking behaviours and experience more negative alcohol-related consequences. On the basis of this hypothesis some academics and health organisations have expressed concern regarding the potential risks associated with AMED consumption.

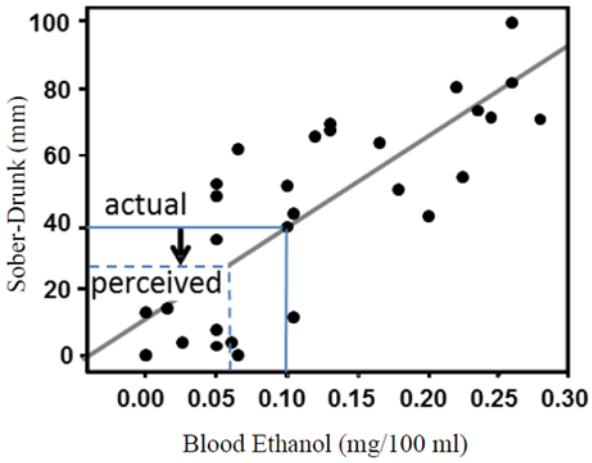

Figure 4. An illustrative example of 'masking' showing differences between actual and perceived intoxication (using data from (Scholey et al, 2012)

Ferré & O'Brien (2011) proposed a mechanism of action to support this hypothesis which they claimed provided the "perfect storm" for greater alcohol consumption and an increase in serious alcohol-related consequences. It suggests that during acute alcohol intake, caffeine largely reduces the unwanted effects of alcohol, such as tiredness and reduced co-ordination, by blocking A_1 receptors that mediate alcohol's somnogenic and ataxic effects. Conversely, alcohol increases the extracellular concentration of adenosine which decreases the anxiogenic effects of caffeine. Furthermore, caffeine increases the stimulant effects of alcohol by potentiating alcohol induced dopamine release via the A2A-D2 receptor heteromer. This mechanism of action explains how consumers of AMED may feel less impaired and less intoxicated than they actually are, but with the functional impairment of alcohol remaining.

In support of this hypothesis, early survey research (Brache & Stockwell, 2011; Eckschmidt et al, 2013; O'Brien et al, 2013; O'Brien et al, 2008) found that compared to those who did not consume energy drinks with alcohol, those who combined these beverages reported consuming more alcohol (both frequency and quantity) and experiencing more negative alcohol-related consequences. These included unsafe sexual behaviour, being hurt or injured and driving whilst intoxicated.

However, research to support the notion that mixing alcohol with caffeinated beverages causes a 'masking' effect is limited. If such an effect exists, lower subjective measures of intoxication would be expected at similar objective intoxication levels, after AMED relative to alcohol alone. However, laboratory studies have consistently failed to find reduced perceived intoxication following the addition of caffeine to alcohol. In a review of the available literature, Benson et al (2014) meta-analysis concluded that at various levels consuming alcohol with caffeinated beverages does not impair subjective intoxication.

In addition, some researchers have raised methodological issues with early between-subjects survey findings in reaching causal conclusions, which they believe have created "an imaginary link between alcoholism and energy drinks" (Skeen & Glenn, 2011) and raised "unjustified concerns" (Verster et

al, 2012). The main reason for criticism is that, even when, as the research shows, AMED consumers drink more alcohol and engage in more alcohol-related consequences than alcohol-only (AO) consumers, this does not imply that mixing alcohol with energy drinks has caused this effect. Verster & Alford (2011) explain that there are many factors between these two consumption groups (AMED and AO consumers) that may explain the observed difference in alcohol consumption and negative alcohol-related consequences, which are not controlled for by this between-subject design. For example, AMED consumers have been shown to have higher levels of sensation-seeking and risk-taking compared to AO consumers. These personality types are associated with lifestyle behaviours characterised by loss of moderation and disinhibition, which may be the primary reason for increased alcohol consumption, with co-consumption of energy drinks being one of many expressions of such a lifestyle.

In order to investigate whether AMED has an independent impact on alcohol consumption over and above personality traits, some studies have utilised within-subjects designs. These compare alcohol consumption and consequences on AMED drinking occasions with other occasions on which the same individuals consume AO. At the time of beginning my DPhil studies, the research that had adopted this within-subject design had yielded contrasting findings. Whilst some studies found statistically significant increases in alcohol consumption and negative alcohol-related consequences on AMED occasions compared to AO occasions (Brache & Stockwell, 2011; Peacock et al, 2012; Price et al, 2010), others found no difference (Verster et al, 2015) or statistically significant decreases in alcohol consumption and negative alcohol-related consequences (de Haan et al, 2012b; Lubman et al, 2013; Woolsey et al, 2010).

Another possible explanation purported for the differences in alcohol consumption and engagement in negative alcohol-related consequences is the motivations underlying the decision to consume AMED. Some qualitative research has indicated that some consumers may use AMED with the intention of reducing the impairing effects of drunkenness and facilitating a more desirable intoxication state (Pennay & Lubman, 2012). Such AMED consumption motives have included to stay awake while drinking and to party longer (Brache & Stockwell, 2011). Such hedonistic motives are associated with

increased risk of alcohol dependence (Droste et al, 2014). An additional concern raised is that young adults may be particularly attracted to mixing alcohol with energy drinks due to their sweet taste which could make consumption of alcohol more palatable and as a consequence increase consumption (Mart, 2011).

3.4 Chapter summary

Problematic alcohol use is an internationally accepted public health challenge with wide-ranging social, health and economic consequences. Much research has been conducted to try and understand the factors that might be contributing to excessive alcohol consumption. A recent consumption trend that has been linked to problematic alcohol use is the rise in popularity of mixing alcohol with energy drinks, particularly among young adults. This combined use has been proposed to mask alcohol-related impairment leading to increased problematic alcohol consumption and negative alcohol-related consequences. However, the limited research into the effects of mixing alcohol with energy drinks have produced contrasting findings and large gaps remain in our knowledge regarding the functional outcomes of AMED use.

3.5 DPhil research aims

The primary research aims on beginning this doctoral journey were to:

1) Examine whether mixing alcohol with energy drinks increases overall alcohol consumption and negative alcohol-related consequences compared to when consuming alcohol alone.
2) Determine whether mixing alcohol with energy drinks masks the intoxication effects caused by alcohol.
3) Assess the motivations for AMED use and the resulting effects on alcohol consumption.

4) Examine any underlying trait or phenotypical differences between AMED consumers and alcohol-only consumers that may explain purported increased alcohol consumption among AMED consumers.

It was hoped that the research conducted would contribute to the current debate regarding the potential harms of mixing alcohol with energy drinks, providing a more informed understanding for consumers and policy makers.

Chapter 4: Critical commentary

Chapter 4 draws upon five research projects that consisted of two systematic/critical review and meta-analyses and three sequential studies. This research resulted in ten published papers between 2016 and 2022, that have been included in this submission for the award of DPhil. Each separate publication contains an updated literature review and critical examination of the methods used, therefore, to avoid unnecessary repetition the critical commentary will take a reflective approach. For each project, I will provide a reflection on the research methods used, ethical considerations and intellectual contribution to the research field. Lastly, I will provide a personal reflection on what I learnt and how I developed from the experience of that project.

4.1.1 Introduction to project 1: systematic review and meta-analysis 1

As outlined in chapter 3 there had been much public health concern regarding the increased prevalence of young adults mixing alcohol with energy drinks and the potential impact on alcohol consumption and adverse alcohol-related consequences. Early survey research which indicated the potential harm of AMED use had utilised between-subjects designs that compared alcohol consumption of AMED users with those who had never mixed alcohol with energy drinks, i.e. consumed alcohol-only (AO).

My supervisors, CA and JV (Verster & Alford, 2011; Verster et al, 2012), among others (Skeen & Glenn, 2011) had criticised the use of between-subjects research in reaching causal conclusions regarding the effects of consuming AMED. They highlighted that whilst between-subjects research may show AMED consumers drink more or less alcohol than AO consumers, there may be many other differences between these two groups, other than the co-consumption of alcohol with energy drinks, that may explain the observed differences in overall alcohol consumption. They suggested that a more appropriate approach would be to use a within-subject design that compared consumption on AMED occasions and AO occasions within a cohort of AMED consumers, therefore controlling for inter-individual differences.

It was at this stage that I began my doctoral journey and became engaged with the academic debate within the literature regarding the most appropriate methodology to study AMED use. At this point research into the effects of mixing alcohol with energy drinks was growing exponentially. Whilst a number of reviews (Ballard et al, 2010; Duchan et al, 2010; Ishak et al, 2012; Kaminer, 2010; L Blankson et al, 2013; Reissig et al, 2009; Verster et al, 2012) had been conducted they either failed to adopt a systematic literature search or had not provided comparable outcomes across the reviewed studies. The most recent and most comprehensive review was provided by Peacock et al (2014). In regard to alcohol intake seven studies were included that compared retrospective self-reported consumption patterns of AMED versus AO consumers (between-subjects) and four studies that compared AMED versus AO consumption patterns among AMED consumers (within-subjects). They found that whilst AMED consumers are more likely to drink more alcohol than AO consumers, due to the equivocal nature of the limited literature no firm conclusions could be drawn regarding the direct effect of AMED on overall alcohol consumption. A limitation of this systematic review was that the analysis approach of using odds ratios for each individual study did not allow a calculation of an overall or 'absolute' effect.

Given the lack of a formal systematic synthesis of the expanding literature and increasing calls for policy response to AMED in several countries (Australian Medical Association, 2013; National Health Service, 2015; United States Food and Drug Administration, 2010), JV suggested that a systematic review and meta-analysis, to examine the fundamental claim that co-consumption of energy drinks has an impact on total alcohol consumption, would be timely and impactful. I was fortunate to be asked by JV to contribute towards this project, alongside CA, and colleagues of theirs with shared interest in AMED research from Swinburne University Australia, Professor Andrew Scholey (AS) and Dr Sarah Benson (SB).

4.1.2 Research methods

In conceptualising this systematic review, as a research team we made the decision to focus on the different methodological approaches and perform separate meta-analyses for studies applying between-subject and within-subject designs. To allow a direct comparison, it was decided that

included studies would need to report alcohol consumption during single drinking occasions. These would need to focus on either the typical number of alcoholic drinks consumed during a single drinking occasion, or the maximum number of alcoholic drinks consumed in a single drinking occasion. To be included, the research also needed to be conducted in healthy volunteers and published in English. This could be considered a limitation, but we did not have the resource to translate manuscripts if required.

The databases were selected based on their suitability to identify alcohol research and the search terms on their ability to capture a wide range of relevant publications. As anticipated the literature search produced a large volume of potentially suitable publications. JV removed duplicates and completed initial eligibility screening. Content assessment was then performed independently by each member of the research team against the publication criteria. This information was captured on a data extraction sheet. Any disagreement regarding inclusion/exclusion of papers were resolved during regular meetings. Three studies (Lubman et al, 2014; Penning et al, 2011; Verster et al, 2015) were discussed at length as they did not quite meet the inclusion criteria of reporting on a typical or maximum consumption occasion. It was decided that whilst they should be omitted from the main meta-analysis, they were worthy of being mentioned in the manuscript and should be included within a separate meta-analysis to illustrate any additional effect. The meta-analysis was completed by JV, who also produced the initial version of the manuscript. Along with the other research team members, I contributed to the revisions of the manuscript and response to reviewer's comments.

4.1.3 Ethical considerations

A systematic review and meta-analysis is a form of secondary research that draws upon publicly available data, therefore formal ethical approval was not required. However, there are practical and ethical issues that must be considered when undertaking this kind of research (Wager & Wiffen, 2011). In relation to this current systematic review and meta-analysis it was important to ensure that the results were not skewed by 'double counting' participants from a study (Tramèr et al, 1997). Within alcohol and energy drink research it has been common practice for researchers to publish findings in more than one format, i.e. conference proceedings and journals, or to conduct additional

analyses of sub-groups from an initial study. Therefore, during the eligibility screening it was important to be aware of the possibility of duplicate publications and to reach a consensus on which data to include.

Another consideration is whether or not the systematic review and meta-analysis will add anything new to the academic literature and help inform decision-making. Avoidance of overlapping or redundant systematic reviews and meta-analyses is important in avoiding confusion among readers, particularly if they reach contrasting conclusions of the same results. It also places a strain upon the peer-review process. Once the content assessment had been performed and we had identified publications that matched our inclusion criteria we checked that this would lead to the creation of new knowledge not included in previous literature reviews.

It is also important to provide sufficient detail about the methodology used in conducting a systematic review and meta-analysis. This allows readers to assess the robustness and applicability of the findings in making policy recommendations, such as the regulation of energy drink use. Therefore, every effort was made in the manuscript to describe in detail the literature review process. This included an account of how and why the studies were identified and selected and what was found. Care must also be taken when extracting data from publications for inclusion in the meta-analysis to ensure accurate transcription. We ensured this by double-checking the data included in the meta-analysis reflected that in the original publication.

Lastly, it was also essential to be transparent about funding and possible competing interests, particularly given there has been much discussion regarding the possible influence of industry funding on energy drink research (Miller, 2013). Whilst there was no industry involvement in this publication, both myself and my co-authors had received research funding from Red Bull GmbH. Therefore, it was important to be clear and open about this in the manuscript. It was also vital for us to reflect on the potential impact of funding source for the studies included in the systematic review and meta-analysis, within the discussion section.

Some of the above ethical considerations could have been overcome more robustly by pre-registering the systematic review in a platform such as PROSPERO. By publishing details of the systematic review prior to beginning the project would have allowed evidence users to assess whether all steps had been performed as planned, thus reducing bias, increasing transparency, and also avoiding unintended duplication. Unfortunately, this opportunity was lost due to a lack of knowledge at the time of such registration platforms and in the haste of getting going with analysis. This was a steep learning curve given its potential effect on impact, particularly given the contentious nature of AMED research.

It must also be acknowledged that the effect size used for the within-subjects comparison in this meta-analysis, as well as the individual studies that follow, may have impacted on the interpretation of the findings and futility to inform future studies. Whilst it was deemed appropriate at the time to use Cohen's d for both the between and within-subject designs to provide a standardised metric to compare the practical significance of the result across designs, such an approach does not take into consideration the degree of correlation between levels inherent of within-subject designs. This could have resulted in an overestimation of the true effect size and have implication for researchers when conducting a-priori power analysis when planning future studies. A suggested alternative which takes the correlation between levels into account and is recently more widely used in within-subject designs is Cohen's d_z (Lakens, 2013). During this DPhil I continuously wrestled with choosing the most appropriate effect size and became frustrated at the lack of concrete guidance. I have since developed an appreciation of the complexity of such decisions and an understanding that not one "effect size" fits all and depends on the research question and the experimental design.

4.1.4 Intellectual contribution

4.1.4.1 Publication 1

The findings from the systematic review and meta-analysis were published in Human Psychopharmacology: Clinical and Experimental journal, and can be accessed here:

Verster, J. C., Benson, S., Johnson, S. J., Scholey, A., & Alford, C. (2016). Mixing alcohol with energy drink (AMED) and total alcohol consumption: a systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, 31(1), 2-10. https://doi.org/10.1002/hup.2513

In summary, the meta-analysis of the studies using between-group comparisons found that AMED consumers drink significantly more alcohol than those who consume AO. However, the meta-analysis of the within-subjects comparisons showed no difference in the amount of alcohol consumed by AMED consumers on AMED occasions compared to AO occasions. We concluded that this suggests that there are phenotypical differences between AMED and AO consumers and proceeded to provide research support for this hypothesis. One of these differences is that AMED consumers drink more alcohol than AO consumers. However, they do this irrespective of whether or not alcohol is mixed with energy drinks.

The significance of this publication is that it is the first systematic review and meta-analysis to integrate findings from several studies into a single estimate of the effects of combined alcohol and energy drink use. In doing so it has directly addressed the ongoing debate regarding the use of between-subject analyses in reaching cause and effect conclusions. It has provided policy makers with a summary of the extant literature, and also indicated where additional research is required. For example, further investigation of personality characteristics could help develop screening tools to identify those individuals most at risk of excessive alcohol consumption and adverse consequences.

This publication has also identified issues with lack of standardisation and operationalisation of concepts that has made it difficult to combine findings from different studies. An example of this is that most studies did not report on how AMED consumption was defined, with it often being left open to participant interpretation. To some participants an AMED occasion may only be interpretated as when both alcohol and energy drinks are mixed in the same beverage and for others it could also include alcohol and energy drinks consumed separately but within the same drinking session (sometimes hours apart). In addition, the included studies used a range of questionnaires with contrasting recall periods, with some reporting consumption with reference to the past week, past

month or past year. The publication highlighted that clearer definitions are required and that standardised validated questionnaires should be used in future research.

4.1.5 Personal reflection

This was my first formal experience of conducting a systematic review and meta-analysis. It was a good starting point for my doctoral journey and provided me with a great opportunity to immerse myself within the literature and identify significant gaps in current knowledge. It allowed me to understand the scale of research conducted thus far and critically evaluate its strengths and weaknesses. I developed an appreciation for the step-by-step process of conducting a systematic review and the need for a methodical transparent approach.

I gained many practical skills which would serve me well as I moved on to further research endeavours. I developed a method to succinctly evaluate and summarise research findings using a data extraction table. By setting email alerts from key journals, I was able to keep updated with the most recent publications within AMED research and add these as they emerged. This meant that I had this information ready for future literature reviews for publications rather than starting from scratch.

I learnt how to successfully work as part of a team in delivering a research project. Whilst I had previously worked as a Research Assistant, this was my first experience as a co-author and having parity with senior researchers in the field. Over time I developed the confidence to express my opinion and judgement in reaching research decisions. I became aware of the importance of planning the research process, setting deadlines and regularly reviewing these, particularly given the competitive and dynamic nature of the research field.

This was also my first experience of the publication process. I was involved in discussions regarding selecting the most appropriate journal for publication and reviewing the manuscript to ensure it complied with the submission guidelines. This included reference formatting, table and figure design and word count compliance. Contributing to the peer review process allowed me to develop an understanding of how to accept and respond to constructive criticism but also how to defend a position with supporting evidence when required. I realised that getting a paper published can take

time and may require multiple peer review rounds as well as submission to alternative journals. It become evident that this was particularly the case for AMED research given the current academic debate and calls for policy reform.

4.2.1 Introduction to project 2: UK-wide student survey

The findings from the systematic review and meta-analysis highlighted how different conclusions had been reached regarding the effects of mixing alcohol with energy drinks depending on the methodology used. Whilst between-subject comparisons showed that AMED consumers drank significantly more alcohol than AO consumers, within-subjects comparisons revealed that AMED consumers drank the same amount of alcohol on AMED occasions as they did on AO occasions. In this paper we proposed that there may be phenotypical differences between AMED consumers and AO consumers that could explain the increased alcohol consumption among AMED consumers and provided research evidence to support this assertion.

In reviewing the available literature, we identified issues with lack of standardisation and operationalisation of concepts that limited the ability to compare the findings. In doing so, we suggested that future research should use standardised and validated questionnaires, such as the Quick Drinking Screen (Roy et al, 2008; Sobell et al, 2003), as well as having a standardised recall period (e.g. past 30 days). We also emphasised the need for a clearer definition of 'mixing' and purposed the consumption of energy drinks within a time period of 2 hours before through to 2 hours after drinking alcohol, therefore taking into account the half-life of caffeine.

The systematic review revealed that only a limited number of studies had conducted within-subjects analysis and some of these (Brache & Stockwell, 2011; Price et al, 2010; Woolsey et al, 2010) had relatively small sample sizes. There was also limited research of AMED consumption within Europe, with the only study being conducted in the Netherlands by my supervisor JV and colleagues (de Haan et al, 2012a; de Haan et al, 2012b).

Given that problematic alcohol consumption was of significant concern in the UK at the time, and there was much public health interest (Drinkaware, 2021; National Health Service, 2015) and media attention (see Figure 5) on the rise in popularity of mixing alcohol with energy drinks and its possible role in excessive alcohol consumption, we decided to conduct a survey to examine energy drink and alcohol use among UK students.

Figure 5. UK media attention on the effects of mixing alcohol with energy drinks

We decided that this survey should be a partial replication of the Dutch AMED survey, which would also be conducted in Australia by SB, to allow cross-cultural comparisons. We thought this was important and would contribute significantly to the research literature as it would allow a direct comparison of the effects of mixing alcohol with energy drinks across cultures known to have different drinking habits and varying social acceptability of alcohol consumption.

The aims of the UK student survey were to:

1) Examine alcohol consumption and its consequences when consumed alone or when mixed with energy drinks
2) Determine the motivations for consuming energy drinks and mixing alcohol with energy drinks
3) Determine individual levels of risk-taking behaviours in order to predict alcohol consumption and its consequences, and its relationship with energy drink consumption
4) Conduct cross cultural comparisons between the UK, the Netherlands and Australia.

4.2.2 Research methods

To allow for cross-cultural comparisons the research methods needed to align with the Dutch student survey (de Haan et al, 2012a) as much as possible, but its suitability also needed to be assessed for UK students. The one standardised measure that required careful consideration for inclusion was the BYAACQ. Whilst several studies in the United States, the Netherlands, Argentina and Australia have demonstrated high levels of reliability and validity (Kahler et al., 2008; Pilatti et al., 2014; Verster et al., 2009; Poulton et al., 2019) the psychometric properties of the measure has not yet been extensively explored in a UK context. Cultural and legal differences between the UK and the validated countries, such as legal drinking age, may mean less confidence can be given to the findings without this validation. Given the time needed to complete this progress and that the measure had been used consistently across AMED research, and was needed for cross cultural validations, we accepted the limitation of using this measure for our primary analyses. Unfortunately, we are yet to revisit this data for secondary analysis to further our understanding of the psychometric properties in UK students.

The first step was to translate the entire survey content into English and address any language inconsistencies. I then built the survey online within Survey Monkey and conducted user acceptance testing to ensure survey flow and that validations were working correctly. This included allocation to consumer groups (see Figure 6).

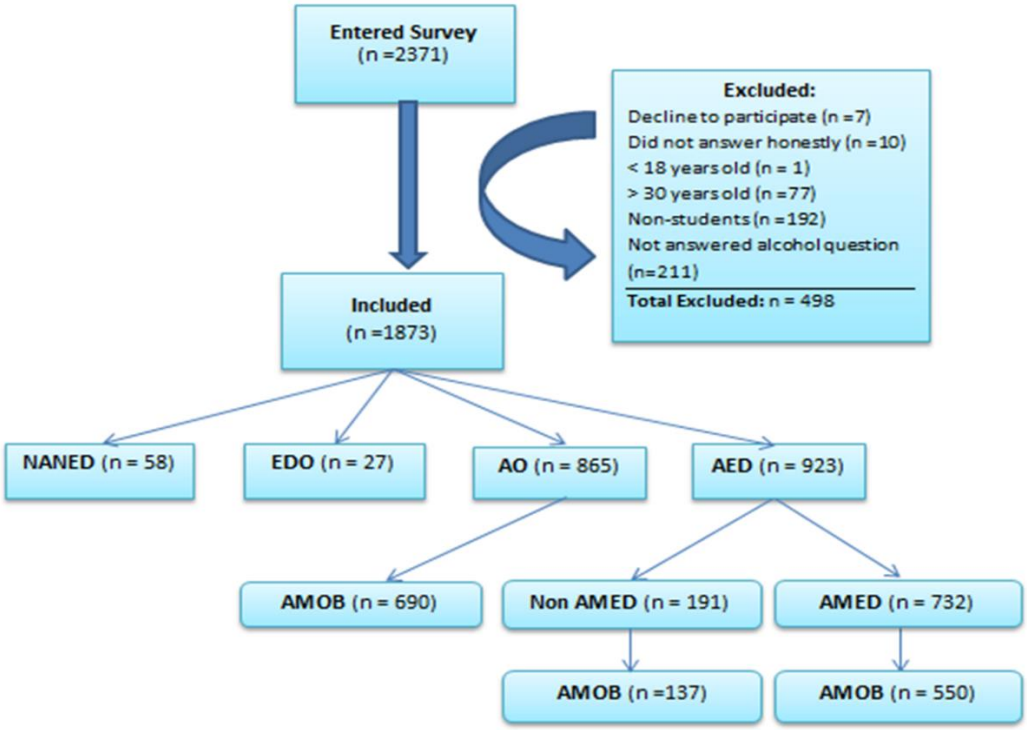

Figure 6. Flowchart of the survey responses with group sizes and exclusions.

Abbreviations: NANED, no alcohol no energy drink; EDO, energy drinks only; AO, alcohol only; AED, alcohol and energy drinks; AMED, alcohol mixed with energy drinks; AMOB, alcohol mixed with other beverages.

We then decided to conduct a pilot with a small group of UWE BSc Psychology students that I was teaching at the time and followed this up with a focus group to discuss their understanding and experience of completing the survey. This not only allowed me to gain valuable feedback to inform the content of the survey but also provided a learning opportunity for students into research methods which could be taken forward into their third-year dissertation projects. The feedback from the focus group was that the standardised recall period (past 30 days, and 12 months) and definition of mixing ($\pm$ 2 hours of drinking alcohol) were understandable and the standardised questionnaires straightforward to complete. However, the general consensus was that part 2 of the survey, which assessed personality aspects, was too long and tedious to complete. Furthermore, the pilot students also felt that the inclusion of how long it may take to complete (up to 60 minutes) on the opening

informed consent page may result in some students deciding not to complete the survey at all. As a research team we discussed the benefits and drawbacks of removing part 2 from the UK survey and decided that focusing on a good response rate to part 1 was crucial in addressing the research aims. Therefore, part 2 was removed.

The initial recruitment plan was to replicate the Dutch student survey and ask the university (UWE) to distribute the survey to all students via email. However, gaining permission to do this was more difficult than anticipated due to the high number of requests the university communications team receive to promote research recruitment and the sensitive nature of examining student alcohol consumption. At this time, I became aware that universities often delegate the responsibility of pastoral care for areas such as mental health, drug and alcohol support to their Student Unions. I arranged a meeting with UWE Student Union and found out that they were running a campaign to promote responsible drinking on campus. After explaining the content of the survey they agreed to promote it via their social media platforms in return for a summary report on the findings which they could use to inform future campaigns. This transaction meant I had the "buy in" of the Student Union to promote the survey to as many students as possible. We realised that this could be seen as beneficial to other university Student Unions and decided to extend the invitation to all Student Unions throughout the UK. This not only allowed us to reach more potential participants but also provided an opportunity to gain a more representative sample of alcohol and energy drink use among all UK students rather than being limited to one geographical area (Bristol). In total, 30% of student unions, including institutions from each country (England, Northern Ireland, Scotland, Wales), responded and agreed to take part.

In choosing to distribute the survey link via Student Union social media, rather than email or other direct methods, we accepted the limitation that we were unable to determine the response rate and that marginalised sections of the student population may have been excluded. However, the demographics of the students included in the data collection did broadly reflect those of the general UK student population (UK Universities, 2013).

It was also important to consider the timing of conducting the survey, particularly given the reference timeframe (past 30 days) which alcohol consumption was reported on. We were careful to avoid exam periods where alcohol consumption was likely to be reduced and holidays where students might not be on campus. The aim was to capture the "typical" student experience. We discussed the length of time the survey should be open to completion for and decided on a five-week data collection period. We wanted to standardise the timepoints that the Student Unions would promote the survey and asked them to post the link on their social media on the opening day, halfway through the data collection period and one week before the survey was due to close. I checked compliance and reminded the Students Union if required.

Once data collection was completed, I was responsible for exporting and cleaning the data. This included ensuring the data was valid and plausible (e.g. over 18 years old and below 30 years old, reported alcohol consumption within previously agreed levels to remove fabricated responses), accurate and consistent (report energy drink consumption if identifying as an energy drink consumer) and uniform (alcohol reported in standard units). In addition, missing data was explored and assessed as missing at random, therefore imputation was not used. I was then responsible for analysing the data, including the summary reports for each Student Union and for the UK specific publications that follow. I was also responsible for combining the datasets from the different countries and preparing them for cross-cultural comparisons.

4.2.3 Ethical considerations

After clicking on the link within the Student Union social media post, students were directed to the opening Survey Monkey page that provided information on the purpose and content of the survey. It was stated that participation was voluntary, and they were free to discontinue at any time without consequence. Participants were also informed that all information provided would be anonymous and kept confidential. No personal identifiers, such as name, date of birth or address were collected. Participants provided informed consent by clicking on the 'agree to participate' button which then took them to the first question of the survey. They were informed to close the browser if they did not wish to participate or wanted to discontinue.

To attract participation and decrease non-response bias, participants were given the opportunity to be entered into a monetary prize draw upon completion of the survey. It was decided that to be comparable the monetary prizes should mirror those provided in the Dutch student survey. Therefore, one prize of £500 and 10 prizes of £50 were allocated. In order to take part in the prize draw, participants were asked to provide an email address so they could be contacted if they had won. To ensure anonymity the email address was captured separately to the survey results. We were unable to contact one of the prize winners, therefore this was redrawn after 6 weeks as stated in the informed consent form.

We were aware that as participants were required to provide information about alcohol consumption, this recall may have been psychologically distressing to those who had experienced previous alcohol-related problems. This could particularly be the case when reporting on alcohol-related consequences from the BYAACQ (Kahler et al, 2005) such as sexual risk-taking and violence. We therefore provided participants with contact details to alcohol support services at the beginning and end of the survey.

The study protocol was reviewed and approved by UWE ethics committee (HAS/14/03/57).

4.2.4 Intellectual contribution

A publication plan was developed for the dissemination of the research findings from the UK student survey. The primary publications focused on the effects of mixing alcohol with energy drinks on overall alcohol consumption and alcohol-related negative consequences (publication 2) and the motivations for consumption and its effect on alcohol intake (publication 3). A secondary analysis was then performed on the UK data to investigate whether energy drinks are unique mixers in terms of their effects on alcohol consumption and negative alcohol-related consequences in comparison to other caffeinated mixers (publication 4). Lastly, the UK student survey data was then combined with data from the Netherlands and Australia to provide cross-cultural comparisons (publications 5 and 6). Each publication will now be presented in turn, with a reflection on how it has contributed to the academic literature.

4.2.4.1 Publication 2

Johnson, S. J., Alford, C., Stewart, K., & Verster, J. C. (2016). A UK student survey investigating the effects of consuming alcohol mixed with energy drinks on overall alcohol consumption and alcohol-related negative consequences. *Preventive Medicine Reports*, 4, 496-501. https://doi.org/10.1016/j.pmedr.2016.09.005

The primary aim of this publication was to determine whether mixing alcohol with energy drinks increased the amount of alcohol consumed and engagement in negative alcohol-related consequences. Therefore within-subjects comparisons were performed comparing AMED drinking occasions with AO drinking occasions among AMED consumers. The analysis found that AMED consumers drank less alcohol and engaged in fewer harmful behaviours on AMED drinking occasions compared to AO drinking occasions. These findings suggested that something other than the co-consumption of alcohol with energy drinks was responsible for the increased alcohol intake and engagement in more negative alcohol-related consequences observed among AMED consumers in the between-subjects analysis. Potential explanations from this publication included AMED consumers being younger, male, more likely to consume alcohol regularly at a younger age, take illicit drugs and smoke compared to AO consumers. Thus, it appeared the type of students attracted to consuming AMED had a higher risk-taking personality in comparison to those who consumed AO, which included increased alcohol consumption regardless of whether or not it was mixed with energy drinks. We therefore concluded that calls for policy changes by some authors (Arria et al, 2011; Howland & Rohsenow, 2013) to reduce the consumption of AMED were premature and lacked sufficient research evidence.

The significance of this publication is that it presented findings from the first UK study, with a relatively large sample size, to investigate the effects of mixing alcohol with energy drinks. In order to determine whether any observed differences in alcohol consumption and negative-related consequences were related to the co-consumption of energy drinks or not, it utilised a more appropriate within-subjects design, therefore controlling for the many demographic and personality variables that may differ between AMED and AO consumers. The findings were comparable with

previous within-subjects comparisons conducted in other countries (de Haan et al, 2012b; Lubman et al, 2013; Woolsey et al, 2010) and provided further support that energy drinks do not increase overall alcohol consumption or the likelihood or experiencing negative alcohol-related consequences.

An additional important contribution of this publication is that it highlighted the worrying levels of alcohol consumption and associated negative consequences experienced by UK students, regardless of consumption occasion. Recommendations were made to focus efforts on protective behavioural strategies to reduce excessive alcohol consumption among students, rather than the pre-occupation with AMED.

4.2.4.2 Publication 3

Johnson, S. J., Alford, C., Verster, J. C., & Stewart, K. (2016). Motives for mixing alcohol with energy drinks and other non-alcoholic beverages and its effects on overall alcohol consumption among UK students. *Appetite*, 96, 588-597. https://doi.org/10.1016/j.appet.2015.10.007

A number of previous studies (Brache & Stockwell, 2011; Jones & Barrie, 2009; Marczinski, 2011; O'Brien et al, 2008; Peacock et al, 2013a) had been conducted to investigate the motivations underlying the decision to consume AMED. These identified a wide-range of motives across a variety of geographies, which could generally be categorised as neutral or negative according to their presumed effects on total alcohol consumption or negative-alcohol related consequences. Negative motives were related to the expectation that the advertised functional effects of energy drinks could counteract the fatigue-related consequences of alcohol, therefore prolonging the duration of the drinking occasion or allowing the consumer to drink more alcohol. Drinking for such intoxication-enhancement motives were of particular concern as it could leave consumers at increased risk of alcohol-related problems. This was shown by Droste et al (2014) who found that those who consumed AMED for such negative motives were at increased risk of negative outcomes, including alcohol dependence, alcohol-related injury and aggression.

Motivations for AMED consumption was investigated by Verster et al (2014) in the original Dutch student survey. They found that the most frequently reported motives were neutral, such as liking the

taste or wanting to drink something else, with only a minority of participants reporting negative motives such as to get drunk or reduce the negative effects of alcohol. Using within-subject comparisons they showed that participants who consumed AMED for negative motives drank less alcohol on AMED occasions compared to AO occasions. Thus, in contrast to Droste et al (2014) the type of motive had no differential effect on total alcohol intake.

Given the limited research and mixed findings, the aim of the current publication was to explore the motivations for consuming energy drinks alone and mixed with alcohol among UK students, and to determine whether the type of motive had a differential effect on overall alcohol consumption.

In summary, the results showed that the primary motives for energy drink consumption related to an appreciation of energy drink taste, as well as the anticipated positive effects of the drinks functional ingredients, such as staying awake and increasing energy. The majority of reasons for consuming AMED were neutral in nature, such as liking the taste, to celebrate a special occasion or to drink something else. In contrast to the Dutch findings, the negative motive of consuming AMED to get drunk was commonly reported. However, participants who consumed AMED for such negative motives reported consuming less alcohol on AMED occasions compared to AO occasions. Thus, negative motives for AMED consumption had no differential impact on alcohol consumption. Motivations for mixing alcohol with energy drinks and other non-alcoholic beverages (Alcohol Mixed with Other Beverages; AMOB) were similar in distribution, but AMED was more commonly consumed as a group bonding experience to make special nights out more enjoyable. This was reflected in fewer AMED drinking occasions being reported compared to AMOB and AO drinking occasions. Whilst more students reported consuming AMED to get drunk compared to AMOB, fewer students reporting feeling able to drink more alcohol when consuming AMED compared to AMOB. This was reflected in lower alcohol consumption reported on AMED occasions compared to AMOB occasions.

This publication has contributed to the literature by providing the first analysis of AMED consumption motivations among UK students. In contrast to previous research and following Verster et al (2014), we were able to determine whether the type of motive had an impact on overall alcohol

consumption and negative alcohol-related consequences by using a within-subjects design. A further advantage of the survey design is that we collected data on motivations for consuming alcohol with other non-alcoholic beverages, allowing direct comparisons with AMED motivations. This is important given that other mixers are more commonly consumed with alcohol.

A limitation of the current publication is that the survey did not capture motivations for consuming alcohol alone. This could have acted as a baseline measure when comparing with AMED drinking occasions. For example, those who reported consuming AMED to get drunk, may also have reported consuming alcohol alone to get drunk.

Furthermore, the operationalisation of consumption motives must be carefully considered when inferring a relationship with the amount of alcohol consumed. Firstly, participants were simply asked whether each motive generally applied to AMED or AMOB occasions. No information was obtained on what specific occasions or how important each motive was, and how this was linked to the amount of alcohol consumed on those occasions. Secondly, participants were categorised into the negative motive group if they reported atleast one of the motives deemed to be associated with increased alcohol consumption. Whilst this definition appears to capture the worse-case scenario and allowed comparisons with previous research, as discussed in the paper their link to increase alcohol consumption is open to debate. Further analysis of the dataset, potentially exploring different ways of categorising the negative motives group, could have provided further insights into alcohol-caffeine consumer groups.

Lastly, when considering alcohol mixed with other non-alcoholic beverages, no differentiation was made between caffeinated (e.g. cola) and non-caffeinated mixers (e.g. lemonade). Therefore, given that the concentration of caffeine could have varied from 80mg in a standard energy drink, 34-46mg in a standard cola and other non-alcoholic beverages (e.g. lemonade) containing no caffeine at all, no conclusions could be drawn on the role of caffeine when comparing AMED and AMOB drinking occasions. This limitation led to the development of publication 4.

4.2.4.3 Publication 4

Johnson, S. J., Alford, C., Stewart, K., & Verster, J. C. (2018). Are energy drinks unique mixers in terms of their effects on alcohol consumption and negative alcohol-related consequences? *International journal of general medicine*, *11*, 15. https://dx.doi.org/10.2147%2FIJGM.S143476

At the time of conceptualising this study some researchers (Thombs et al, 2010) were also questioning the exclusive focus on energy drinks as a unique mixer when combined with alcohol, given that the purported active ingredient, caffeine, is also contained in other beverages that are more frequently consumed with alcohol, such as cola. Therefore, the UK student survey was developed further to include information on what other non-alcoholic beverages were consumed with alcohol, with the aim of determining whether there was a difference in alcohol consumption and associated negative consequences when mixed with energy drinks or other caffeinated mixers. It was hoped that these findings would inform public health recommendations on the potential dangers of combining all sources of caffeine with alcohol.

Prior to conducting this analysis, research investigating the differential impact of caffeinated mixer (energy drink versus other caffeinated beverages) on overall alcohol consumption was limited. Whilst there was consensus between studies that those who consumed alcohol with caffeinated mixers in any form drank significantly more alcohol than those who consumed alcohol-only, there were mixed findings when comparing those who consumed AMED and those who consumed Alcohol mixed with Other Caffeinated Mixers (AOCM). Whilst some researchers found increased alcohol consumption among AMED consumers compared to AOCM consumers (Kponee et al, 2014), others found no difference (Cobb et al, 2015; Thombs et al, 2010) or reduced consumption (Penning et al, 2011). As previously highlighted these studies were limited in their ability to reach causal conclusion given their use of between-subject comparisons. Whilst these publications explained any observed findings in alcohol consumption as being caused by the different mixer consumed, these findings could equally be explained by the many phenotypical differences between these groups.

Given the paucity and methodological limitations of previous research, the current publication used a within-subjects design comparing alcohol consumption and associated negative consequences on AMED, AOCM and AO drinking occasions. The findings showed that AMED was consumed significantly less often and at lower levels of intoxication compared with consuming AOCM. Alcohol related negative consequences were similar between AMED and AOCM drinking occasions. Alcohol consumption and negative alcohol related consequences were higher on AO occasions compared with AMED and AOCM occasions.

The significant contribution of this publication to the literature is that it was the first study to utilise a more appropriate within-subjects design to investigate the relationship between the consumption of different caffeinated mixers and the frequency and quantity of alcohol consumed. The findings illustrated that the public health focus on energy drinks as a unique mixer is unwarranted, and may actually be downplaying the wider concern of excessive alcohol consumption per se. The publication informed the regulatory and public health debate by suggesting that alcohol-caffeine consumption may be useful to identify those at increased risk of excessive alcohol consumption. However, these problematic consumption patterns occur regardless of whether alcohol is mixed with caffeinated beverages and may even be higher when alcohol is consumed alone. Therefore, educational programs, interventions and regulatory change that focus on energy drinks will not address the underlying problem of excessive alcohol consumption among students.

One limitation acknowledged in this publication was that the consumption of just 1 mixed beverage resulted in the drinker being classed as part of this drinking group. Thus, the impact of the amount of caffeine consumed (via energy drinks or other caffeinated beverages) and its relationship to overall alcohol consumption was not investigated. Publication 6 went some way to address this limitation.

4.2.4.4 Publications 5

Benson, S., Johnson, S. J., Alford, C., Scholey, A., & Verster, J. C. (2021). A Cross-Cultural Comparison of the Effects of Alcohol Mixed with Energy Drink (AMED) Consumption on Overall

Alcohol Consumption and Related Consequences. *International Journal of Environmental Research and Public Health*, *18*(14), 7579. https://doi.org/10.3390/ijerph18147579

As outlined in publication 5 previous research had suggested that cross-cultural differences in AMED consumption may exist. However, discrepancies between studies and the different designs employed meant a direct comparison between findings to reach firm conclusions was not possible. The decision to conduct a partial replication of the Dutch AMED survey, which was also subsequently repeated in Australia, was to allow for such a direct comparison of the effects of mixing alcohol with energy drinks across cultures known to have different drinking habits and varying social acceptability of alcohol consumption.

Therefore, the aim of publication 5 was to explore how cultural context may influence the effects of AMED by comparing alcohol consumption, its consequences and motivations for use between the three countries. Between and within-subject analyses were conducted to examine both inter and intra-group effects. The direction of findings were consistent across countries, with increased alcohol consumption and higher risk-taking scores among AMED consumers compared to AO consumers, and lower alcohol consumption and fewer negative alcohol-related consequences on AMED occasions compared to AO occasions among AMED consumers. However, some interesting cross-cultural differences were observed. For instance, it was shown that the UK sample consumed significantly more alcohol and engaged in a greater number of negative alcohol-related consequences across both AMED and AO drinking occasions compared to the Dutch and Australian samples. In addition, a higher proportion of the UK sample reported consuming AMED "to get drunk".

The significance of this publication is that it is the first to use the same methodology and design to provide a direct comparison of cross-cultural differences in drinking behaviour that may have an impact on AMED consumption. The consistent between and within-subject findings across countries provide support to our previous hypothesis (Verster et al, 2018) that co-consumption of energy drinks may be one of many expressions of a high risk-taking lifestyle and personality type. In addition, the direct comparison with other countries highlighted the unique challenge the UK faces with regard to excessive alcohol intake and its consequences among students.

4.2.4.5 Publications 6

Johnson, S. J., Benson, S., Scholey, A., Alford, C., & Verster, J. C. (2021). Risk-taking behavior and the consumption of alcohol mixed with energy drink among Australian, Dutch and UK students. *International journal of environmental research and public health*, *18*(10), 5315. https://doi.org/10.3390/ijerph18105315

Publication 5 demonstrated a consistent pattern of findings across the three countries, indicating that compared to when alcohol is consumed alone, mixing alcohol with energy drinks does not significantly affect overall alcohol consumption or negative alcohol-related consequences. We concluded that excessive alcohol consumption per se seems to be the cause of the negative consequences, with the co-consumption of energy drinks being just one of many expressions of a high risk-taking personality.

The purpose of publication 6 was to explore this claim further by investigating the possible interplay between energy drink and alcohol consumption and its relationship with risk-taking and negative alcohol-related consequences. Indeed, a limitation of the analyses conducted in the previous publications is that membership to the AMED consumption group, was defined as the consumption of at least one energy drink within a period of 2 hours before through to 2 hours after drinking alcohol. Therefore, the relationship between the number of energy drinks consumed and the amount of alcohol consumed or negative alcohol-related consequences had not yet been examined. In line with our previous findings, we hypothesised that there would be a direct positive relationship between the level of risk-taking behaviour and the amount of alcohol consumed and number of alcohol-related negative consequences, but that this would be independent of energy drink consumption. Combined and separate analyses of the data from the three countries were conducted to verify any findings across different drinking cultures.

In summary, the findings indicated that whilst there was a strong positive relationship between the amount of alcohol consumed, level of risk-taking behaviour and number of reported negative alcohol-

related consequences, energy drink intake was not related to level of risk-taking behaviour and only weakly related to the number of negative alcohol-related consequences experienced.

This publication contributed to the existing literature by demonstrating across countries that the relationship with risk-taking is driven by the amount of alcohol consumed and not by the amount of energy drinks consumed on AMED occasions. Thus, mixing alcohol with energy drinks does not influence alcohol consumption levels and subsequent negative alcohol-related consequences.

4.2.5 Personal reflection

This study was the first large scale survey to collect data on alcohol and energy drink use among students from across the UK, and the first across any country. It has resulted in a significant number of research outputs that have provided useful insights into AMED consumption patterns, motivations and consequences. In particular, it has highlighted the methodological limitation of using between-subjects designs in reaching causal conclusions regarding the effects of mixing alcohol with energy drinks. The findings have contributed to the ongoing debate regarding the safety of AMED use and possible legislative restrictions. These publications, alongside poster and oral presentations at international conferences, have allowed me to develop as a recognised researcher within the global AMED research community.

Whilst I was fortunate to be able to replicate and extend the Dutch student survey, meaning the methodology was already developed, successfully delivering the project wasn't without its challenges. The initial rejection from UWE Bristol to advertise the survey to students, required persistence and initiative to find an alternative recruitment strategy. Contacting all Students Union's throughout the UK to introduce the project, respond to any questions they may have had and manage expectations in the content of the summary report took a significant amount of time and effort. Even though I was confident this recruitment strategy would mean the advert to the survey would be seen by a significant proportion of the student population, I was still nervous about whether it would gauge enough interest to provide the number of responses required to perform meaningful statistical comparisons. Watching the return of survey responses during the data collection period was exciting but nerve-wracking as

bursts in responses were followed by periods of inactivity. I was over the moon with the final number of responses, particularly given the spread throughout the UK and that the demographics of the sample reflected those of the general student population.

However, caution must be taken when inferring these findings to the wider population. As convenience sampling via social media was used it was not possible to determine a response rate and therefore identify whether participant bias occurred. It is reasonable to assume that marginalised sections of the student population may have not taken part in the study for various reasons. In addition, we cannot preclude the possibility that there may be a selection bias, with individuals who are pro, or even anti, energy drinks being more likely to complete the survey. The sample was also restricted to UK universities, therefore given their unique drinking practices, results cannot be generalised beyond the UK or deduced to the general population. Despite these limitations, the current survey progressed the regional methodology adopted in previous AMED surveys.

The large sample size meant I needed to quickly develop good data management skills in statistical software to collate, clean and code the data, particularly for defining the consumption groups. Whilst I had previously used SPSS during my undergraduate degree, the statistical analysis for the publications required me to learn new techniques. I became aware of the value of using SPSS syntax to document what you have done and to build a library of commands that could be drawn upon for future analyses. This has served me well, particularly when responding to reviewer's comments that require you to revisit your data analysis or when combining the data for cross cultural comparisons.

This project allowed me to gain an appreciation of the importance of international collaboration in research. Being part of this research group enabled my findings to have wider impact, particularly through joint symposium submissions at international conferences. It also provided an opportunity for me to obtain career advice and learn directly from established scholars in the field.

As the academic debate regarding AMED use matured, 'opposing camps' developed which meant navigating the peer review process became increasingly difficult. It seemed like this had become a political issue rather than being purely based on scientific credibility. This was evident in publication

2 being submitted to five different journals with numerous peer review rounds before being accepted. I found this extremely frustrating but was grateful to my supervisors for helping me tease out which comments could usefully improve the publications, and which were simply aimed at blocking publication as the findings did not comply with the reviewers opposing position, and which formed the basis of their funding applications.

Having now spent some time away from the AMED research arena and reading my publications back to inform this commentary, I can see how, during the early years of my DPhil journey, I may have developed an unconscious bias towards my academic group and industry funders (Red Bull GmbH) position. At times during the peer review process or during conference presentations, it felt like you were in the trenches, and this is evident is the use of some biased language (e.g. preoccupation with AMED). I feel that this is something I became more aware off and improved upon as the following studies progressed.

4.3.1 Introduction to project 3: On-premise study

Whilst the UK wide student survey allowed us to gain an understanding of AMED consumption patterns and investigate its possible effects on overall alcohol consumption and consequences, there were limitations inherent of its methodology which we aimed to address with project 3. The survey relied on students to retrospectively recall the frequency, quantity and type of alcohol consumed, either in the past 30 days or 12 months. It is therefore likely that the ability to accurately recall this information would have been affected by the time frame passed and the amount of alcohol consumed.

Alternative research methods at the time to investigate the effects of AMED on subjective intoxication included experimental studies (Benson et al, 2014). However, these consistently failed to find any significant differences between alcohol alone and alcohol with caffeine. On suggestion for these findings, it that ethical approval limited the amount of alcohol and caffeine that could be administered, and laboratory settings were unable to replicate the real-world context in which consumption takes place.

To address these limitations some researchers (Devilly et al, 2017; Lubman et al, 2013; Lubman et al, 2014; Miller et al, 2013; Pennay et al, 2015; Thombs et al, 2009) began using on-premise studies to investigate the effect of AMED consumption. This involved asking people about their drinking experience as they exited night-time entertainment venues. However, in line with the survey research the majority of these studies used between-subject comparisons to reach and causal conclusions regarding the impact of energy drinks on alcohol consumption.

My supervisor, JV and colleagues (Verster et al, 2015) were the first to apply a within-subjects design to an on-premise study, by asking participants to also recall consumption on other drinking occasions. However, this study did not investigate the impact of other caffeinated mixers. Therefore, it is likely that alcohol-caffeine consumers (other than energy drinks) may have been included within the alcohol-only consumption occasions. The purpose of the current project was to address this limitation by examining whether AOCM had a differential effect on objective and subjective intoxication compared to consuming AMED or AO.

4.3.2 Research methods

In designing this project one of the first considerations was who the target population should be and the best location to collect this data. The decision was between continuing our focus on students through our established relationships with Student Union's in the Bristol area or widening this out to the wider public. Following a number of observational visits, we realised that mainly first year students who lived on campus used the Student's Union as their regular drinking venue and even they tended to move on to the city centre to finish off their drinking occasion. We therefore decided to examine the wider population by conducting the study outside the most popular night-time entertainment venues in Bristol city centre. This also allowed us to address the limitation acknowledged as part of project 2 of being unable to generalise beyond the student population.

Once the locations were identified I set about recruiting research assistants to help with data collection. Whilst I was fortunate to have a keen group of students from the courses I was teaching on, I needed to ensure they had the required skill set for the project. I was required to follow university

advertisement and recruitment processes and was responsible for providing formal training, managing rota's, ensuring safety and welfare and liaising with the HR department for timely payment of wages. This was a steep learning curve in the management of others.

The methodology was similar to that successfully employed by (Verster et al, 2015), but with the ability to differentiate between AOCM, AMED and AO drinking occasions. We had considered the inclusion of further standardised measures to allow us to perform additional analyses, however this needed to be balanced against the short time frame to engage with participants.

4.3.3 Ethical considerations

Project 3 presented many ethical challenges that needed to be addressed before the study could commence. Alcohol intoxication can impair cognition and judgement that are essential in order that potential participants can fully understand what participation in the research involves, and thus may compromise informed consent. Therefore, it was essential that we developed a robust process for ensuring informed consent and that adequate training was provided for the research assistants. I investigated previously conducted on-premise studies to find out how they had acknowledged intoxication in the informed consent process, and after discussion with my supervisory team and advice from our University ethics committee we decided to adopt the recommendation by (Aldridge & Charles, 2008). These included training researchers to be sensitive to the signs of excessive intoxication that may preclude participation, checking participants comprehension of information provided in spite of levels of intoxication and being alert to any changing signs of willingness to participant in the study. We also provided participants with a business card that could serve as a reminder that they had taken part as well as emailing them the information sheet and a copy of their data the following day. This allowed the participant to contact us if they wished for their consent to be retroactively withdrawn. Thus, the time frame over which the process of providing consent was extended into a period in which the participant was no longer under the influence of alcohol. Complying with these recommendations required additional resource but was considered necessary to ensure informed consent.

Another significant ethical consideration was the safety and welfare of research assistants. Collecting data from the night-time economy where the majority of people are under the influence of alcohol introduces the possibility of verbal or physical aggression. It was therefore important that measures were put in place to prevent our research team from coming into any harm. In advance of data collection, we gained consent from the night-time entertainment venue owners and local police. On arriving we introduced ourselves to the bar/club security staff to ensure they were aware of what we were doing and that they were willing to assist the research team if any problems occurred. The research team all wore hi-visibility tops labelled "alcohol researcher" and carried an alarm that emitted a loud bleeping noise to attract attention if required. Research Assistants worked in pairs so that they could assist each other and provide support if necessary. I stayed as close to the research team as was practical and monitored them throughout the data collection periods. We had considered using ipads to collect the data directly into the database, however this was considered to present an additional risk to the research assistants with possible theft, therefore pen and paper were used.

The study protocol was reviewed and approved by UWE ethics committee (HAS/16/03/117).

4.3.4 Intellectual contribution

4.3.4.1 Publication 7

The findings from the on-premise study were published in Brain and Behavior journal and can be found here:

Johnson, S. J., Verster, J. C., & Alford, C. (2022). An on-premise study to investigate the effects of mixing alcohol with caffeinated beverages. *Brain and behavior*, e2445. https://doi.org/10.1002/brb3.2445

The significance of this publication is that it is the first on-premise study to be conducted in the UK, and the first known worldwide to differentiate alcohol-caffeine consumers using both between and within-subject comparisons. The between-subject findings showed that alcohol-caffeine consumers

drank more alcohol and had higher objective and subjective intoxication that those who consumed AO. This was regardless of whether or not they mixed alcohol with caffeinated mixers or consumed AO on the night of the interview. These findings build upon publication 4 by further demonstrating that increased alcohol consumption is not unique to AMED consumers only but extends to all alcohol-caffeine consumers. Combined with the within-subject findings that mixing alcohol with caffeine in any form does not increase total alcohol consumption, the implication of this publication is that healthcare practitioners may want to include alcohol-caffeine use, and not just AMED, as an indicator to identify those most at risk of excessive alcohol consumption per se, who could benefit most from harm reduction strategies.

When plotting subjective intoxication against BAC (between-subjects), the study failed to reveal any masking effects for either AMED or caffeinated mixers. One possible explanation could be a lack of statistical power due to the small sample size resulting in a type II error. When considering mean differences at different BAC ranges the subjective intoxication scores were elevated compared to AO scores. This may give an indication of the direction of difference future sufficiently powered studies may find. Potential pharmacological explanations that may explain higher subjective intoxication in AMED versus AO at higher BACs include caffeine attenuating rather than masking the effects of alcohol. Other ingredients contained in caffeinated beverages, such as taurine in energy drinks, may also play a role in influencing subjective intoxication.

The methodology used in this study went some way to address the limitation of retrospective recall inherent of the survey design in project 2 by collecting alcohol consumption data in an ecologically valid setting. However, it must be acknowledged that in order to provide a within-subject comparison data was collected on a past drink occasion to compare with the on-premise evening. Therefore, it may be possible that this measure was affected by recall bias or alcohol related amnestic effects. A further limitation of the on-premise methodology in general is that it only captures information from a single drinking occasion which may not be representative of the participants general drinking behaviour. These limitations were considered in the design of project 4.

4.3.5 Personal reflection

During the process of conducting this on-premise study I faced many challenges that I feel have developed me significantly as an independent researcher. This was my first experience of creating a research team and managing them in the delivery of a project. This required good interpersonal skills and communication to ensure they fully understood the research process and were confident in collecting the data in a live, and potentially volatile, environment. I also needed to manage research assistant availability across the data collection nights and balance the needs of the study with their other university commitments and paid employments.

The nature of the study presented substantial ethical hurdles that required careful consideration to ensure adequate processes were in place to safeguard the participants and research assistants. This involved working closely with the University ethics committee and relevant stakeholders. Despite having confidence in the recruitment and training, ensuring the safety and welfare of the research assistants was a significant burden and worry during the initial data collection night. However, I was soon reassured as the project progressed without any incidents. We were commended by the local police and venue owners on our positive impact of engaging with participants and I was subsequently invited to join Bristol City councils' independent advisory group, Bristol @ night. In this role I utilised the data collected in this DPhil submission to provide advice on the challenges of excessive alcohol consumption and adverse consequences in the night-time economy and support the development of interventions to address this problem. It was satisfying to draw upon the project outcomes to address practical issues in the local community.

I found the two-week data collection period exhausting and think this may have had a detrimental impact on the number of responses obtained during the last few nights as enthusiasm and motivation ebbed. This was not helped by torrential rain on the last night which made data collection difficult. In hindsight it may have been better to spread the data collection over a longer period of time. By doing this we could have tried to collect data within-subjects across different consumption occasions, rather than relying on retrospective recall. However, this needed to be balanced with the time constraints of

conducting this research. Overall, I was pleased with how well we all worked as a team and the quality of the data we collected.

4.4.1 Introduction to project 4: Prospective study

Since the publication of our systematic review and meta-analysis (publication 1) there had been a substantial increase in the number of studies applying both between and within-subject designs. These have consistently demonstrated that whilst AMED consumers usually drink more alcohol than AO consumers, this is irrespective of whether energy drinks are consumed with alcohol or not, thus refuting the causal link between AMED and alcohol outcomes. Despite the building evidence, these studies were mainly reliant on cross-sectional survey designs given that this methodology is quick to conduct, convenient for participants and cost-effective.

Whilst project 3 went some way to address the limitations of retrospective recall inherent in survey designs by collecting data in an ecologically valid setting, the within-subject comparison still required recall of a past consumption occasion. Similarly, to the limitations of survey designs, this recall is likely to have been affected by the amount of time passed since the consumption occasion, and the volume of alcohol consumed. A particular criticism that could have impacted the conclusion drawn from these studies, is that this recall bias could differentially affect memory of AMED occasions versus AO occasions (Linden-Carmichael et al, 2018), given that AMED consumers tend to drink AO on the majority of drinking occasions (Scholey et al, 2018).

Some researchers (Linden-Carmichael & Lau-Barraco, 2017; Patrick & Maggs, 2014) adopted daily diary designs to try and address the potential inaccuracy with retrospective methods. However, these studies did not collect sufficient data on AMED consumption occasions to provide meaningful comparisons or conduct true within-subject analyses (see publication 10 for an in-depth critique). This method is also not immune to the limitations of retrospective recall, since next day recollection could be clouded by alcohol-related amnesic effects (Verster et al, 2003).

On completion of project 3, ecological momentary assessment (EMA) techniques were emerging as a new methodology to collect data on alcohol consumption behaviours (Clapp et al, 2017; Dulin et al, 2017; Kuntsche & Labhart, 2013; Merrill et al, 2017). This involves using smartphone applications to capture an individual's drinking behaviour as it occurs over a period of time. Thus, this technique addresses the biases inherent of retrospective recall of alcohol consumption and allows repeated measurement of the same participants. Given that the majority of AMED research findings were based on retrospective survey methods, as a research team we were interested in exploring the use of EMA techniques to design a study that would allow us to validate this data collection method. This led to the development of project 4.

4.4.2 Research methods

On conducting a literature search of currently used EMA techniques at the time, it was evident that the majority of alcohol studies used bespoke mobile phone applications to collect data. Whilst there were many applications available to track personal consumption, customisable EMA applications, such as metricwire, were still in their infancy and not readily available. We therefore created a project brief and reached out to app developers to tender for the service required. Unfortunately, the cost and timeline for completion was far beyond our resources for this project.

I then had the idea of using WhatsApp as our data collection tool. From my daily communication with students through teaching I was aware that this was the most commonly used method of communication among young people – those most likely to mix alcohol with energy drinks and therefore our target population. This app is free to use across all smartphone platforms and allows users to communicate with selected contacts with text, picture and video content.

In contrast to the pre-defined options and drop-down menus used in other study apps, the unrestricted nature of WhatsApp meant that whilst it was possible to collect rich data it would have made the data cleaning and analysis difficult. As a research team we discussed the best way to standardise the reporting of alcohol consumption to ensure the data collected met our primary outcome measures, was

accurate, not burdensome to participants and reflected the way in which they already engaged with the app on a daily basis. We decided that participants would inform us of the initiation of an alcohol consumption occasion, then provide a photo of the beverage consumed along with a short description of the brand, volume, price and location. I was responsible for monitoring responses in real-time and querying participants for further information if the number of alcoholic units could not be deduced from a standardised list. There were occasions when this information could not be obtained. As a research team we discussed these incidents and reached consensus on the alcohol content of these remaining beverages from the information available.

Given that this was the first known study to utilise this app within alcohol consumption research, we decided to include a 2-week familiarisation period before collecting the data that would be compared with retrospective recall. This allowed us to test the feasibility of using this app and to address any user-acceptance issues. It was made clear to participants that after this period, they could decide whether or not they wanted to continue in the study. We were pleasantly surprised with how well the familiarisation period went, with only minor additional training required to standardise responses and a small number of withdrawals (6). The preliminary data collected also allowed us to calculate the best time (8pm) to remind participants to record their alcohol consumption or to recollect if they had forgotten to do so.

To assess compliance with the study protocol we also thought that it was important to include a prompt the following day so that participants could either confirm that they had not consumed alcohol or provide them with the opportunity to recall if they failed to report this in real-time. Careful consideration was given in balancing the need to ensure compliance against placing an unnecessary strain on participants which may have actually led to disengagement.

Students were selected as the recruitment population given the existing links with UWE students union, which also provided a convenient location for conducting baseline and follow-up visits. Publication 2 demonstrated that on average UK students were high AMED consumers compared to the general population. We hoped that selecting them as our sample would allow us to collect sufficient AMED drinking occasions to make meaningful within-subject comparisons. In deciding on

this recruitment strategy, we accepted the limitation that these findings could not be generalised beyond the student population.

4.4.3 Ethical considerations

In developing our recruitment strategy, we needed to carefully consider the level of incentive provided for participation in the study. Whilst we wanted to attract participants and appropriately compensate them for their time, this needed to be balanced with having an undue influence on their decision to take part or their decision to withdraw. This is particularly the case for EMA research which has often provided generous compensation for high levels of participation. After investigating previously used incentives, discussions with students themselves and advice from our university ethics committee, we decided on a total of £50 reimbursement. It was explained to participants that they were free to withdraw at any time and reimbursement would be paid pro-rata based on the number of days compliant with the study protocol, rather than the number of reported drinking occasions therefore not encouraging drinking behaviour.

As in projects 2 and 3, it was important to consider the potential psychological impact of taking part in this study. Participants were asked to report alcohol-related consequences which they may have found distressing or stigmatising. This is heightened in EMA research as participants are required to recall this information repeatedly over a period of time. We had considered whether suitable advice and guidance should be provided in real-time for certain reported consequences (sexual assault, drug use) but felt that this wasn't appropriate given that it was an observational study. Communication of support services were standardised for all participants, and were communicated in the information sheet, sent as a picture via WhatsApp at the beginning of the study so they could be accessed anytime, and highlighted again during debriefing.

Due to the nature of EMA research and the constant sharing of electronic data there was also the potential for harm from disclosure of information about participants. This was particularly important in this study whereby possible illegal behaviour through the reporting of alcohol-related consequences

were being shared by participants. Confidentiality was ensured by the end-to-end encryption of WhatsApp meaning only the researcher and participant could read what was sent, and nobody in between, including WhatsApp, could access this information. In addition, it was imperative that a robust process for the transmission and storage of participant data was developed.

The study protocol was reviewed and approved by UWE ethics committee (HAS/16/03/116).

4.4.4 Intellectual contribution

4.4.4.1 Publication 8

The findings from the prospective study were published in Alcohol and Alcoholism journal and can be found here:

Johnson, S. J., Verster, J. C., & Alford, C. (2022). A Comparison Between Ecological Momentary Assessment and the Adapted-Quick Drinking Screen: Alcohol Mixed With Energy Drinks. *Alcohol and Alcoholism*. https://doi.org/10.1093/alcalc/agab086

This publication provided an original contribution to research by being the first study to utilise EMA to investigate the effects of AMED, and to use the data collected to validate retrospective survey methods. It was reliably found across both data collection methods that alcohol is consumed more frequently and at higher levels, and risk-taking behaviours are experienced more often on AO occasions compared to AMED occasions. This consistent finding provided further support to the growing body of evidence (Verster et al, 2018) that indicates mixing alcohol with energy drinks seems unlikely to be responsible for the increased alcohol consumption or associated risk-taking observed among AMED consumers compared to AO consumers. The results also revealed that, consistent with previous research (Dulin et al, 2017; Heeb & Gmel, 2005; Monk et al, 2015; Poulton et al, 2018), the quantity of alcohol reportedly consumed, and the number of risk-taking behaviours were higher when reported via EMA compared to retrospective survey methods. Of significant importance to the field of AMED research, these findings were consistent across AO and AMED drinking occasions. This is in contrast to claims Linden-Carmichael et al (2018) that recall could be

differentially affected across AMED and AO drinking occasions and provides assurance in the direction of findings from previous studies using retrospective survey methods to assess AMED consumption. These findings contributed to the public health debate regarding the safety of AMED use, by suggesting that whilst caution must be taken when reaching policy decisions based on underreported retrospective methods, the focus should be on addressing excessive alcohol consumption per se rather than the preoccupation of AMED.

The study also advances scholarship beyond the AMED research field by demonstrating that it is feasible to collect alcohol consumption data from students using commonly available apps with a high degree of compliance. This approach could be adopted by other researchers, who similarly don't possess the necessary skills to develop an app or are restrained financially to purchase bespoke solutions. In hindsight, I wish I had included a qualitative investigation to examine participant experience in-depth to further inform future application of this methodology.

4.4.5 Personal reflection

The prospective study was the culmination of the proceeding research projects to sequentially address the methodological limitations within AMED research. It provided an opportunity to validate the within-subject findings from my early survey research. During the study conception, design, implementation and dissemination many challenges were faced which I believe have helped me develop as an independent researcher.

As already discussed, it was not financially feasible to develop a bespoke app to collect our data. Whilst the decision to use WhatsApp overcame this issue and reduced the need for development time at the beginning of the study, it presented additional challenges downstream. Whereas bespoke apps used defined drop-down menus to record alcohol consumption, our decision to use pictures and a short description meant I needed to monitor the responses in real-time in order to raise queries if necessary. Participant responses then also needed to be converted to alcohol units and consumption occasions defined as AMED or AO. This required substantial data cleaning in preparation for analysis

which was both time consuming and draining. This experience taught me the importance of developing a robust data management plan from the outset to consider the flow of data from first collection to analysis. I also learnt how important determination and persistence were in seeing a project through.

Initial interest in taking part in the study was higher than anticipated. This provided some justification in the level of incentive included. However, a significant proportion of students did not meet the inclusion criteria of reporting two AO and two AMED drinking occasions in the past two months. In addition, even those that met this inclusion criteria nearly half of participants (45.3%) did not report an AMED drinking occasion during the 30-day data collection period. Potential explanations for this have been provided in the publication, with suggestions on how to address this in future studies, however this broadly reflects the infrequent and sporadic nature of AMED consumption.

Whilst the previous published papers required submission to a number of journals and several peer-review rounds, this paper was accepted following a short but informative peer review process within Alcohol and Alcoholism. The comments and recommendations received substantially improved the paper, particularly the methods section and suggested inclusion of pertinent publications within EMA research. I feel this was because the reviewers were leading EMA scholars rather than AMED researchers engaged in the academic debate regarding its use.

In conceptualising this study the aim was always to compare EMA with retrospective methods (e.g. a-QDS) in order to substantiate previous findings within AMED literature. However, the event-level data collected lends itself to a more nuanced examination of the socio-environmental factors, such as location, price etc, that may contribute to heavy and risky drinking. It has been frustrating that moving into different job roles has meant I have been unable to spend time conducting these additional analyses, using techniques such as multilevel modelling, which could have further shed light on excessive alcohol consumption practices among UK students. I hope to explore this further on completion of this thesis.

4.5.1 Introduction to project 5: Critical review and meta-analysis 2

Since beginning this doctoral journey in 2014 the growth in research investigating the effects of AMED has been exponential. This has been driven by the rise in popularity of AMED consumption world-wide and the subsequent public health interest regarding its use. The research to date has focused on investigating the prevalence of AMED use and its correlates across countries, as well as its potential to increase alcohol consumption, reduce feelings of subjective intoxication and result in increased risk-taking behaviour and adverse negative alcohol-related consequences.

Whilst our previous systematic review and meta-analysis (project 1) focused on the different methodologies employed (between-subject versus within-subject) to examine whether co-consumption of energy drinks had an impact on total alcohol consumption, in the two-year period since that publication, many additional studies have been conducted to investigate this concern.

In 2012, my supervisors CA and JV (Verster et al, 2012) reviewed the available literature against the above suggested health risks and concluded that there was insufficient evidence at the time to draw any firm conclusions regarding the effects of mixing alcohol with energy drinks. Given the substantial increase in the available published literature within AMED, the purpose of the current critical review and meta-analysis was to revisit those public health concerns and provide an update on the possible impact of mixing alcohol with energy drinks.

4.5.2 Research methods

As a research team we decided on the relevant databases to conduct the literature search and agreed on the search terms. The initial search was conducted by JV and provided 1039 hits. I was then involved in removing duplicates, reviews, commentaries, and editorials and preparing the remaining abstracts for screening against the aims of the critical review. The screening was completed in an Excel document uploaded to a shared drive so each researcher could indicate the relevance of the publication against each topic. Any discrepancies in the screening process were discussed and resolved, leaving 80 publications to be included in the critical review.

These publications were then checked to see if the necessary outcome measures were reported so that an effect size could be calculated for inclusion in a meta-analysis. Sufficient data was available on alcohol consumption and subjective intoxication and JV was responsible for conducting and reporting the meta-analyses. I was involved in drafting the manuscript and creating the tables to succinctly summarise the findings, as well as responding to reviewer comments and approving the final manuscript.

4.5.3 Ethical considerations

The main ethical considerations when conducting a systematic review and meta-analysis have been reflected upon for project 1 (section 4.1.3). These are also pertinent to this current project and for brevity have not been repeated here.

4.5.4 Intellectual contribution

4.5.4.1 Publication 9

The findings from the critical review and meta-analysis were published in Human Psychopharmacology: Clinical and Experimental and can be found here:

Verster, J. C., Benson, S., Johnson, S. J., Alford, C., Godefroy, S. B., & Scholey, A. (2018). Alcohol mixed with energy drink (AMED): A critical review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, *33*(2), e2650. https://doi.org/10.1002/hup.2650

In summary the critical review and meta-analysis found that only a minority of the population consume AMED, usually infrequently, for mainly hedonistic and social motives. AMED consumers were found to differ from AO consumers across a range of characteristics, including higher alcohol intake, sensation-seeking and risk-taking. However, within-subject comparisons showed that among AMED consumers the co-consumption of alcohol with energy drinks had little to no significant effect on total alcohol consumption, subjective intoxication, and alcohol-related risk-taking behaviour or other negative consequences compared to consuming alcohol alone. Based on these findings we concluded that AMED consumption may be one of several manifestations of an underlying trait for

greater alcohol consumption along with a cluster of other risky behaviours, but that further research addressing the limitations outlined may be needed to reveal the full effects of AMED.

The significance of this publication is that it is the most recent review to provide a comprehensive synthesis of the extant literature on the prominent health concerns regarding AMED using meta-analytic techniques. By providing a precise estimate of the effects, this approach overcomes the limitations of previously published narrative reviews (Marczinski & Fillmore, 2014; McKetin et al, 2015; Reissig et al, 2009; Vida & Racz, 2015) providing an objective measure of the integrated quantitative evidence.

The findings are important as they further highlight the issue that association between AMED use and excessive alcohol intake should not imply causation, given that alcohol consumption remains high among AMED consumers, regardless of whether energy drinks are consumed or not. Whilst further research is required to fully understand the effects of AMED, this current critical review and meta-analysis, along with the individual studies presented within this thesis, suggests that the preoccupation with AMED may be diverting attention away from the more pressing issue of excessive alcohol consumption per se.

4.5.4.2 Publication 10

Shortly after the publication of our critical review and meta-analysis (publication 9) we received notification that a 'Letter to the Editor' (LTE) had been submitted by Linden-Carmichael et al (2018) and we were invited to respond.

Scholey, A., Benson, S., Johnson, S., Alford, C., Godefroy, S. B., & Verster, J. C. (2018). Why meta is better: A reply to Linden-Carmichael et al.(2018). *Human Psychopharmacology*, *33*(4). https://dx.doi.org/10.1002%2Fhup.2663

The premise of Linden-Carmichael et al (2018) LTE was to highlight the methodological limitations of the studies included in our critical review and meta-analysis and point to their recent daily diary study (Linden-Carmichael & Lau-Barraco, 2017) as addressing these shortcomings and providing contrasting findings. Unfortunately, their daily diary study had been published after our critical review

and meta-analysis and thus was not included. Whilst we understood the limitations inherent of the study designs employed in previous research, the purpose of the critical review and meta-analysis was to provide an objective account of the available literature on the functional consequences of AMED at the time of the review. In hindsight, a more in-depth consideration of these limitations could have been included in the discussion section, but this was due to word count restrictions rather than purposefully downplaying the potential harms of AMED, as suggested by the authors of the LTE. Indeed, as demonstrated throughout the publications included in this thesis, our aims as a research team have always been to fully understand the potential effects of AMED by increasingly developing the methodology employed.

In responding to the LTE, we welcomed the contribution of the recent publication by Linden-Carmichael & Lau-Barraco (2017) to the AMED literature, especially given the lack of prospective study designs, but cautioned against refuting all previous AMED research in light of this single publication. As highlighted in our response, this is of particular importance given the advantage of meta-analyses to objectively synthesise a field of research rather than single studies which can be influenced by selective reporting. Whilst acknowledging the original contribution of Linden-Carmichaels study in progressing the methodology employed in AMED research, several limitations regarding data analysis and reporting were identified in our response, which further calls into the question the suggestion that this single publication supersedes all previous AMED research. The opportunity to respond to this LTE allowed us to reaffirm the validity of the meta-analysis findings and that further research may be required to fully understand the effects of AMED.

4.5.5 Personal reflection

This critical review and meta-analysis was more demanding than project 1 as it encompassed all of the health risks associated with AMED consumption, such as prevalence, motivations, subjective intoxication and risk-taking, rather than just overall alcohol consumption. This presented additional challenges when identifying, managing, and summarising the vast number of publications. It was important to differentiate between the studies included in the original literature review (Verster et al,

2012) and those published since in order to compare findings and indicate if anything had changed. This highlighted the growth of AMED research during this timeframe and provided justification for the timing of this publication. Condensing such a comprehensive review to meet the journal requirements was challenging and required difficult decisions and multiple revisions as a research team.

I was more involved in the meta-analysis this time around and took responsibility for screening publications for the necessary outcome measures for inclusion. By shadowing JV, I gained an understanding of the assumptions and techniques used when applying this statistical approach. I have taken the knowledge gained during this process into my current position where I am involved in conducting meta-analyses within blood cancer research.

Given the contentious nature of AMED research at the time, we were not surprised to hear about the LTE by Linden-Carmichael et al (2018). It was unfortunate that their daily diary study had been published after we had conducted our review and it was understandable that they wanted to highlight their findings in light of this. However, we felt the claims made were overzealous particularly given the limitations we identified in critically reviewing their study.

There was pressure to submit the response to the LTE within a short space of time so that it could be included in the same issue. We worked well as a team to meet this deadline and ensured the response was measured, supported by research findings and not defensive or reactionary. Coming up with a punchy, effective title was probably the most difficult task. Frustratingly, we were unable to refer to the UK prospective study findings (project 4) given that they had not yet been accepted for publication.

Chapter 5: Conclusion and implications

Through the submission of this critical commentary on the ten peer-reviewed publications detailed herein, this doctoral thesis has demonstrated a contribution of new knowledge to the field of alcohol mixed with energy drinks. This programme of research was developed in light of public health concerns (Drinkaware, 2021; National Health Service, 2015) that consuming AMED posed greater risk, above and beyond consuming alcohol by itself, and therefore a behaviour worth targeting to reduce excessive alcohol consumption. To advance the scholarship of AMED research and to further inform the safety of its use, the studies included have provided sequential methodological improvements to overcome the limitations of previous research. This has included addressing the limitations associated with application of between-subject designs in reaching causal conclusions on the effects of mixing alcohol with energy drinks, as well as the use of retrospective data collection methods.

The key findings of the included publications have been broadly consistent across the different methodologies employed. AMED consumers have been shown to differ from AO consumers across a range of characteristics, including higher alcohol intake and risk-taking behaviours. However, within-subject comparisons have indicated that among AMED consumers mixing alcohol with energy drinks does not significantly increase total alcohol consumption, subjective intoxication or negative alcohol-related consequences compared to consuming alcohol alone. Based on these findings we conclude that AMED consumption may be one of several manifestations of an underlying trait for greater alcohol consumption along with a cluster of other risky behaviours. The triangulation of methodologies utilised in the studies included in this thesis, alongside the synthesis of the wider literature through the systematic/critical review and meta-analyses, provides credibility and validity to the conclusions drawn.

These findings have important implications given calls for policy changes (Arria & O'Brien, 2011; Howland & Rohsenow, 2013) to reduce the consumption of AMED based on early between-subject designs. They suggest that AMED use, and more widely alcohol-caffeine use, may be a valuable

indicator for healthcare practitioners to identify individuals who may benefit the most from risk and harm reduction strategies for excessive alcohol consumption per se. However, the research findings to date do not justify the restriction of AMED over other forms of alcohol. Thus, it appears that whilst alcohol-caffeine consumption may be a useful indicator for increased alcohol consumption and adverse consequences, it is not the driver.

Whilst there was much debate between opposing positions during the early rise in AMED research, more recently there has been consensus towards our conclusions amongst the AMED research community. This is evident in a shift towards within-subject designs (Newcombe et al, 2020) and reduced research activity in this area given the increasing evidence discrediting the link between AMED and increased alcohol consumption. There has been an indication that our findings are beginning to filter into practice. For example, Health Canada recently approving the removal of the label statement "do not mix with alcohol". This followed their acknowledgment that 'there is currently limited evidence supporting a direct risk to health resulting from the co-consumption of CEDs and alcohol. As well, there is limited evidence that CED consumption causes risky behaviours or masks signs of alcohol-induced inebriation that could promote risky behaviour' (Canada Gazette, 2022, p. 3759).

However, public health recommendations in the UK (Drinkaware, 2021; National Health Service, 2015) and beyond are still based on early research findings and require updating in line with the available evidence. These recommendations could more usefully focus on the recommended upper limit of caffeine that can be safely combined with alcohol, as well as recommended limits for alcohol consumption itself, and provide advice to consumers on this basis.

However, it must be acknowledged that further research may be necessary to fully reveal the effects of AMED as there may be other processes, not examined in the publications contained herein or the wider AMED research literature, which may leave AMED consumers at increased risk. For example, future research could usefully examine the longitudinal effects of alcohol-caffeine consumption on tolerance. It has been suggested (Fillmore, 2003) that repeated alcohol-caffeine consumption can lead to increased alcohol tolerance compared to consuming alcohol alone. Thus, a history of caffeine-

alcohol co-consumption, may increase alcohol tolerance and contribute to alcohol abuse by encouraging escalating levels of intake.

Indeed, a limitation of the research included in this thesis, is that it was mainly reliant on convenience student samples. Therefore, it is not known to what extent these findings are representative of the wider population. Future research should continue to examine group differences between the different types of AMED consumers, to assess the factors that might predict the association between problematic AMED use and negative alcohol-related behaviours.

Whilst additional research into AMED is warranted this should not divert from the more pressing issue of excessive alcohol consumption per se. What was evident in our findings is that alcohol consumption remains a significant public health problem, particularly among students. Alcohol research and preventive interventions rarely focus on drinking at the event-level since drinking events are complex, dynamic, and methodologically challenging to observe. The prospective study conducted as part of this thesis has illustrated that is it possible to collect event-level data from students using EMA techniques. Future research should build upon this work to identify the socio-environmental factors that that may be contributing to heavy and risky alcohol consumption in order to develop appropriate interventions.

Chapter 6: Summary evidence of meeting the UWE Bristol doctoral descriptors

In this chapter I will provide a summary of how, in submitting this evidence of scholarship, the UWE doctoral descriptors have been met:

1) Has conducted enquiry leading to the creation and interpretation of new knowledge through original research or other advanced scholarship, shown by satisfying scholarly review by accomplished and recognised scholars in the field.

The five projects conducted as part of this research programme have contributed new knowledge to the field of alcohol and energy drink research. The findings have been peer reviewed in relevant high impact journals and accepted as contributing scientifically robust original research. Collectively, the ten publications included in this thesis have currently been cited 152 times, a respectable contribution given that four of these papers have been published in the last year. In addition, the findings have been subject to the scrutiny of recognised international scholars on alcohol conference review panels, including in the United States and Australia, and accepted for presentation.

2) Can demonstrate a critical understanding of the current state of knowledge in that field of theory and/or practice.

To conceptualise the research programme reported herein, required a constant examination of the existing evidence to identify limitations and gaps in research. The published papers critiqued the methodological weaknesses in current alcohol and energy drink research. This included the reliance on retrospective recall of alcohol consumption and the use of laboratory studies that do not capture the levels of alcohol consumed in real-world drinking occasions. In addition, the use of between group designs to (wrongly) infer causation in explaining differences in alcohol consumption between groups, when mixed designs including within and between-subject comparisons were required.

A critical understanding of the current state of knowledge within AMED research was demonstrated through the publication of two systematic/critical review and meta-analyses. This first (publication 1)

focused on how the study design effects the results and conclusions made, and the second (publication 9) provided a complete review of the available literature on AMED.

3) Show the ability to conceptualise, design and implement a project for the generation of new knowledge at the forefront of the discipline or field of practice including the capacity to adjust the project design in the light of emergent issues and understandings.

In the successful delivery of projects 2, 3 and 4 I have demonstrated the ability to work with colleagues to conceptualise, design and implement research to generate new knowledge in the field of alcohol mixed with energy drinks. Each project has built upon the methodological weaknesses of previous research, including my own publications, and emergent issues, such as considering the impact of other caffeinated mixers, resulting in innovative studies to further advance knowledge into the effects of AMED. This has included an on-premise study where participants were breathalysed and completed a short questionnaire as they exited popular night-time entertainment venues. As well as a prospective EMA technique that utilised an available mobile phone application to repeatedly sample participant's alcohol-related behaviours and experiences in real time, in their own natural environment. This approach has allowed us to study the outcomes of mixing alcohol with energy drinks in real-world contexts, a novel approach in this field of research.

4) Can demonstrate a critical understanding of the methodology of enquiry.

A key theme to the research conducted has been the critical examination of the methodology employed in previous research. When conducting a review of the literature, it became apparent that the majority of studies had used between-subjects designs (comparing alcohol and energy drink consumers with alcohol-only consumers) to reach causal conclusions on the effects of mixing alcohol with energy drinks on overall alcohol consumption. However, correlation does not imply causation. In addition, between-subjects designs introduce the possibility of a third variable between the two groups that may explain the observed differences in alcohol consumption. Therefore, we employed within-subjects designs to investigate this effect across our three studies. Thus, a critical understanding of the methodology in this field of research has been demonstrated throughout the published papers.

5) Have developed independent judgement of issues and ideas in the field of research and / or practice and are able to communicate and justify that judgement to appropriate audiences.

The research conducted as part of this thesis demonstrates my independent judgement of issues and ideas within AMED research. This is illustrated in the development of new study designs that contrast to the prominent approach in alcohol and energy drink research. I have communicated and justified this judgement in peer reviewed journals and at both national and international conferences. This has included presenting at a symposium at the American Psychological Association (APA) conference 2015, as well as giving both oral and poster presentations at the Australasian Professional Society on Alcohol and Other Drugs (APSAD) and the US Research Society on Alcoholism (RSA) in 2014, 2015, 2016 and 2017. I have also demonstrated my independent judgement of issues and ideas within AMED research when acting as a reviewer of publications across several journals.

6) Can critically reflect on their work and evaluate its strengths and weaknesses including understanding validation procedures.

The evolution of the research conducted as part of this DPhil has demonstrated that I can reflect critically on my own work and evaluate its strengths and weaknesses. For example, by identifying the strengths (within-subjects design) and limitations (retrospective recall) of project 2, I then developed additional research designs that would address these weaknesses and validate the outcomes. This ultimately led to project 4, and the first publication within alcohol and energy drink research to validate retrospective survey data with real-time recall. This supporting critical commentary provides further evidence of my ability to examine the value, both strengths and weaknesses, in more depth.

Chapter 7: Current and future planned research activity

Completing this critical commentary has been a cathartic experience, allowing me to reflect on my DPhil journey, the challenges I have faced and the many skills and attributes I have developed which I will take forward into future endeavours. Whilst my current career path has taken me away from the field of alcohol mixed with energy drinks, my enthusiasm and passion for research remains.

In my present Data Analyst role at Cardiff University, I am enjoying being part of a large Centre for Trials Research (CTR) and contributing to the statistics team in the delivery of clinical trials across a range of research themes. Currently I have taken a lead role on a large-scale international data sharing project within blood cancer research. This has involved the harmonisation of existing trial data from diverse studies throughout the world with other datasets including genomic or routine data. This collaboration has led to many publication opportunities and has ignited an interest in utilising secondary data for analysis.

I have also continued my collaboration with colleagues at UWE. I was co-applicant on the WST3 project (Chief Investigator: AT) that received additional funding from the Department for Transport in 2021 to progress the intervention to a randomised control trial (RCT). I continue to provide data management and statistical advice via regular trial management meetings. I have also continued my interest within psychopharmacology, and I'm currently involved in a funding application with my supervisor, CA, to assess the effect of a novel sleep enhancer food supplement in self-declared insomniacs.

In the near future, I have aspirations to complete a MSc Statistics alongside my Data Analyst role. This will allow me to improve upon the skills obtained as part of this DPhil and further progress as an independent researcher.

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Appendix 1: Completion of necessary training requirements

Module code	Module name	Completion date
USSJLK-30-M	Research in contemporary context	February 2018
USSKDB-30-M	Research training and professional development	February 2018

Appendix 2: Co-author signed statements of intellectual contribution to works submitted

Project 1: systematic review and meta-analysis 1

Publication 1: Verster, J. C., Benson, S., **Johnson, S. J.,** Scholey, A., & Alford, C. (2016). Mixing alcohol with energy drink (AMED) and total alcohol consumption: a systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, 31(1), 2-10.

- I contributed to the systematic review of the literature
- I worked collaboratively to draw conclusions and corresponding implications
- I contributed to the first draft of the manuscript and subsequent revisions in response to reviewer's comments
- I contributed to the review and approval of the final manuscript.

Project 2: UK-wide study survey

UK specific contributions:

Publication 2: **Johnson, S. J.,** Alford, C., Stewart, K., & Verster, J. C. (2016). A UK student survey investigating the effects of consuming alcohol mixed with energy drinks on overall alcohol consumption and alcohol-related negative consequences. *Preventive Medicine Reports*, 4, 496-501.

Publication 3: **Johnson, S. J.,** Alford, C., Verster, J. C., & Stewart, K. (2016). Motives for mixing alcohol with energy drinks and other non-alcoholic beverages and its effects on overall alcohol consumption among UK students. Appetite, 96, 588-597.

Publication 4: **Johnson, S. J.,** Alford, C., Stewart, K., & Verster, J. C. (2018). Are energy drinks unique mixers in terms of their effects on alcohol consumption and negative alcohol-related consequences? *International journal of general medicine*, 11, 15.

- I was responsible for managing study budget and timelines
- I contributed to the design and methodology of the study
- I led the process of writing and submitting the application for university ethical approval
- I was responsible for designing and drafting the study documentation including consent forms, information sheets and case report forms, which were also reviewed by my supervisory team
- I co-ordinated project team meetings

- I designed and implemented data management processes ensuring the data was collected and stored in a secure manner
- I developed and tested the survey using Survey Monkey
- I was responsible for the design and implementation of the recruitment strategy
- I undertook the data cleaning, data analyses and led the interpretation of the results
- I wrote the first drafts of these papers, and working in collaboration with my supervisors, prepared the manuscripts for publication and redrafted them in response to reviewer's comments
- I disseminated the findings at scientific meeting, including poster and oral presentations at international conferences. Findings were also disseminated by my supervisors and collaborators.

Cross-cultural specific contributions:

Publication 5: Benson, S., **Johnson, S. J.,** Alford, C., Scholey, A., & Verster, J. C. (2021). A Cross-Cultural Comparison of the Effects of Alcohol Mixed with Energy Drink (AMED) Consumption on Overall Alcohol Consumption and Related Consequences. *International Journal of Environmental Research and Public Health*, 18(14), 7579.

Publication 6: **Johnson, S. J.,** Benson, S., Scholey, A., Alford, C., & Verster, J. C. (2021). Risk-taking behavior and the consumption of alcohol mixed with energy drink among Australian, Dutch and UK students. *International journal of environmental research and public health*, 18(10), 5315.

- I was responsible for combining the datasets from the different countries and preparing them for analysis
- I contributed to the first draft of these manuscripts
- I contributed to revisions of the manuscripts in response to reviewer comments
- I disseminated the findings at scientific meetings, including presentation at international conferences, alongside the collaborative team.

Project 3: On-Premise study

Publication 7: **Johnson, S. J.,** Verster, J. C., & Alford, C. (2022). An on-premise study to investigate the effects of mixing alcohol with caffeinated beverages. *Brain and behavior,* e2445.

- I was responsible for managing study budget and timelines
- I contributed to the design and methodology of the study
- I led the process of writing and submitting the application for university ethical approval
- I was responsible for designing and drafting the study documentation including consent forms, information sheets and case report forms

- I co-ordinated project team meetings
- I designed and implemented data management processes ensuring the data was collected and stored in a secure manner
- I took the lead in the recruitment of research assistants, including drafting of job description, shortlisting, interviewing, candidate selection
- I was responsible for training and supervision of research assistance during data collection
- I gained permission from night-time entertainment venues and police to conduct the research and ensure the safety and welfare of research assistants
- I was responsible for the design and implementation of the participant recruitment strategy
- I undertook the data cleaning, data analyses and led the interpretation of the results
- I wrote the first draft of the paper, and working in collaboration with my supervisors, prepared the manuscript for publication and redrafted it in response to reviewer's comments
- I disseminated the findings at scientific meetings, including presentation at international conferences, alongside the collaborative team.

Project 4: Prospective study

Publication 8: **Johnson, S. J.,** Verster, J. C., & Alford, C. (2022). A Comparison Between Ecological Momentary Assessment and the Adapted-Quick Drinking Screen: Alcohol Mixed with Energy Drinks. *Alcohol and Alcoholism.*

- I was involved in the funding acquisition required to conduct the study
- I was responsible for managing study budget and timelines
- I conceived the idea to conduct the study and developed research aims with supervisory team
- I led the process of writing and submitting the application for university ethical approval
- I was responsible for designing and drafting the study documentation including consent forms, information sheets and case report forms
- I co-ordinated project team meetings
- I developed and tested the ecological momentary technique using commonly used mobile phone application
- I designed and implemented data management processes ensuring the data was collected and stored in a secure manner
- I was responsible for participant recruitment and retention
- I undertook the data cleaning, data analyses and led the interpretation of the results
- I wrote the first draft of the paper, and working in collaboration with my supervisors, prepared the manuscript for publication and redrafted it in response to reviewer's comments

- I disseminated the findings at scientific meetings, including presentation at international conferences, alongside my collaborators

Project 5: Systematic review and meta-analysis 2

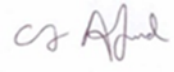
Publication 9: Verster, J. C., Benson, S., **Johnson, S. J.,** Alford, C., Godefroy, S. B., & Scholey, A. (2018). Alcohol mixed with energy drink (AMED): A critical review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, 33(2), e2650.

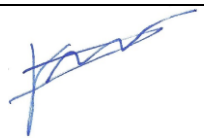
- I contributed to the systematic review of the literature
- I worked collaboratively to draw conclusions and corresponding implications
- I contributed to the first draft of the manuscript and subsequent revisions in response to reviewer's comments
- I contributed to the review and approval of the final manuscript

Publication 10: Scholey, A., Benson, S., **Johnson, S.J.,** Alford, C., Godefroy, S. B., & Verster, J. C. (2018). Why meta is better: A reply to Linden-Carmichael et al. (2018). Human Psychopharmacology, 33(4).

- I worked collaboratively to critically review and provide a response to the commentary of publication 9
- I contributed to the first draft of the manuscript and subsequent revisions in response to reviewer's comments
- I contributed to the review and approval of the final manuscript

I am a co-author on one or more of the studies listed above. I have read and agree with the statements regarding Sean Johnson's contribution to the published works on which I am a co-author.

Author	Signature	Date
Chris Alford		08 June 2022

Joris C. Verster		08 June 2022
Karina Stewart		09 June 2022
Andrew Scholey		13 June 2022
Sarah Benson		13 June 2022
Samuel Benrejeb Godefroy	See notes	See notes

Notes: At the time of this submission, it was not possible to contact Samuel Benrejeb Godefroy to obtain signatory for the authorship contribution statement.

Appendix 3: Bibliography of published works and conference presentations (in chronological order)

Publications

Tazi, T., Arango-Ossa, J.E., Zhou, Y, Bernard, E., Thomas, I., Gilkes, A., Freeman, A., Pradat, Y., **Johnson, S.J.,** … Papaemmanuil, E., (2022). Unified classification and risk-stratification in Acute Myeloid. medRxiv.

Coats, T., Bean, D., Basset, A., Sirkis, T., Brammeld, J., **Johnson, S.J,** ... & Dillon, R. (2022). A novel algorithmic approach to generate consensus treatment guidelines in adult acute myeloid leukaemia. British Journal of Haematology, 196(6), 1337-1343.

Johnson, S. J., Verster, J. C., & Alford, C. (2022). An on-premise study to investigate the effects of mixing alcohol with caffeinated beverages. *Brain and behavior*, e2445.

Johnson, S. J., Verster, J. C., & Alford, C. (2022). A Comparison Between Ecological Momentary Assessment and the Adapted-Quick Drinking Screen: Alcohol Mixed With Energy Drinks. *Alcohol and Alcoholism*.

Benson, S., **Johnson, S. J.,** Alford, C., Scholey, A., & Verster, J. C. (2021). A Cross-Cultural Comparison of the Effects of Alcohol Mixed with Energy Drink (AMED) Consumption on Overall Alcohol Consumption and Related Consequences. International Journal of Environmental Research and Public Health, 18(14), 7579.

Johnson, S. J., Benson, S., Scholey, A., Alford, C., & Verster, J. C. (2021). Risk-taking behaviour and the consumption of alcohol mixed with energy drink among Australian, Dutch and UK students. International journal of environmental research and public health, 18(10), 5315.

Alford, C., Broom, C., Carver, H., **Johnson, S. J.,** Lands, S., Reece, R., & Verster, J. C. (2020). The impact of alcohol hangover on simulated driving performance during a 'commute to work'—Zero and residual alcohol effects compared. Journal of clinical medicine, 9(5), 1435.

Merlo, A., Abbott, Z., Alford, C., Balikji, S., Bruce, G., Gunn, C., Iversen, J., Iversen, J., **Johnson, S.J.,** Kruisselbrink, L.D. and van de Loo, A.J., (2020). Proceedings of the 10th Alcohol Hangover Research Group Meeting in Utrecht, The Netherlands. MDPI Proceedings (4).

Verster, J. C., Kruisselbrink, L. D., Slot, K. A., Anogeianaki, A., Adams, S., Alford, C., **Johnson, S. J.,** ... & Stock, A. K. (2020). Sensitivity to experiencing alcohol hangovers: Reconsideration of the 0.11% blood alcohol concentration (BAC) threshold for having a hangover. Journal of clinical medicine, 9(1), 179.

Johnson, S. J., Alford, C. , Stewart, K. and Verster, J. C. (2018) Are energy drinks unique mixers in terms of their effects on alcohol consumption and negative alcohol-related consequences? International Journal of General Medicine, 2018 (11). pp. 15-23.

Scholey, A. , Benson, S. , **Johnson, S. J.** , Alford, C. , Godefroy, S. B. and Verster, J. C. (2018) Why meta is better: A reply to Linden-Carmichael et al. (2018). Human Psychopharmacology: Clinical & Experimental, 33 (4). e2663.

Verster, J. C. , Benson, S. , **Johnson, S. J.** , Alford, C. , Godefroy, S. B. and Scholey, A. (2018) Alcohol mixed with energy drinks (AMED): A critical review and meta-analysis. Human Psychopharmacology: Clinical and Experimental, 33 (2). e2650.

Mackus, M. , Adams, S. , Barzilay, A. , Benson, S. , Blau, L. , Iversen, J. , **Johnson, S. J.** , Keshavarzian, A. , Scholey, A. , Smith, G. S. , Trela, C. , Vatsalya, V. and Verster, J. C. (2016)

Proceeding of the 8th alcohol hangover research group meeting. Current Drug Abuse Reviews, 9 (2). pp. 106-112.

Johnson, S. J. , Alford, C. , Stewart, K. and Verster, J. C. (2016) A UK student survey investigating the effects of consuming alcohol mixed with energy drinks on overall alcohol consumption and alcohol-related negative consequences. Preventive Medicine Reports, 4. pp. 496-501.

Verster, J. C. , Benson, S. , **Johnson, S. J.** , Scholey, A. and Alford, C. (2016) Mixing alcohol with energy drink (AMED) and total alcohol consumption: A systematic review and meta-analysis. Human Psychopharmacology: Clinical and Experimental, 31 (1). pp. 2-10.

Johnson, S. J. , Alford, C. , Verster, J. C. and Stewart, K. (2016) Motives for mixing alcohol with energy drinks and other non-alcoholic beverages and its effects on overall alcohol consumption among UK students. Appetite, 96. pp. 588-597.

Abstracts

Alford, C., Broom, C., Lands, S., **Johnson, S.J,** & Verster, J. C. (2018, June). Alcohol hangover induced decrements in simulated driving performance during a short commute to work. Alcoholism Clin Exp Res 2018, 42 , 75A-57A.

Johnson SJ, Alford, C., Stewart K., Verster JC. An on-premise study to investigate the effects of mixing alcohol with energy drinks on overall alcohol consumption and subjective intoxication. Alcoholism Clin Exp Res 2017, 41 (Supplement S1): 18A-264A.

Alford, C., **Johnson SJ**, Stewart K., Verster JC. Drinking patterns and risk-taking behaviours among students who combine alcohol with energy drinks. Alcoholism Clin Exp Res 2017, 41 (Supplement S1): 18A-264A.

Verster JC, Benson S, **Johnson SJ,** Alford, C., Scholey A. Alcohol mixed with energy drink (AMED): Meta-analyses on the effects on alcohol consumption and subjective intoxication. Alcoholism Clin Exp Res 2017, 41 (Supplement S1): 18A-264A.

Verster JC, Benson S, **Johnson SJ,** Alford, C., Scholey A. Maximum alcohol consumption at heaviest drinking episodes: alcohol mixed with energy drink (AMED) versus alcohol only occasions. Alcoholism Clin Exp Res 2017, 41 (Supplement S1): 18A-264A.

Johnson SJ, Alford C, Verster JC, Stewart K. A Comparison of the Motivations for Consuming Alcohol Mixed with Energy Drink Compared to Other Caffeinated Beverages. Drug & Alcohol Review, Australasian Professional Society on Alcohol and other Drugs, 2016, Sydney, Australia.

Johnson SJ, Alford C, Verster JC, Stewart K. A preliminary investigation of Perceived Parental Care and Drug Use Amongst UK Students. Drug & Alcohol Review, Australasian Professional Society on Alcohol and other Drugs, 2016, Sydney, Australia.

Verster JC, Benson S, **Johnson SJ**, Alford C, Scholey A. Mixing alcohol with cola or energy drink: does the mixer matter? Drug & Alcohol Review, Australasian Professional Society on Alcohol and other Drugs, 2016, Sydney, Australia.

Johnson SJ, Verster JC, Stewart K, Alford C. Are energy drinks unique mixers in their effects on alcohol consumption and negative alcohol-related consequences? Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 583A-583A.

Johnson SJ, Verster JC, Stewart K, Alford C. Investigating the impact of a high risk-taking propensity on alcohol consumption when consumed alone and when mixed with energy drinks. Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 584A-584A.

Benson S, Verster JC, **Johnson SJ**, Alford C, Scholey A. A cross cultural study of motives for alcohol consumption during occasions where alcohol is mixed with energy drink and other non-alcoholic beverages. Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 619A-619A.

Johnson SJ, Benson S, Scholey A, Stewart K, Alford C, Verster JC. Effects of age at which students began consuming alcohol regularly on current alcohol consumption both alone and mixed with energy drinks. Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 826A-826A.

Johnson SJ, Benson S, Scholey A, Stewart K, Alford C, Verster JC. A comparison of alcohol consumption when mixed with energy drinks and mixed with cola. Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 827A-827A.

Scholey A, Benson S, **Johnson SJ,** Alford C, Verster JC. A statistical comparison of outcome from industry funded and non-industry funded studies of alcohol mixed with energy drinks. Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 858A-858A.

Verster JC, Benson S, **Johnson SJ,** Alford C, Scholey A. Alcohol consumption patterns on alcohol only occasions and occasions alcohol is mixed with energy drinks or other non-alcoholic beverages. Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 861A-861A.

Johnson SJ, Verster JC, Benson S, Alford C, Scholey A. A cross cultural comparison of negative alcohol-related consequences when mixing alcohol with energy drinks compared to other drinking occasions. Alcoholism Clin Exp Res 2016, 40 (Supplement S1): 862A-862A.

Johnson SJ, Alford C, Verster JC, Stewart K. Alcohol consumption and risk taking behaviours among those who consume alcohol mixed with energy drinks. British Psychological Society Psychobiology Section - Annual Scientific Meeting. September, 2015, Windermere, U.K.

Broom C, Alford C, Land S, **Johnson SJ**, Verster JC. Decrements in simulated driving during a short commute to work as a result of alcohol hangover. British Psychological Society Psychobiology Section - Annual Scientific Meeting. September, 2015, Windermere, U.K.

Johnson SJ, Alford C, Verster JC, Stewart K. A comparison of the frequency and quantity of alcohol consumed when mixed with energy drinks and mixed with cola. Drug & Alcohol Review, Australasian Professional Society on Alcohol and other Drugs, 2015, Perth, Australia.

Johnson SJ, Alford C, Verster JC, Stewart K. Does the age at which students begin consuming alcohol regularly have an effect on current alcohol consumption, both alone and mixed with energy drinks? Drug & Alcohol Review, Australasian Professional Society on Alcohol and other Drugs, 2015, Perth, Australia.

Alford C, Connabeer K, **Johnson SJ**, Tiplady B, Verster JC, Vierhout D. Effects of caffeine and sleep restriction on risk taking. Journal of Psychopharmacology 2015 (British Association for Psychopharmacology)

Johnson SJ, Alford C, Verster JC, Stewart K. A survey of energy drink consumption patterns and motivations for use among UK students. Journal of Psychopharmacology 2015 (British Association for Psychopharmacology)

Alford C, Connabeer K, **Johnson SJ**, Verster JC, Vierhout D. Effects of caffeine and sleep restriction on risk taking. Centre for Research in Biosciences (CRIB) Annual Meeting, Bristol, UK, 16 January 2015.

Verster JC, **Johnson SJ**, Alford C, Stewart K. The type of motives (neutral or negative) for mixing alcohol with energy drinks has no differential effect on the frequency and quantity of alcohol consumed by UK students. APS 2015, New York, USA.

Alford C, **Johnson SJ**, Verster JC, Stewart K. A comparison of alcohol consumption and motivations for use among UK students who consume alcohol mixed with energy drinks (AMED) and alcohol mixed with other non-alcoholic beverages (AMOB). Association for Psychological Science 2015, New York, USA.

Verster JC, Benson S, **Johnson SJ**, Alford C, Scholey A. The effect of mixing alcohol with energy drink on total alcohol consumption: a meta-analysis. Association for Psychological Science 2015, New York.

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Lectures & Keynotes

Johnson SJ, Tapp A. Wheels, Skills & Thrills: A social marketing approach to tackling risky driving amongst young males from challenging backgrounds. Rhiannon Jade Smith Road Safety Conference, Celtic Manor, Wales, September 2019

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Johnson SJ, Alford C, Benson S, Scholey A, Verster JC. Alcohol mixed with energy drinks (AMED): Misconceptions, myths, facts revisited. Swinburne University, Melbourne, Australia, November 2016.

Alford C, **Johnson SJ**, Stewart K, Verster JC. An on-premise study to investigate the effects of mixing alcohol with energy drinks on overall alcohol consumption and subjective intoxication. British

Psychological Society Psychobiology Section - Annual Scientific Meeting. September, 2016, Windermere, U.K.

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Symposium

Scholey A, Alford C, **Johnson SJ**, Benson S, Verster JC, Marczinski, C. Functional consequences of mixing alcohol with energy drinks. Association for Psychological Science 2015, New York, USA.