ALICE RAP WA3: WP9.2

D9.2: Determinants of reductions in or cessation of harmful substance use and gambling: model report and transition probabilities

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Contents

ABSTRACT

The reduction of harmful substance use and gambling does not refer only to cessation, but also changes in patterns of use and the environment of use that result in a reduction in harmful outcomes to the individual, friends and family, and wider society. Within this work we have examined the determinants of such changes with a focus towards non-formal treatment. Such 'natural recovery' methods remain largely unexamined, yet are the most common method of cessation and harm reduction from addictive substances and gambling. We present the work of a multidisciplinary team who have focused on the identification of the determinants of reductions in and cessation of harmful use, with input from disciplines as wide ranging as anthropology, economics and genetics. Our expert group of researchers representing many of the disciplines that study addiction have worked together to produce the substance specific models presented here. We have categorised determinants in each substance specific model into key themes, which we anticipate will support their use in targeting policy interventions to prevent the harms resulting from these behaviours. It is apparent from this work that determinants of reductions in harmful use are present at all levels of analysis, from the social environmental to the molecular and cellular. However, our understanding of the social environmental impact upon reductions in harmful substance use and gambling is more nuanced than at the biological level. We identified an absence of existing research on 'natural recovery' as well as reductions in harmful use that did not prioritise cessation. This report also presents methodologically updated transition probabilities and hazard ratios for the transitions between different stages of alcohol use, (abstinence, risky use, harmful use and cessation), calculated with reference to the different covariates age, gender, and socioeconomic status. These clearly demonstrate that youth are at an increased risk of developing such harmful drinking behaviours and that both gender and the socioeconomic status of the user influence the onset and progression of such behaviours, demonstrating the complex determinants at play in an individuals' substance use career.

1. INTRODUCTION

This is the last of three reports outlining the development of a series of models that map the determinants of different stages of addictive behaviour. These reports run in parallel to the evidence synthesis reports of the multidisciplinary group of Work Area 3 of ALICE-RAP. Work Area 3 (WA3) examines evidence surrounding the determinants of different stages of addiction, derived from expert reviews of the prevailing literature within a

range of scientific disciplines. The disciplines that have contributed to this project are; anthropology, economics, genetics, neurobiology, public policy, psychology and sociology, with further input from experts on marketing, history, youth studies, cross-European perspectives and, finally, gambling.

WA3 examines three stages of the addiction process; 1) the transition from use or no use to risky substance use and gambling, 2) the transition from risky use to harmful substance use and gambling, and 3) reductions in harmful substance use and gambling. This report focuses on the development of models concerned with the third stage: transition from harmful use of substances or gambling to a reduction in this harm. The aim of the model presented here is to demonstrate the available evidence concerning the determinants of a reduction in harmful substance use or gambling in an easy-to-access format. The substances studies are alcohol, tobacco and illicit drugs, with gambling also being included as a key example of a behavioural addiction. The models are intended for use by policy makers and researchers within the addiction field, both to guide policy decisions and highlight areas for future research. By bringing together research in a visual format from the wide range of disciplines that inform addiction studies, we have been able to identify knowledge gaps where research is needed to improve our current understanding and facilitate the development of new multidisciplinary theories on substance use and gambling.

1.1 Model and Transition Probabilities - Aims and Approach

1.1.1 Model

The work presented here draws on a companion evidence synthesis report (1). This was formulated from evidence reviews of a range of the different scientific disciplines which study addiction to identify discrete determinants that influence an individual's progression from harmful use to a reduction in the harm stemming from substance use or gambling. The aim of the present work was to provide a visual representation of these determinants and, furthermore, to explore how evidence from multiple disciplines, which differ in their scientific approach, may be brought together into an accessible visual format. The key criteria applied when developing our model to enhance utility to both policy makers and researchers, were:

- Clear display of the range of determinants identified across all participating disciplines;
- Visualisation of determinants at different levels of abstraction;
- Demonstration of the relationships and dynamics between the different determinants;
- Identification of determinants that are researched by several disciplines and may be candidates for further research by multidisciplinary collaborations.

Through the models presented here, we are able to highlight potentially important interactions between determinants identified in distinct disciplines which may be examined further in future multidisciplinary research. These models are intended for use by addiction researchers to aid in the process of hypothesis and theory development around the reduction of harmful addictive behaviours. We also envisage policy makers engaging with these models to improve the design and targeting of policy responses and interventions.

This report is structured as follows: First, we present and explain our working definition of a reduction in harmful substance use and gambling and briefly explore how this is operationalised in our research. Subsequently, we describe the method for producing the models, including our definition of a determinant and how we extracted determinants of a reduction in harm from each of the disciplines, the key themes within our model and the process of evidencing and validating the model. We do not describe the process of developing the generic model design, such as decisions around how to most effectively present data in the model and the level of abstraction of determinants, as this is described elsewhere (2). Next, we present the model and describe key findings around determinants that vary by substance and those common to multiple disciplines. Finally, we discuss the limitations of our approach and implications for research and policy.

1.1.2 Transition probabilities

In addition to the development of multidisciplinary models for the reduction in or cessation of harmful use, we have calculated transition probabilities that identify the probability of moving between different stages of use (no use, use, risky use and harmful use). We have used a sample of adolescents and young adults to simulate age- and gender-specific prevalence over the early life course (14-30 years). We derived the following hypotheses about the influence of core covariates (age, gender and SES) on the probability of transition between different stages of use:

- Gender is particularly important for 'early' transitions with males having higher probabilities to transition to use and lower to go back to abstinence;
- For persons with lower SES higher transition probabilities from use to more risky patterns of use and lower transition probabilities from risky patterns of use to use are expected;
- Drinking patterns are expected to stabilize with increasing age and transitions become less likely.

1.2 Definition of a reduction in harmful substance use or harmful gambling

The harms associated with harmful substance use and harmful gambling take many forms, including negative consequences for physical and mental health as well as financial, legal and social costs for the individual and those around them. Equally the reduction of harm from substance use or gambling may arise through a variety of changes, such as that of a reduction in the level of an individual's use or changing to a pattern of less harmful use, such as not binge drinking, but drinking more frequently or smoking outdoors to reduce health harms to others. We have utilised the following definition of a reduction in harmful substance use or gambling for the work contained herein:

> *"Determinants of material reductions of harmful behaviour of social, mental or physical nature which are experienced by the user, other individuals or society at large, which is related to substance use or gambling"*

1.3 Overview of a reduction in harmful substance use of harmful gambling

The most intuitive reduction in harmful substance use or harmful gambling may stem from a reduction in the individual's levels of use. To reduce one's use or abstain completely should limit further health harms, diminish financial costs associated with drug use or gambling, and facilitate the individual, with time, to return to a more normative role within society.

Beyond the harm derived directly from substance use or gambling, changes in an individual's behaviour may result in a reduction in harm to those around them or wider society. For example, if an person with alcohol problems stops beating his wife when drunk (e.g. having attended counselling for anger management), yet continues to drink at the same level, despite the individual harm remaining constant, the harm to his immediate family has decreased. Equally, changes in the social, physical or political environment may change the context of use in such a way that behaviour becomes less harmful without a direct change in drinking. For example, the de-penalisation of cannabis may not change an individual's level of use, but may reduce the harm associated with the behaviour as use is no longer criminalised.

Individuals with diagnosed substance or non-substance use problems may be directed to treatment, either clinical or psychotherapeutic, and the relative merits and outcomes of such treatments have been widely analysed (3-7). However, the majority of individuals who engage in harmful behaviours do not access conventional treatment, and instead reduce or cease their use either by themselves or with the help of those

within their immediate social circles. Such 'natural recovery' has remained largely unexamined, yet it is estimated that 75% of alcohol dependents (8) and 54-69% of smokers (9) who do recover, do so without professional help. Given this apparent success of natural recovery methods for reducing harmful substance use, it is important that we understand and are able to maximise the use of informal mechanisms to help harmful users to reduce harm to themselves and others. Consequently, within this report we focus upon reductions in harm that occur without clinical or psychotherapeutic intervention. This approach poses methodological challenges given that, by definition, natural recovery operates outside of traditional treatment settings and therefore it is significantly harder to study for many of the disciplines included in the current research. Thus, in disciplines where literature surrounding natural recovery is limited, we present the available expert review of literature regarding determinants that prevent cessation or promote relapse of harmful substance use or harmful gambling, rather than determinants of the reduction in harmful substance use or harmful gambling.

Within this work we have examined reductions in harmful use of substances including alcohol, tobacco and illicit drugs and also reductions in harmful gambling. Until recently, gambling was considered separately to psychoactive substance addiction because of the absence of an ingested pharmacologically active substance, which was assumed to negate the potential for physical adaptations, cravings and compulsion to continue (10). However, recent research has highlighted commonalities between each of these harmful behaviours, with all exhibiting common behavioural patterns and exerting strong effects upon reward system neurocircuitry. Behaviours displayed by harmful users of both substances and gambling include tolerance and withdrawal effects, the prioritisation of immediate gratification followed by delayed deleterious effects, compromising social, occupational or recreational activities in order to persist with their behaviour, financial and relationship problems and high rates of relapse (11). Indeed, the American Psychiatric Association recently classified gambling as an addiction (12). Thus, the inclusion of harmful gambling within our research reflects relatively recent changes in scientific and political interest in gambling as an addictive behaviour with potentially similar determinants to substance use disorders.

2. METHODS

2.1 Definition of a determinant

The disciplines involved in ALICE RAP WA3 implemented different research approaches which were dependent upon the epistemological underpinnings of their subject. For many, use of the term 'determinants' was challenging as they tended to describe factors influencing an outcome or contextual variants of an outcome. In contrast, 'determinant' was used often by other disciplines in a more literal and deterministic way. Thus, it was important to discuss and develop a definition of 'determinant' which could be applied by all disciplines. During a WA3 meeting the expert panel agreed upon the following definition:

> *"A factor which alone or in combination acts to increase or decrease the likelihood of whether something happens or not. That influence can operate directly or through other factors. For this work package, determinants are used to describe the range of factors at the molecular and cellular, individual, and social environmental levels which, alone or together, increase the likelihood of harmful use. To use the word determinant does not mean that we believe that any of these factors or combination of factors are deterministic in a causal manner."*

2.2 Methods for extracting determinants from the discipline reviews

The models presented here include each of the determinants identified from analysis of the individual discipline reports on the transition from harmful use to a reduction in the harm deriving from substance use or gambling. Determinants were classified by substance (alcohol, tobacco, cannabis, stimulants, opioids, club drugs and gambling) and level of analysis (cellular and molecular, individual or social and environmental). For the purposes of this report and the model presented herein our use of the term club drugs refers to ecstasy,

alkyl nitrates, GHB, ketamine and also includes studies which in themselves use the categorisation of club drugs. Following extraction of the determinants from the discipline reviews, an early version of the model was circulated to the WA3 discipline experts in March 2014 and further discussed as part of a WA3 meeting in Amsterdam in May 2014, in order to ensure that no determinants had been omitted and that the determinants included within the model were both relevant and themed correctly.

2.3 Barriers to the development of testable models

Our ambition was to use the evidence generated to develop interdisciplinary testable models of addiction. These testable models would illustrate evidenced and hypothesised relationships between different determinants of addiction, providing a road-map for future addiction researchers. However, during the initial collation of evidence from the disciplines around the determinants of the first work stage, considering the transition to risky substance use and gambling (2), it became evident that developing such testable models would not be possible for two key reasons.

Firstly, there was an absence of evidence. After further consideration of the available research pertaining to a reduction in harmful substance use or gambling, we concluded that there is a lack of evidence to support a comprehensive mapping of hypothesised relationships between determinants. Given that lack of supporting evidence, we felt that illustrating these relationships in the model may mislead researchers and policymakers regarding the importance of different determinants and the relationships between them.

Secondly, the diversity of disciplinary approaches to generating evidence around the factors influencing a reduction in harmful substance use or gambling has hampered the process of drawing together evidence from across the disciplines. The determinants displayed in Figures 2-9 span a wide range of levels of abstraction, from broad constructs such as institutions of social control to narrowly defined concepts such as features of neurocircuitry. To develop coherent testable models that incorporate such fundamentally different constructs requires the development and nurturing of multidisciplinary relationships that will enable scientific debate around the intricacies of such relationships. Whilst we have initiated such connections over the duration of this project, to produce models with greater interactions between determinants and that consider the range of research methods and different types of data that the disciplines use would require substantially more interaction between researchers.

Given these challenges, we have prioritised utility of the models and have focused on clarity and accessibility for policy makers. At the same time, we have sought to capture and display the full complexity of determinants contributed from all the involved research disciplines involved. The models that we present below do illustrate some of the relationships between determinants by the level of analysis at which they have been included in the model (e.g. molecular and cellular, individual or social environmental) and through the themes under which they have been grouped. Such broad research themes can be used as a guide for further research, highlighting areas for potential multidisciplinary collaboration which would enable us to develop more detailed testable models in the future.

2.4 Key themes in the model

To allow readers to easily interact with the models and rapidly interpret the results, clusters of determinants were arranged into key themes identified by the expert panel. All determinants for each substance were organised within these key themes, with determinants appearing in multiple domains where applicable. The panel decided to cluster by theme rather than discipline both to highlight the disciplinary overlap between determinants and to encourage engagement from non-specialist audiences and policy makers. Using themes facilitates the quick identification of key messages from our work and may help to target policy responses for different substances.

2.5 Evidencing the model

All determinants within the model are derived from discipline-specific reports written by the expert panel. These reports identify the key evidence on the determinants of the transition from harmful substance use and gambling to a reduction in the harm stemming from such use, and are synthesised within a companion report (1). We have not included the citation for each determinant within the model, because it was perceived that this would make the model too cluttered and difficult to read. However, the evidence is presented in tabular format in Appendix 2 (p.70) and within the associated synthesis report (1).

2.6 Model validation

To address the challenge of merging evidence drawn from a range of different disciplines with diverse epistemological traditions, we relied particularly on bringing together discipline experts through teleconferences and face-to-face meetings. Such sessions have enabled us to identify challenges and work together to find solutions to emerging problems.

During the development of the model illustrated below we engaged frequently with discipline experts. Experts were consulted regarding which determinants to include and exclude from the model and in the development of key themes in which to cluster determinants. Early versions of the model were circulated to all discipline experts for comment in April 2014. Feedback was then sought during a meeting of ALICE RAP WA3 members, in Amsterdam in May 2014. This feedback stimulated discussions around the advantages and limitations of different aspects of the models presented and the suitability of the chosen themes to the different addictive behaviours. Following these initial consultations with discipline experts the models were adapted and a final draft disseminated to all team members for comment and validation at the end of May 2014. All comments were integrated into this final version of the models.

2.7 Methods for calculation of transition probabilities

The transition probabilities calculated within this report are concerned with alcohol, as in D7.2. However, in this report we present a major revision of the methods applied: we propose the use of Markov models to investigate substance use related transition probabilities based on panel data. The new method (compared to that presented in D7.2) enabled us to statistically test covariate influence on single transitions using a hazard ratio approach. Furthermore, we were able to estimate uncertainty for transition probabilities as well as hazard ratios, a major shortfall of the transition probabilities reported so far. We thereby developed a methodological approach for investigating transition probabilities and covariate influence that allows testing hypotheses derived from literature reviews. However, given the four consumption states (abstinence, use, risky use, harmful use) the calculation of transition probabilities bears great uncertainty with regards to substances that are consumed infrequently within populations. A large sample and several time points are needed in order to get enough transitions especially between stages of use such as risky and harmful consumption. Of course the introduction of covariates requires even bigger datasets.

In this report we present a methodological approach that we recommend for future research. As compared to the first two reports the new methodological approach enabled us to quantify the level of uncertainty of our calculations. Furthermore, we were able to statistically test hypotheses on covariate influence on single transitions. This knowledge adds to that which we have learned from literature reviews and gives hints as to how covariates might be structured with respect to their relative importance for different transitions. Panel data from three waves assessing a sample of German adolescents and young adults were used to calculate a Markov model for transition probabilities between distinct drinking states. Hazard ratios (HRs) were calculated for the covariates age, gender, and SES, all simultaneously introduced into the model. Age- and gender-specific transition probabilities were used to simulate the prevalence of drinking states over the life course (age 14 to 30). All calculations were conducted using R software v.3.1.0 (13). Details on the methods are described in the following.

2.7.1 Operationalizations for states of alcohol use and covariates

The model was based on four hierarchically structured drinking states referring to the past year: abstinence, use, risky use, and harmful use. Operationalizations of risky and harmful use differ considerably within and across country-specific literature (14-16). Since quantity and pattern of use both determine the riskiness of drinking (17), risky use was defined via grams per day as well as binge drinking occasions. For the grams per day we applied the widely used thresholds suggested by the World Health Organization in order to assure comparability (18). As there is no commonly used operationalization of binge drinking, we decided for a gender-specific operationalization that seemed to be most commonly used in Europe (14, 15). Harmful use was operationalized via grams per day (again as suggested by the WHO (18)) as well as presence of an AUD as defined by the 4th revision of the Diagnostic and Statistical Manual of Mental Disorders (10). The operationalizations are summarized in Table 1.

Table 1 Hierarchical operationalization of abstinence, use, risky use and harmful use.

Drinking category	Operationalization	
Abstinence	12 or less drinking occasions in the past 12 month	
Use	13 or more drinking occasions in the past 12 month	
Risky use	Females: 21-40g of pure alcohol per day or 40 g of pure alcohol on one occasion	Males: 41-60g of pure alcohol per day or 61 g of pure alcohol on one occasion
Harmful use	Females: At least 41g of pure alcohol per day or a diagnose of alcohol abuse or alcohol dependence	Males: At least 61g of pure alcohol per day or a diagnose of alcohol abuse or alcohol dependence

2.7.2 Sample description

As a database we used a German (Munich and the surrounding area) sample from a prospective-longitudinal study called the Early Developmental Stages of Psychopathology Study (EDSP). The EDSP study aimed to investigate and describe the course of substance use and related disorders in youth and early adulthood. The design is described in detail elsewhere (19, 20). The study consisted of one baseline assessment in 1995 (T0) and three follow-ups. Since the first follow-up comprised only a subsample, we used second (T2) and third follow-up (T3) that took place in 1998/1999 and 2003 to 2005, respectively. The mean delay from T0 to T2 was 3.47 years (standard deviation (SD) 0.25) and from T2 to T3 it was 5.19 years (SD 1.34).

In 1994 the sample was drawn randomized from the population register of Munich and surrounding areas (for details see (20)). Age groups 14-15, 16-21, and 22-24 were sampled in a ratio 4:2:1. About 71% of the initially drawn 4, 263 persons completed the assessment. The resulting sample consisted of 3,021 persons with German citizenship. Of this baseline sample 36.2% were in school and 26.4% at university. Another 19.7% had a job at baseline and 1.1% were unemployed. This conforms with socio-demographic features of the region (19). The majority of the sample was still living with their parents (62.4%) and only a few were married (3.4%). Response rates of T2 and T3 are 84% and 73% of baseline participants, respectively (21).

2.7.3 Covariates and drinking states

The covariates gender, age, and SES were used. Both genders were roughly equally frequent with 49.3% females and 50.7% males. Age was operationalized as a continuous variable reported at each wave. At T0 age varied between 14 and 25, at T3 the participants were 21 to 34 years old. SES was operationalized as the self-reported financial situation at each wave, categorized into very bad/bad, neither good nor bad, good and very good (for details see (19)). At T0 7.1% reported a very bad or bad, 27.5% a neither good nor bad, 54.1% a good and 11.4% a very good financial situation. The respective figures at T2 were 6.0%, 29.2%, 54.1%, and 10.7%. Frequencies and percentages of the four drinking states at each of the three waves are shown in Table 2.

Table 2 Frequencies and percentages of drinking states at T0, T1 and T3.

	T0	**T1**	**T2**
Abstinence (%)	1,492 (49.4)	595 (23.6)	380 (17.2)
Use (%)	1,103 (36.5)	1,298 (51.4)	1,368 (61.9)
Risky use (%)	168 (5.6)	289 (11.4)	333 (15.1)
Harmful use (%)	258 (8.5)	344 (13.6)	129 (5.8)
***Total* (% of T0)**	3,021 (100)	2,526 (83.6)	2,210 (73.2)

After exclusion of missing values due to non-participation as well as non-response to alcohol-related questions in one of the waves 4,736 single transitions were available for analysis. Table 3 below shows how they distributed over single transitions between all four states.

Table 3 Transition count matrix: number of single transitions from time A to time B available for analysis.

	Time B			
Time A	**Abstinence**	**Use**	**Risky use**	**Harmful use**
Abstinence	698	837	118	144
Use	219	1383	276	155
Risky use	21	188	111	63
Harmful use	37	258	117	111

2.7.4 Assessment

Data was collected using different questionnaires as well as the computer-assisted personal interview version of the Munich-Composite International Diagnostic Interview (M-CIDI) (22). Validity and reliability of the M-CIDI have been investigated and shown to be satisfactory (23, 24). The M-CIDI assessed information about symptoms, syndromes and diagnosis of 48 different mental disorders, as well as information on their onset, duration, and severity in a fully standardized manner. Both lifetime and 12-month related questions were applied. The interview section assessing information on alcohol use and AUDs was only accomplished when the participant reported at least 13 drinking occasions in the past year. Information on quantity and frequency of present alcohol consumption, age of onset and offset were assessed, followed by questions concerning abuse and dependence as defined by DSM-IV (10). The financial situation as measure of SES was assessed with the question “How would you overall judge your financial situation?” (very good to very bad

on a four point Likert scale). In most cases the interview was carried out by psychologists in training after accomplishing an interview training of two weeks and several exercise interviews. Consent was given by the participants or their parents. Most interviews were accomplished at the participant's home.

2.7.5 Modelling

The transitions between the defined drinking states were modelled using a discrete-time Markov model (25). The model is memory less, in the sense that the probability of transition to a new state depends purely on the current state. The transition probabilities within the model were estimated by fitting a time-homogenous (i.e. it is assumed that state to state transition probabilities remain constant over time) continuous-time Markov chain to the dataset. In this approach, we estimated continuous rates of transition (so-called transition intensities, q_{rs}) between the different states as well as transition probabilities referring to one year. It is often difficult to estimate all of the transition intensities between the states simultaneously (26) and so we necessarily restricted the set of transitions that were permissible.

The following Q-matrix of the four-state Markov model was defined, with $q_{rs}(t)$ representing the transition intensity to transition from state *r* to state *s* at time *t* and 0 indicating that no instantaneous transition was allowed:

	Abstinence	Use	Risky use	Harmful use
Abstinence	$-q_{12}$	q_{12}	0	0
Use	q_{21}	$-(q_{21}+ q_{23}+ q_{24})$	q_{23}	q_{24}
Risky use	0	q_{32}	$-q_{32}$	0
Harmful use	0	q_{42}	0	$- q_{42}$

Transition intensities add up to 0 within each row. A transition intensity of 0 does not prevent the estimation of transition probabilities, and in this case the underlying model assumption was that people might transition to that state passing through other states within one cycle of e.g. a year.

We estimated the transition rates using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) quasi-Newton optimisation algorithm (27-30). The optimisation criterion was a Pearson-type contingency table test statistic (31), comparing observed rates of transitions between states to the ones predicted by the candidate Markov-model. The test is based on a parametric bootstrap algorithm procedure, which is useful for Markov models based on panel data, where periods between observations and the number of observations may vary between individuals. CIs were calculated by repeatedly sampling (N=1000) from the distribution of the maximum likelihood estimates of the $\log(q_{rs})$. To model the impact of covariates (age, gender and SES), we considered covariate-adjusted transition probabilities, using a hazard ratio (HR) approach. The HRs are used to compare hazard rates that quantify event rates over time. If a certain subgroup (e.g. males) has higher hazard rates (which can be compared to transition probabilities) than another (e.g. females) the HR is above one. For analysing covariates, the covariate value of the state before transitioning was applied. All transition probability estimation procedures were undertaken using version 1.3 of the msm package for R (32).

2.7.6 Simulations

Simulations of the discrete-time Markov model were based on age- and gender-specific transition probabilities. As starting values we applied the gender-specific prevalence of drinking categories of participants aged 14 at T0 to an illustrative sample of 1000 14-year olds in each gender category. Male

starting prevalence was 91.5% abstainers, 7.5% users, 0.5% for risky as well as harmful users, female respective values were 90.9% abstainers, 7.6% users, 1.0% risky users, 0.5% harmful users.

To simulate drinking state prevalence in the artificial cohort we computed age- and gender-specific transition probability matrices from a fitted four-state model. Transition probabilities and HRs were then calculated based on the number of observed transitions in the relevant dataset. For each gender we performed 1000 simulation runs, and for each individual across each year we constructed an individual transition probability matrix (P_i), which sampled from a truncated normal distribution (33) using the mean and upper and lower bounds of the relevant age- and gender-specific transition probability matrix. Each individual was simulated between the ages of 14 and 30. To calculate the drinking state at time t+1 we merely sampled from the row of P_i that corresponded to the drinking state at time t.

2.7.7 Sensitivity analyses: Application of sample weights

Two sensitivity analyses were performed in order to investigate if sample weights accounting for different sampling probabilities (described above) as well as biases due to nonresponse (with respect to gender, age and geographic location, for details see (19)) would impact HRs and transition probabilities.

The msm package includes no functionality to incorporate sample weights (32, 34), therefore, we expanded the original sample (N_0) by replicating each individual respondent *n* times, where given the sample weight (*wt*) and the number of decimal places in that weight (*d*). Sample weights extend to four decimal places within the dataset, and as a result the number of replicate individuals should have been however, there were technical issues when attempting to fit a model with such a large sample expansion. Within R and the msm environment, the BFGS optimisation algorithm and the msm package had difficulties computing a Markov model with large source datasets, specifically for models with covariates. The authors of the package acknowledge this fact (32), however, without a more detailed analysis and modification of the original source code, we have found no immediate solution to achieve model convergence using the correctly expanded dataset. We were however able to compute Markov models for datasets expanded with *d* values of less than 150, and we report the results of a sample of those analyses, for *d* values of 10 and 100.

The expansion of the sample led to an artificial downsizing of the transition probability and HR associated CIs which was corrected by adjusting the standard error (SE_1). The original standard error (SE_0) was estimated as follows and then applied to calculate the adjusted CIs. We repeated this procedure in a both sensitivity analyses. Transition probabilities as well as simulations for both expansions can be found in the Appendix.

3. RESULTS

3.1 The models

A series of models (one for each substance and gambling) illustrating the determinants identified by each discipline have been developed and are displayed below (p.15-21). The substance to which each model refers appears in the top left hand corner of the page. Within these substance-specific models the determinants are grouped by level of analysis (molecular and cellular, individual, and social environmental), with each level of analysis distinguished by different background shading and a legend down the left-hand side of the model. The base level of this model has a molecular and cellular focus, the middle layer an individual focus, and the top, darkest layer illustrates determinants with a social environmental focus.

Within the models, determinants are grouped according to different expert-agreed themes in each level of analysis (see Section 2.4, p.8). At the molecular and cellular level the themes identified were ‘Impact on and/or Dysregulated Neurocircuitry’, ‘Impact on and/or Dysregulated Neurotransmitters’ and ‘Drug Characteristics’. At the individual level the themes identified were ‘Consumption’, ‘Emotional and Cognitive

Processes', 'Health' and 'Life Circumstances'. At the social environmental level of analysis the themes identified were 'Market Characteristics and Availability', 'Social and Cultural Norms', 'Formal Social Control', 'Social Structural Factors' and 'Environment of Use'. Those determinants that could be considered in multiple themes appear once in each of the themes where they exert an effect, for example within the alcohol model (Figure 1) 'level of education' can be found within both 'Social Structural Factors' and 'Life Circumstances'.

The gambling model presents an alternative theme of 'Game Characteristics', in place of the theme 'Drug Characteristics' which is found in the rest of the models. This theme within the gambling model attempts to describe characteristics of the gambling activity including the speed of the game and the size of the jackpot. Within our models this alternative theme name highlights the key difference between gambling and substance use, as in gambling no substance is ingested into the body to cause chemical effects. However, as many studies now clearly demonstrate a physical manifestation of harmful gambling, we have located and coloured this theme the same as 'Drug Characteristics' within our models to signify the presence of physical effects at the biological level (Figure 7, p.21).

We now present each of the substance specific models followed by a brief description of the meaning and content of each expert-agreed theme.

Figure 1: the alcohol model

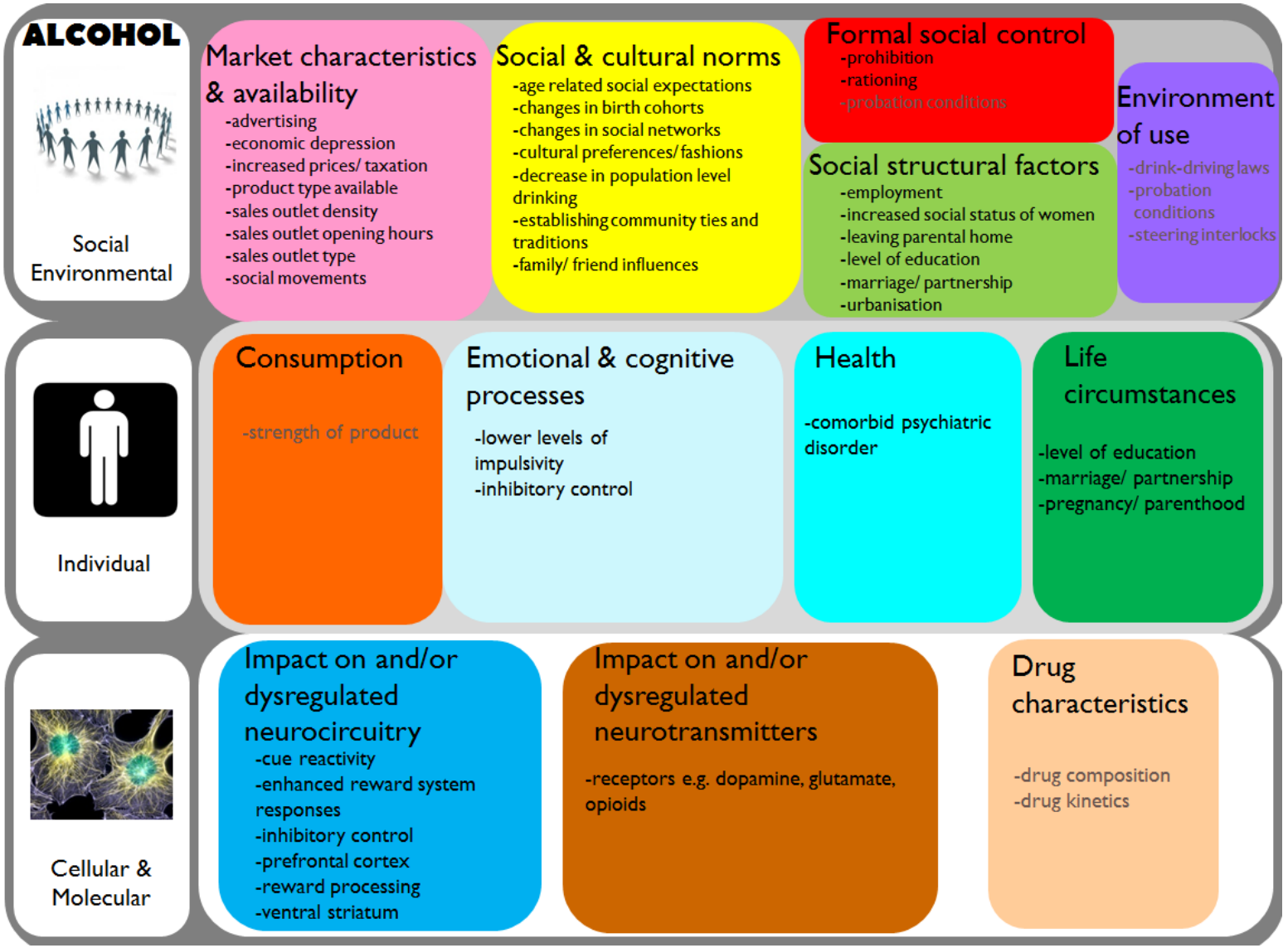


Figure 2: the tobacco model

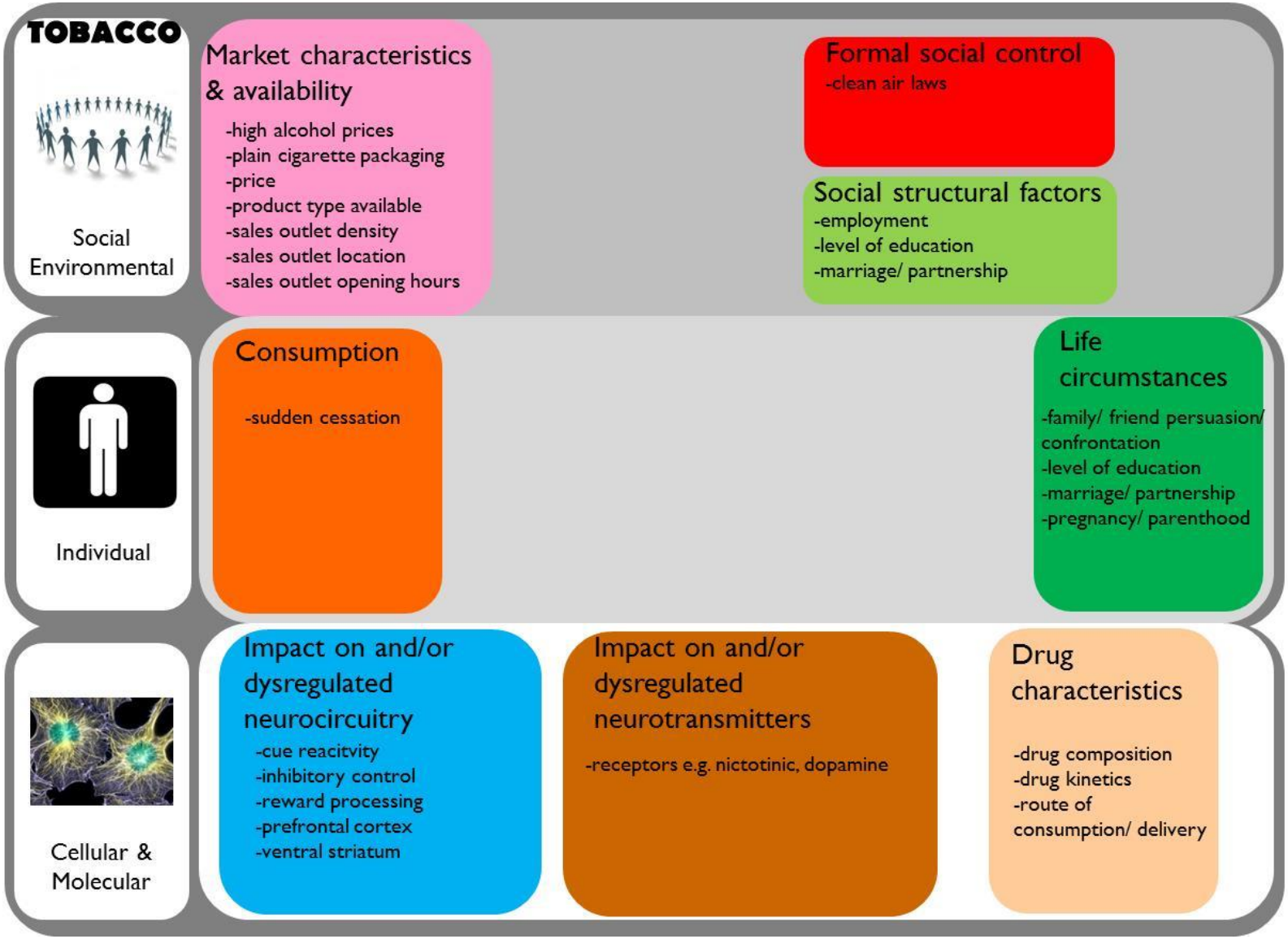


Figure 3: the cannabis model

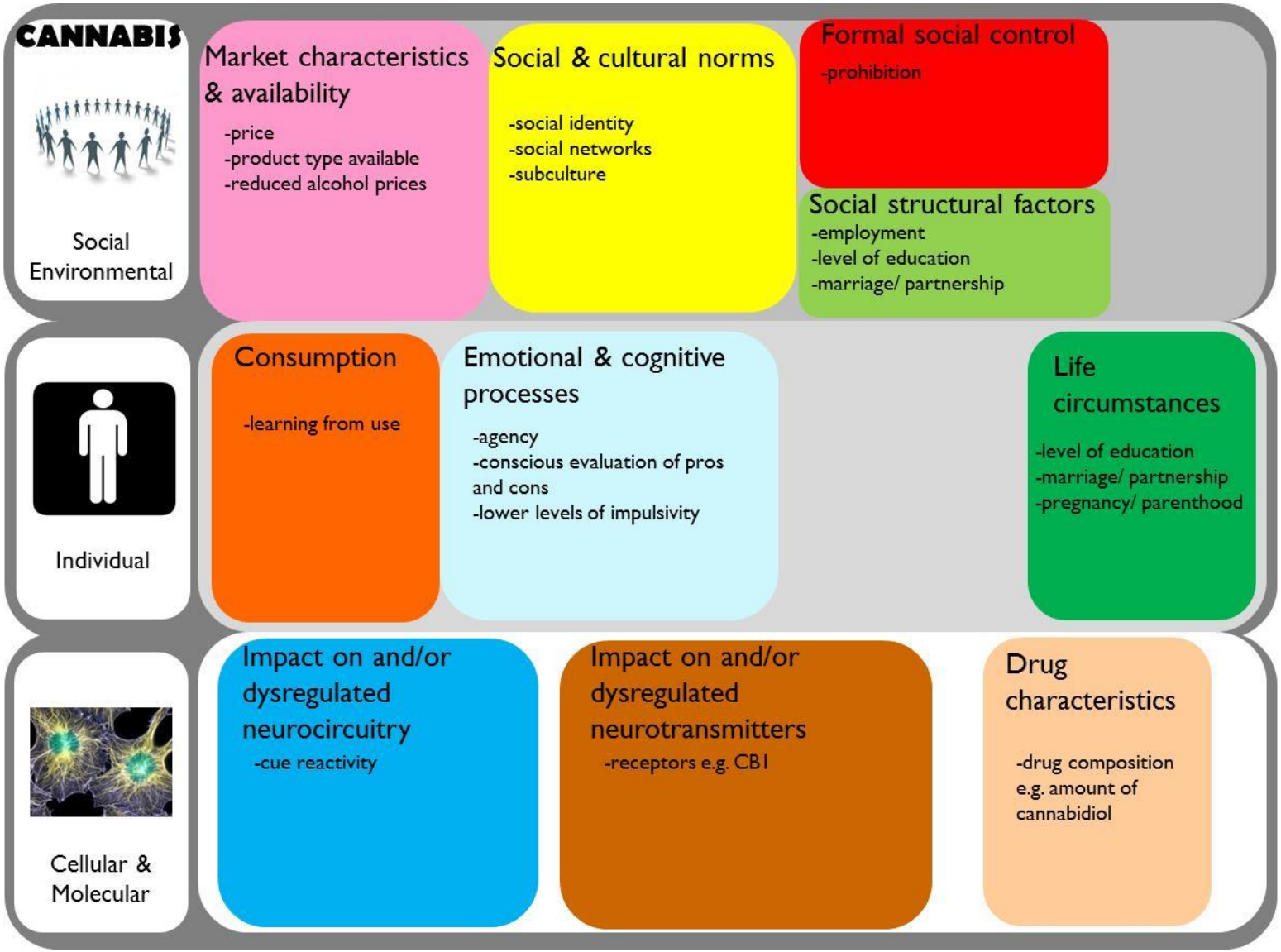


Figure 4: the stimulants model

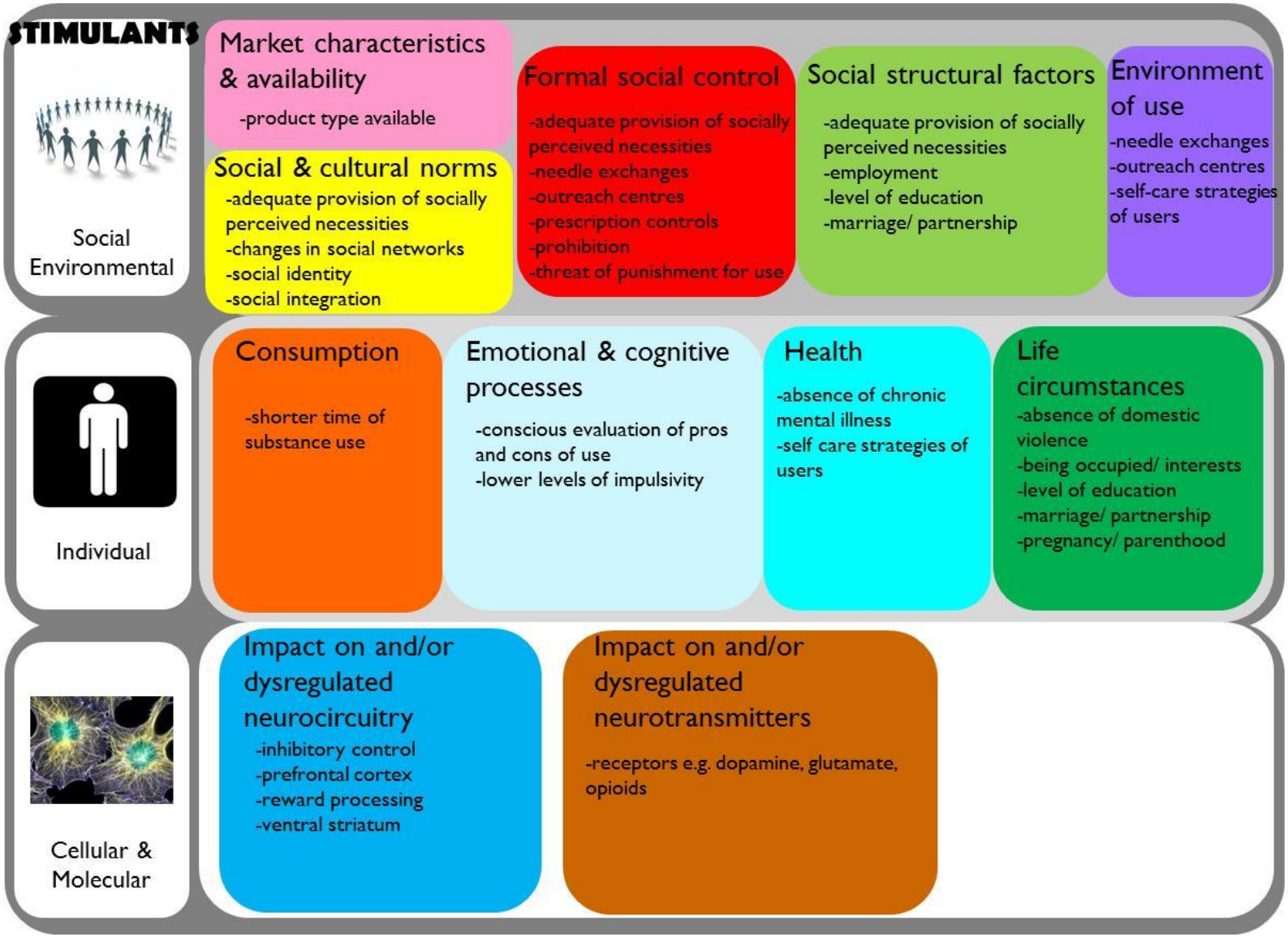


Figure 5: the opioids model

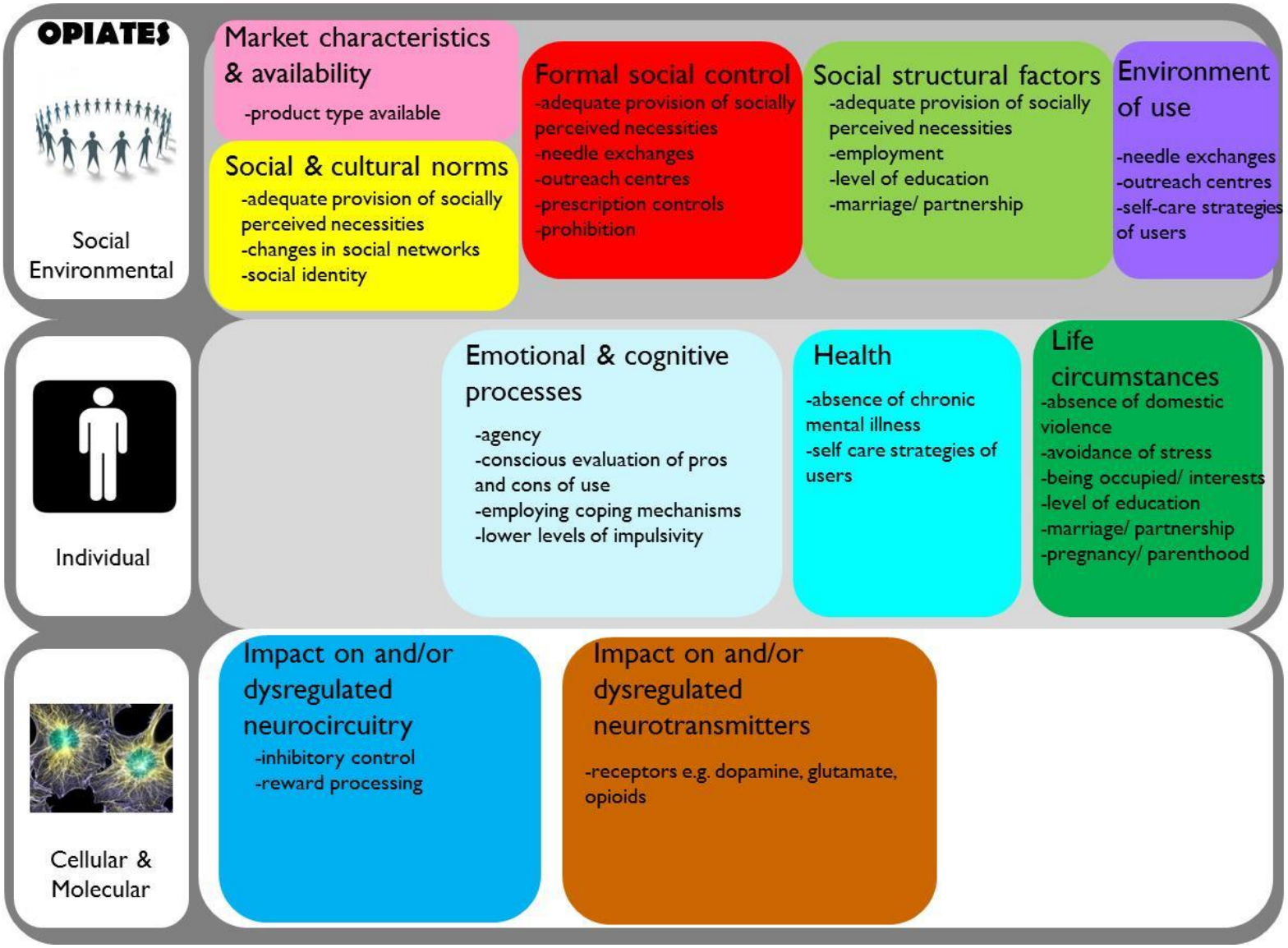


Figure 6: the 'club drugs' model

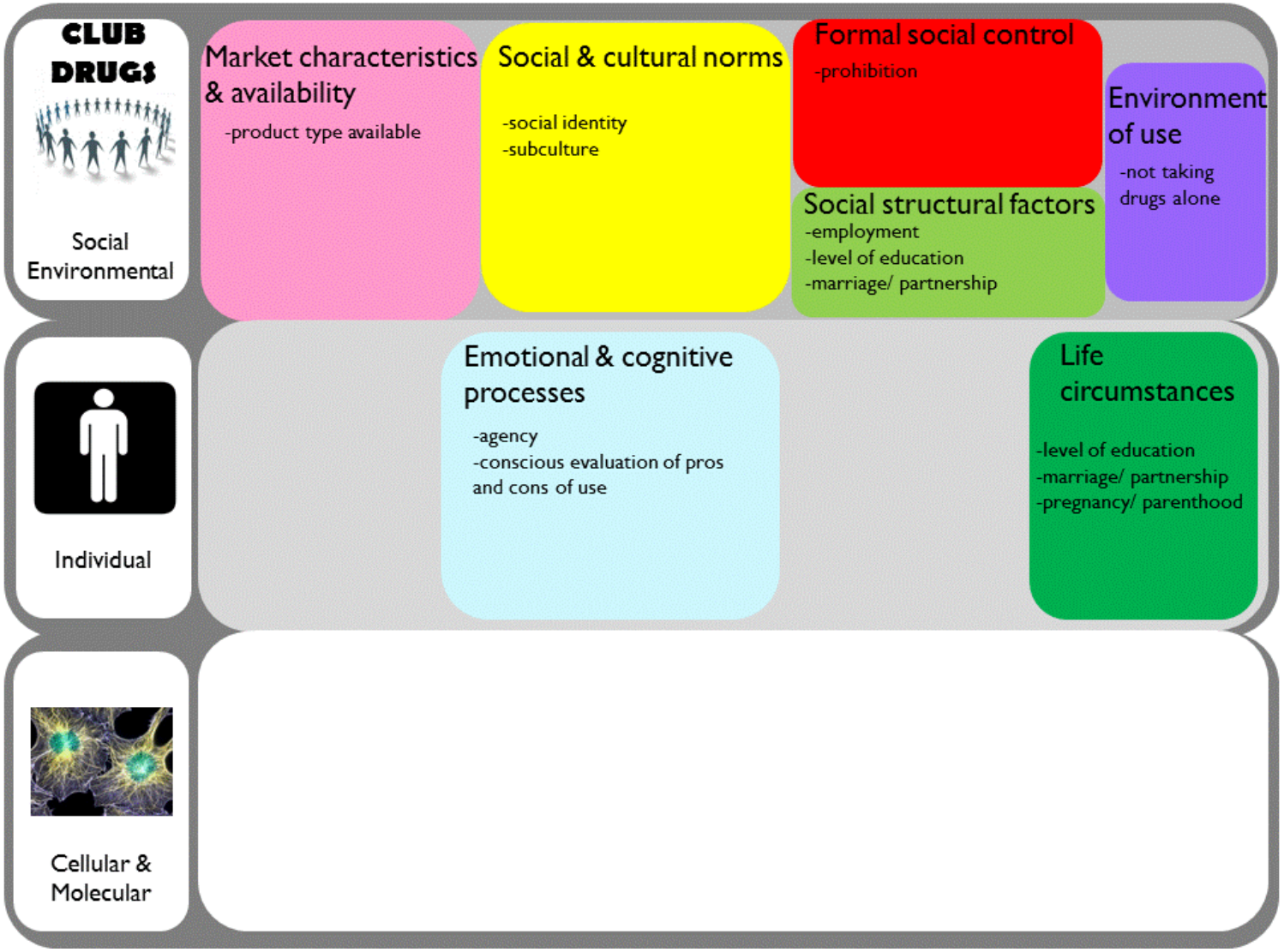
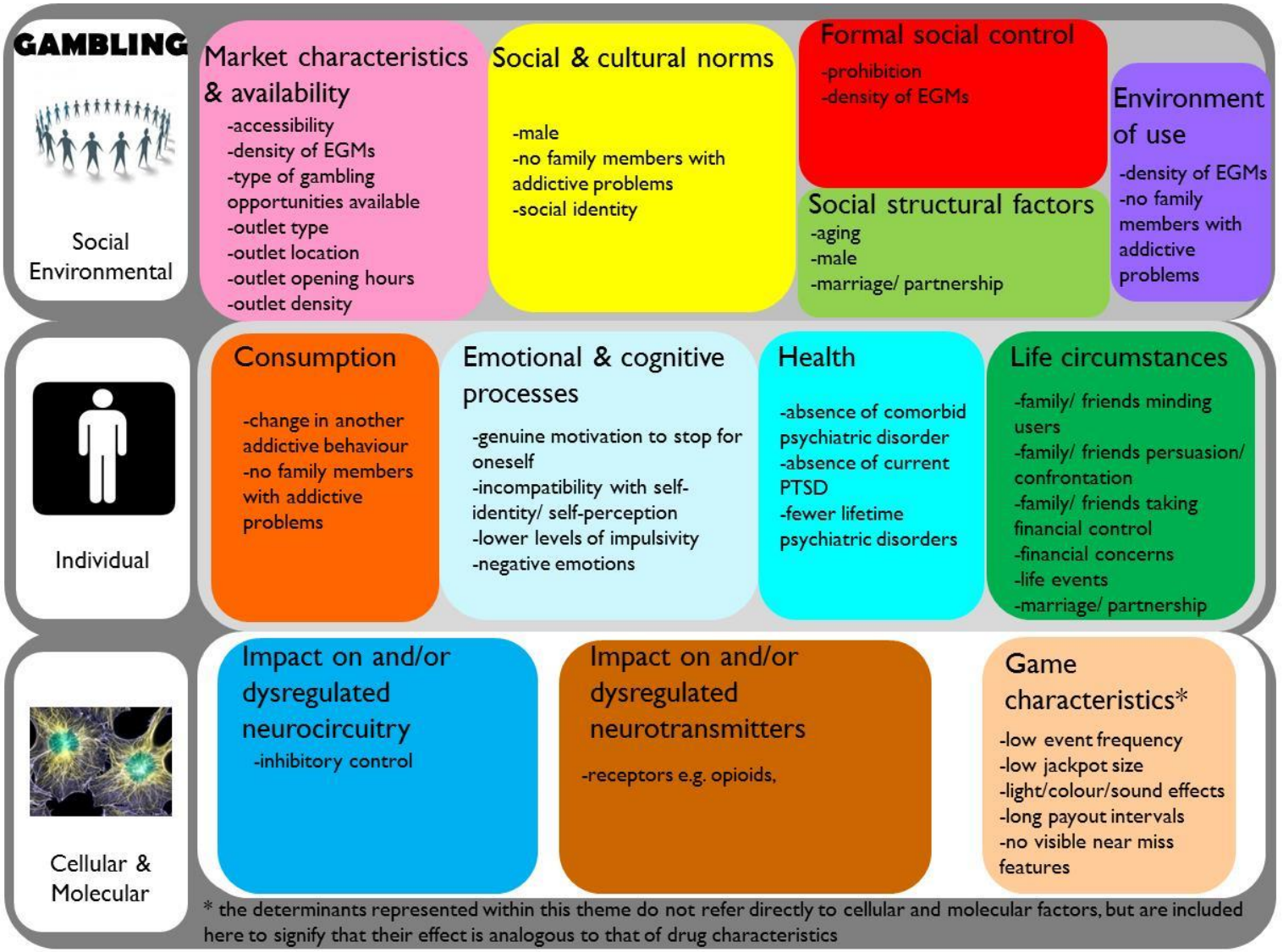


Figure 7: the gambling model



3.1.1 Market Characteristics and Availability

At the social environmental level the first theme recognises the impact of market characteristics and the availability of substances and gambling opportunities upon reductions in harmful use. Control of the market through factors such as increased price and taxation have been associated with a reduction in alcohol (35-43), tobacco (44-53) and cannabis (54) related harms (Figure 1, alcohol & Figure 3, cannabis, p.15 & p.17). There is also evidence that price increases in one substance can result in reduced consumption of another, complementarity substance; for example, high alcohol prices result in a reduction in harmful tobacco use, as alcohol and tobacco are complimentary substances and when the price of alcohol rises leading to reduction consumption, tobacco consumption also declines (55). Conversely low alcohol prices are associated with reduced harmful cannabis use, as users may switch their use from cannabis to alcohol consumption (55). Thus, the markets for different addictive behaviours can perhaps not be considered in isolation.

Regulation of sales outlet density, opening hours, location and type, as depicted in the models for alcohol (35, 56), tobacco (46) and gambling (57), can also be used to control the availability and accessibility of substances and has been associated with reductions in harmful use. Controlling availability in these ways can reduce harm by limiting accessibility for the whole population, generating a downward shift in population consumption (58-60), and also by targeting heavy drinkers and those with harmful patterns of drinking such as binge drinkers, as they buy more alcohol and so are more strongly affected by, for example, increases in price.

The society in which a substance is used can affect whether or not use results in harm. For example, the availability of alcohol is limited by both periods of economic depression (61) and social movements such as the temperance movement (Figure1, alcohol, p.15) (62-66); these environmental conditions reduce availability, constraining use and therefore potentially reducing harm. However, we must highlight evidence that suggests where temperance movements have culminated in prohibition of substances, this may result in the development of black markets for products, with separate challenges and potential harms to substance users (e.g. methanol in alcohol) arising from supply through these alternative channels (64).

Another source of influence at the social environmental level is industrial bodies, which through the advertising and marketing of products, may hinder reductions in the harmful use of legal substances (Figure 1, alcohol, p. 15) (43, 67-71). Research has examined the impact of controls over marketing practices, for example the use of plain packaging for cigarettes, and has identified significant changes in the perceptions of users, with more smokers feeling able to reduce or cease use when presented with plain packaging over traditional branded packets (72). Thus, controlling marketing may enable a reduction in harmful use of substances and gambling.

Product type of legal substances, illegal substances and gambling, can all influence an individual's ability to reduce their harmful use. For example in relation to alcohol, an increase in the availability of lower strength alcohol and restrictions upon or a reduction in the availability of higher strength alcohol (such as in Sweden where alcohol over 3.5%ABV is only available via the state-run off-licence) may support reductions in harmful drinking (35). For tobacco, a reduction in the variety of tobacco available (such as menthol and reduced nicotine cigarettes), may support reductions in use as certain types of tobacco have been shown to encourage a maintenance cigarette use (46, 73, 74). For illegal substances, a reduction in harm may be generated through the wider availability of reduced strength drugs and drugs that have not been cut with harmful substances (75). Finally for gambling, harm reductions may occur if games that enable users to bet large amounts of money in a short timeframe (such as fixed odds betting terminals) are less widely available (57).

3.1.2 Social and Cultural Norms

Each society operates under a set of widely supported beliefs and practices that control and inform how its members should behave if they desire to uphold customs and conform to the norms of the societal group. Determinants associated with reductions in harmful use in this theme of 'Social and Cultural Norms' are social identity, age-related expectations and global movement.

An individual's social identity may not conform to the society in which that individual lives; for example, the identity of an 'addict' or 'harmful user'. Identifying one's own behaviour to be in conflict with the norm in a given society may prompt a harmful user to change their behaviour, reducing the associated harm (76, 77). Equally, an individual may experience an event whilst using a substance, for example involvement in alcohol-related violence, and in reaction to this experience and because they do not want to be associated with the harmful outcome, may change the way they use a substance to avoid future occurrence of a similar event.

An individual's social network or subculture may trigger a reduction in harmful use if continued use is not compatible with network membership yet they want to remain part of the network or subculture. This determinant appears across all the models except tobacco and gambling. Changes in social networks often promote a change in harmful substance use or gambling, as substance use is often a social activity and people may find it difficult to change their behaviour whilst situated within networks where harmful use is normal. Self-help groups, such as alcoholics anonymous, use this idea to encourage members to develop new social relationships and indeed provide them with opportunities to develop new social networks of non-users (e.g. during meetings), which helps members to establish new habits around the use of or abstinence from a substance (78).

Many societies also have age-related social expectations surrounding alcohol use. For example, in the UK youth and young adulthood is generally associated with high levels of alcohol use, particularly heavy episodic drinking. This behaviour in young adulthood is usually followed by a reduction in such harmful behaviours as people transition into adulthood, where they are burdened with increased responsibilities. (See also 'Environment of Use'). This process of behaviour changing during the transition into adulthood is often called 'maturing out' (79).

Finally, with increased global movement, particularly within the European Union where there are no internal borders, people may find themselves living in different cultures. Finding oneself in a 'foreign' culture may result in feelings of isolation and dislocation, as individuals' are separated from their communities and may experience a lack of social integration. This may manifest in harmful behaviours such as alcohol and stimulant use as part of a coping strategy (Figure 1, alcohol & Figure 4, stimulants). The experience of dislocation can be reversed by re-establish community traditions and ties, for example, studies analysing populations of Canadian Indians have demonstrated that such actions can reduce such harmful behaviour as individuals become more socially integrated in the communities of their new region (80).

3.1.3 Formal Social Control

Legislation or advice from authorities, such as public health bodies, may result in a reduction in harmful substance use or gambling, for example by preventing access to certain substances or gambling opportunities, or by increasing knowledge and understanding around the potential risks of addictive behaviours and sharing strategies for behaviour change.

One extreme form of formal social control is the prohibition of use of substances or gambling. Prohibition is purported to be associated with a reduction in harmful substance use, as a reduced availability makes is difficult for people to maintain a high frequency and level of consumption (57,

64, 81-83). Prohibition is a determinant of a reduction in harm in all the models, with the exception of tobacco. Evidence supports that the only concerted effort to prohibit the use of tobacco has been in Bhutan, the legislation for which was only recently passed under the 'Tobacco Control Act of Bhutan 2010' (84). However, movements towards such a tobacco prohibition are underway in many countries including Iceland, New Zealand and Australia. Previous attempts at the prohibition of alcohol and gambling have been reversed within Europe and the Western world. This occurred largely as a result of the development of extensive black markets, with many substandard and harmful products becoming available as black markets developed in sophistication over time. With the legalisation of such behaviours, regulations were put in place to ensure the quality of, for example, alcohol products, in order to prevent health harms. Additionally legalisation allowed for the taxation of such behaviours, which is of benefit to governments in terms of the income it can provide (64). Indeed, there is currently speculation that the prohibition of tobacco within Bhutan will be overturned in order to ameliorate the problems which have arisen in the country concerning a black market in tobacco sales (85).

Whilst tobacco prohibitions are yet to become widespread, clean air laws are an example of a successful legislation that has reduced the harmful use of tobacco (86, 87). By preventing consumption in public spaces, users are forced to extricate themselves to a suitable location to engage in use. This has resulted in a reduction in tobacco use and also the cessation of many users, both because of the increasing difficulty of smoking outside the home and the increasing stigmatisation of use.

Within the stimulants and opiates models the determinants of 'needle exchanges' and 'outreach centres' are both forms of formal harm reduction services. Whilst abstinence from illicit drug use is perceived to be optimal, it is widely acknowledged that the achievement of complete abstinence is an unrealistic or undesirable end-point for many substance users. As such, services including needle exchanges act to reduce the harm associated with consumption through improving the conditions of drug use and users' access to health services, as well as reducing the risks associated with use, such as in contracting blood-borne diseases through the use of contaminated needles for drug injection (88-102).

Regulation or control of the availability of certain drugs, such as those used by the medical profession, is widespread across Europe. Many users legitimately access both stimulants and opiates through medical prescriptions; however, abuse of the prescription system exists (103, 104). Consequently, strict controls on prescriptions covering both the quantity and frequency for which doctors are able to prescribe to patients may result in a reduction in harmful use by limiting availability.

3.1.4 Social Structural Factors

Influences within the social structure of a society may determine a reduction in harmful substance use or gambling behaviours through the influences of an individual's social network and the desire to uphold social norms and customs and also through increased responsibilities and opportunities to engage in activities other than harmful substance use or gambling.

Both the level of an individual's education and being employed are considered determinants of a reduction in harmful substance use for all substances considered herein. A greater level of education is associated with a reduction in harmful substance use, as with increasing education people become more aware of the harms of substance use and so may reduce their use. Also, individuals who have a higher level of education may more frequently associate with peers who do not engage in harmful substance use, and the influences of one's social network may prompt a reduction in harmful use to maintain perceived social norms within a network (105). Similarly, being in employment can

determine a reduction in harmful use, as those who are employed are perceived to have greater responsibilities (to their workplace), which may not align with harmful substance use or gambling behaviour. Being employed also keeps people busy, potentially reducing harmful behaviour through limiting the possibilities for engagement with it (105-108).

Marriage or being in a long term partnership is a determinant of a reduction in harmful use of substances and gambling. This may function either through the unspoken effect of a close partner who does not engage in such harmful addictive behaviours influencing the individual to reduce their harmful behaviours, or through explicit persuasion from the partner, where such harmful use may otherwise have a negative effect on an individual's relationships (76, 105, 109). Many people in Western societies engage in long term relationships and marriage from their mid- to late-twenties and early-thirties onwards, and this period is associated with 'maturing out', a socially and biologically determined developmental phase. 'Maturing out' is influenced by social expectations regarding the transition to adulthood (110-113) and biological adaptations, which support risky behaviour prior to the development of the prefrontal cortex in the mid-twenties, when engagement with risky activities declines as the brain develops the necessary cognitive control (114, 115).

Finally, living in deprivation is a risk factor for the use of substances such as stimulants and opiates, both through increased availability of substances within social networks and the consequent normalisation of their use, and also as a coping strategy for living in challenging circumstances (108, 116). Thus, measures to reduce absolute and relative poverty within the population should facilitate a reduction in harmful substance use, as a result of both decreased availability on the black market and a reduced need for coping strategies to mediate challenging living conditions.

3.1.5 Environment of Use

The social environment in which harmful use takes place may promote a reduction in such use. For example, it is evident that in environments where outreach centres and needles exchanges exist that the users of such services should experience a reduction in the harm associated with aspects of their drug use, as they reduce the risk of infection from the use of contaminated needles and have improved access to healthcare and education sources regarding safe practices for substance use (Figure 4, stimulants & Figure 5, opiates) (88-102, 117). Also, such facilities may remove users from the street environment during substance use, removing the potential for dangerous situations arising, such as violence and abuse, which may occur as drug users are often stigmatised within societies. Similarly, to reduce potential harms whilst engaging in substance use, the users of club drugs have stated that they purposefully do not take drugs alone (Figure 6, club drugs), so that if something should go wrong whilst drug-taking there are others around who may assist, for example, with phoning an ambulance (118).

Determinants of a reduction in harmful gambling include the density of electronic gaming machines, as a reduced density is associated with reduced gambling and vice versa (119-126), and the lack of any family members within a user's family with addiction problems (127). The importance of a family environment without any addictive problems may reflect the requirement for an adequate support network, which may not exist if addiction problems exist within a family and such behaviours are normalised. It may also indicate that if heritable factors denoting a vulnerability to addictive behaviours exist, then reducing such behaviours is more challenging.

3.1.6 Consumption

Changes in the consumption patterns of either the substance from which harm is derived, or other substances which the individual uses, may result in a reduction in harm. The successful achievement

of abstinence from stimulant use, which reduces the harm associated with use both to the user and those around them, is associated with a shorter history of use which has been hypothesised to be a result of addiction being less entrenched within the user (Figure 4, stimulants, p.18) (128). For tobacco use, successful abstinence has been found to be most likely achieved if the method of cessation is abrupt, rather than through a gradual reduction or the use of replacement medication (Figure 2, tobacco, p.16) (129, 130). A reduction in harmful cannabis use was associated with users themselves developing knowledge of patterns and practices for safe usage (Figure 3, cannabis, p.17) (131, 132). Such knowledge was found to be shared between users and developed through user experience to reduce harm without necessarily reducing the level of consumption of the user.

A reduction in the consumption of any co-occurring addictive behaviour may influence individuals with harmful gambling behaviours to reduce their gambling (77). This may occur either where the determinants of a reduction in harmful use are similar across behaviours, or where one behaviour change triggers other changes in behaviour that have a consequential impact on harm.

3.1.7 Emotional and Cognitive Processes

The different psychological processes that individuals exhibit may impact to reduce the harm associated with their substance use or gambling behaviour. Determinants identified across the disciplines which contribute to this theme include impulsivity and inhibitory control. Individuals who possess lower levels of impulsivity show an increased likelihood to be successful in reducing their harmful substance use (133). Impulsivity is associated with low levels of constraint, novelty seeking, sensation seeking and poor response inhibition, which may cause an individual to act before they are able to process the significance of such actions (134-138). Impulsivity has previously been outlined as both a determinant of risky and harmful use across the different addictive behaviours (1, 2), thus individuals who are less impulsive may be more able to consider the harm stemming from their use and act to prevent this occurring again, either through reducing their consumption or tackling the harm outcomes directly, through perhaps use of needle exchanges to prevent the risk of using disease-contaminated needles for drug injection. Related to impulsivity is the determinant of inhibitory control (Figure 1, alcohol, p. 15). Inhibitory control is the ability of an individual to inhibit or regulate their behavioural responses to different situations, such as to engage in harmful substance use or gambling, thus with increasing inhibitory control there is an increase in potential for a reduction of harmful use by the individual (139). This lower level of impulsivity may be an inherent trait of the individual or may be the result of developmental neurobiological changes which are known to occur in the mid-twenties, when the prefrontal cortex responsible for inhibitory control matures (114, 115). This neurobiological change occurs much later than the initial development of the striatal circuits, which are associated with reward processing and occurs in early adolescence (114). The development of such inhibitory control is often associated with the sociological process of ‘maturing out’. Additionally, increased inhibitory control can be taught, with the result of controlling individuals’ impulsivity levels (140), which may provide an opportunity to target a reduction in harmful use in impulsive users.

Observation of those individuals who engage in harmful substance use or gambling has demonstrated that they employ their own individual strategies to reduce the harm associated with these behaviours, whilst still engaging in use. Such strategies include a conscious evaluation of the pros and cons of use, by those engaging in illegal drug use (118, 132, 141). Here the user is fully aware of the possible consequences of engaging in use, and if they decide to continue they have considered that the benefits, such as pleasure, may outweigh the consequences. This balance of the possible outcomes by the user may result in their recognition of the potential harm stemming from their substance use or gambling and subsequent action to prevent this. Additionally, some studies of cannabis, opiate and club drug users (Figure 6, club drugs) have shown that the users themselves

display a sense of agency, and show the adoption of self-care strategies, in terms of improving their health in conjunction with their substance use (118, 131, 132, 141-143). Such strategies include improved nutrition, physical activity, reduced sexual risk taking, regulating their substance use and addressing medical concerns, and serve to reduce the health harms individuals may experience as a consequence of their substance use, whilst allowing them to continue to engage in use (142).

3.1.8 Health

The theme of health represents determinants which promote a reduction in harmful substance use or gambling due to a change in the mental or physical health of the individual. For example, the absence of chronic mental illness has been identified as a determinant of reduce use for both stimulants and opiates (108, 116). Similarly, the absence of a comorbid psychiatric disorder has been associated with reduced harmful use (144-147). Further determinants of a reduction in harmful gambling behaviours associated with mental health are the absence of current post-traumatic stress disorder in a user (147) and having suffered fewer lifetime psychiatric disorders (127). Individuals with mental illness may develop harmful substance use habits as a method of coping, and the lack of ill health in a user may reduce the number of obstacles to reducing an individual's' substance use. Equally an improvement in the mental health of those suffering with such problems may give rise to the desire or ability within an individual to reduce their use (127, 147).

3.1.9 Life Circumstances

The circumstances in which individuals live may affect their substance use or gambling to produce a reduction in the associated harm. Determinants which are common to many of the models within this theme include being involved in a marriage or partnership and pregnancy or parenthood (76, 105, 109, 113). These factors influence individuals' lifestyles, increasing their responsibility level, limiting the financial resources available for engagement in substance use or gambling as it is committed to one's partner or child and exerting influence through the relationships to prevent substance use or gambling at harmful levels as it takes time away from the maintenance of such relationships. Additionally, harmful substance use or gambling is in conflict with the socially perceived concept of a good partner or parent, and the desire to fit in with this social norm may prompt individuals to reduce their harmful behaviour. Such determinants generally occur during the life phase whilst individuals are transitioning to adulthood, and thus are considered as factors which influence the process of 'maturing out' of harmful substance use and gambling (76, 105, 109, 113).

With an increase in education level, there is an increasing likelihood of a successful reduction in harmful substance use, across all the substances analysed (105). This determinant is based upon US studies and demonstrates that in individuals that obtain a college level education there is an increased chance of them reducing their harmful substance use. This reduction in harm may be linked to those with increased education being more likely to be employed, have successful peers through their employment and education and the result of these social networks exerting influence through peer pressure and social norms, and so this determinant shows overlaps into the social environmental level of analysis. Also with increased education levels the individuals are more likely to be aware of the potential harms resulting from substance use and take action to reduce this.

The influence of both family members and friends of harmful users of tobacco or gamblers may encourage a reduction in their harmful behaviour. This effect was noted in that family and friends may confront users regarding their use and persuade them to reduce this use or abstain completely (76, 77, 127, 148). Additionally for gambling, family and friends were seen to play a role in aiding harmful users to cease their behaviour through taking over control of users finances, thereby removing their ability to gamble further, or through minding users, to ensure they do not enter

arenas in which they are able to gamble and ensuring they do not participate in such activities should they present themselves (76).

3.1.10 Impact on and/or Dysregulated Neurocircuitry

The most common determinant across all the models in the theme of 'impact on and /or dysregulated neurocircuitry' is that of inhibitory control, appearing in all models except cannabis and club drugs. Harmful substance use is known to arise from an imbalance between the neurological centres for reward processing and inhibitory control, and thus studies addressing a reduction in harmful use have focused on these two regions (149-152). An improvement in the inhibitory control of abstinent users has been demonstrated, with former cocaine addicts showing similar inhibitory control to non-users as quickly as one month following cessation of use (153). Similarly, an increase over time in inhibitory control was noted in former heroin addicts using the Iowa Gambling Task as a form of assessment, with those who were recently abstinent (<30 days) showing reduced inhibitory control compared to those with longer periods of abstinence (>3-24 months), and no difference between former addicts and controls noted beyond 24 months of cessation (154). These changes show that the brain's neurocircuitry can recover from the effects of harmful use, with such changes being associated with increased activation of the neurocircuitry underlying cognitive control in both cocaine addicts and former smokers, where longer abstinence was associated with increased activity within the prefrontal cortex (155, 156). Abstinent addicts can demonstrate increased activity in these brain areas compared to both addicts and drug-naïve individuals, thus it has been hypothesised that this 'supernormal' level of activity in abstinent users may indicate that the recovery from addiction is a distinct process rather than a reversion to the pre-addicted state of the individual (136).

Increased activation in different brain regions has been noted as a determinant of a successful reduction in harmful substance use of both alcohol and stimulants (Figure 1, alcohol & Figure 4 stimulants), with increased activity noted in ventral tegmental area (VTA), the midbrain and the thalamus, and increased connectivity between the different regions (157, 158). However, such increased activity levels in the brain regions of abstainers have previously been associated with relapse in harmful users of alcohol, stimulants and tobacco, as it was assumed that increased activity would indicate an increased drive to engage in use (159-162). Nevertheless, further studies have demonstrated that relapsers tend to show atrophy in the regions of the brain responsible for error monitoring and behavioural control, the bilateral orbitofrontal cortex and in the right medial prefrontal and anterior cingulate cortex (157).

A reduced level of cue reactivity has been shown to be linked to a reduction in the harmful use of cannabis, alcohol and tobacco (6, 163-167). Cue reactivity is the manifestation in individuals of physiological and subjective responses, such as cravings, in response to the presentation of drug-related stimuli. At the neural level this translates into increased activation of the brain regions associated with addiction. Individuals with a reduced neural cue reactivity to cannabis related stimuli showed reductions in their use up to six months following the initial psychological assessment (Figure3, cannabis) (6, 168). Much effort has been concentrated on the re-conditioning of harmful substance users cue reactivity to promote the maintenance of abstinence (7, 169).

3.1.11 Impact on and/or Dysregulated Neurotransmitters

Dopamine is often the neurotransmitter most associated with substance use, and there is a substantial volume of literature demonstrating its role in the development and maintenance of harmful use (170). Despite this, comparatively little is known regarding its function in a reduction of such harmful use. Reduction in dopamine receptor (DRD2) availability under chronic cocaine use has been noted in studies of non-human primates, and following cessation of cocaine use receptor

availability was seen to increase (Figure 4, stimulants). However, this was not the case for all animals, particularly following longer periods of exposure, and in the animals whose DRD2/3 availability did not recover a reduced response to food was observed prior to any cocaine exposure, suggestive of a pre-existing dysregulated reward circuit (171, 172). These results demonstrate that although many can return to normal function following harmful stimulant use, some individuals may be pre-disposed to drug use through the dysregulation of neurotransmitters. Indeed, it is supposed that in stimulant users and alcoholics that a hypodopaminergic state is a vulnerability factor for continued use and relapse (173-176). Further, carriers of different variants of the dopamine receptors may suffer more severe withdrawal symptoms, with variants of both *DRD3* and *DRD5* having been associated with increased withdrawal severity, and thus a reduced likelihood of a reduction in harmful alcohol use (Figure1, alcohol) (177, 178). Additionally a specific variant of the *DRD4* gene variable number tandem repeat has been associated with increased craving sensations for alcohol, tobacco and heroin upon cessation, again increasing the likelihood of relapse in the harmful use of such substances (179).

This rebalance of neurotransmitter levels following abstention from substance use has been similarly noted for μ-opioid receptors in individuals abstaining from alcohol, cocaine and heroin use (174, 180-183), with these changes having been linked to the increased feelings of craving by abstainers from both alcohol and cocaine (174, 182, 183). Such cravings may promote the relapse of harmful use of such substances. Moreover, dramatic increases in the neurological level of glutamate, a key excitatory neurotransmitter operating within the amygdala, hippocampus, prefrontal cortex and nucleus accumbens, have been observed in early alcohol withdrawal (184-186). These rises in glutamate levels may account for the neurotoxicity of withdrawal including consequences such as seizures, blackouts, amnesia and neuronal death (187-189). Such severe withdrawal effects are a common driver for many to continue with their harmful drinking behaviours (190).

3.1.12 Drug Characteristics

The characteristics of a substance and chosen mode of delivery can influence the level of harm that stems from use, and thus may determine a reduction in harmful use.

For tobacco, the evidence highlighted within our model includes determinants such as drug kinetics and the route of consumption/ delivery. For example, as snus does not involve the inhalation of chemicals such as tar (that are present in smoked tobacco) it is not associated with cancer or respiratory diseases in users. It is also associated with a reduced risk of cardiovascular disease compared with smoking. Thus a shift in the method of tobacco use, from smoking to snus use, could result in a decrease in tobacco related harm, as found in Sweden where snus is popular (191).

The composition of the substance used may give rise to a reduction in the harm experienced by the user. For tobacco products, this may relate to a reduction in the levels of nicotine or tar in cigarettes, or for cannabis may relate to the level of cannabidiol within the substance. Such reductions may reduce both the toxicological properties and the physiological effects of use, thus aiding users to move towards cessation of use.

3.1.13 Game Characteristics

Not all forms of gambling are the same, for instance, playing the national lottery once a week is very different to gambling on a fruit machine. The structural characteristics of the gambling activity have been shown to be important in the maintenance of gambling behaviours. It has been suggested that the structural characteristics of games, such as fruit machines, have the potential to induce excessive gambling regardless of an individual's innate tendencies (192, 193). As such, game characteristics

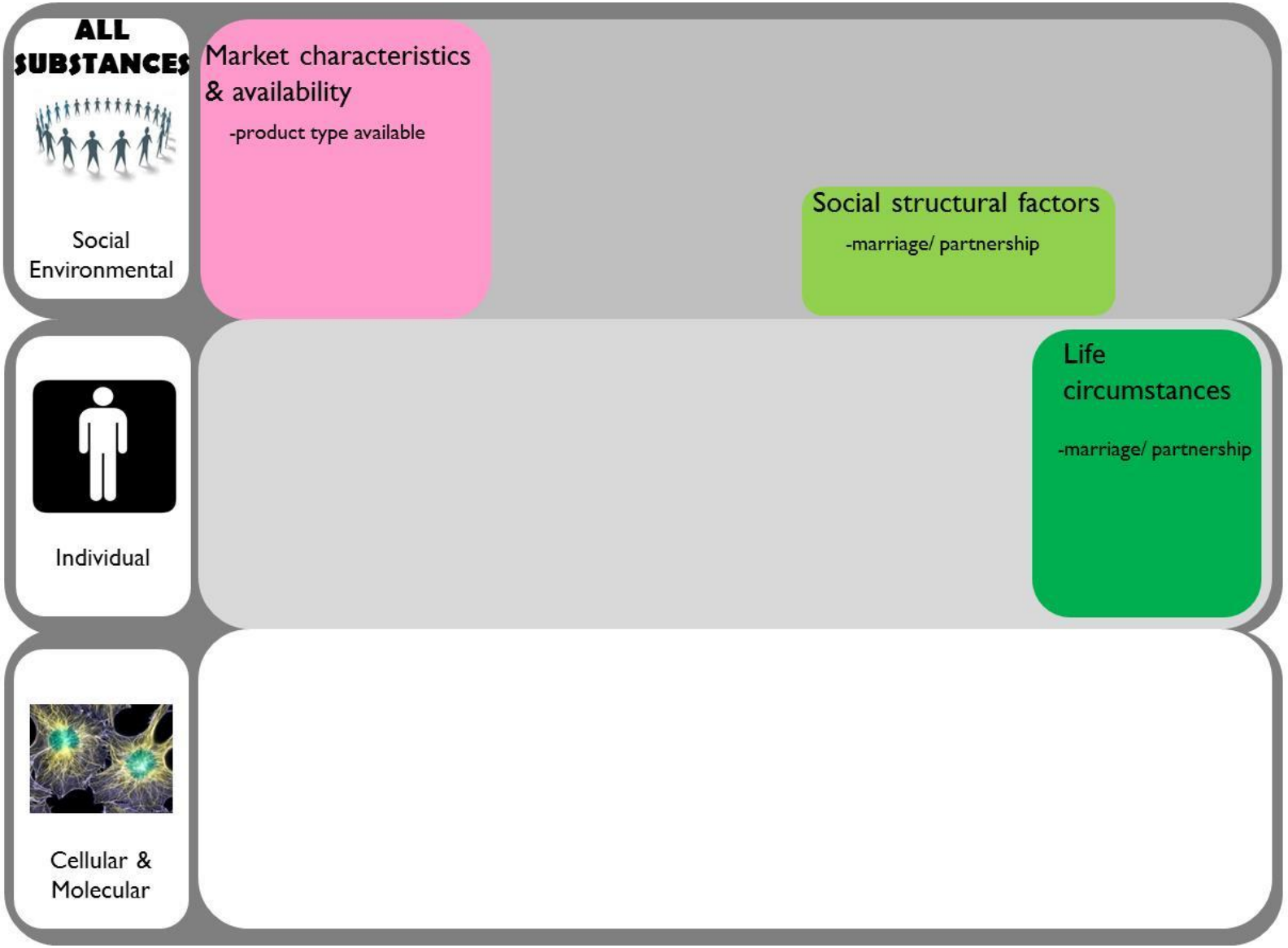
may be seen as comparable to drug characteristics or drug kinetics, where drugs that show a rapid action appear to be more addictive than those which are slower to take effect.

Characteristics of the game appear to influence the relative addictiveness of the activity, with games that have a high event frequency and short pay out intervals with a high jackpot size showing a greater capacity for harmful use. Awareness that these determinants support maintenance of gambling behaviours can be used to develop approaches that might promote reduced harmful gambling, for example through providing gambling opportunities with low event frequencies and high pay out intervals with low jackpot sizes (Figure 7, gambling, p.21). This may avoid the stigmatisation of individuals who wish to engage in gambling, whilst ensuring that the determinants of gambling which are associated with increased levels of harm are not available.

3.2 Determinants common to multiple substances

Whilst it is evident from the various substance models (Figure1-7) that there are many differences in the determinants of a reduction in harmful use, we have attempted to distinguish the determinants that are common to the different substances and present these within Figure 8, below. Across all the models there are only two determinants that lie within three different themes, that indicate a reduction in harmful use of all the substances and gambling considered within our work.

Figure 8: Determinants common to multiple substances



At the social environmental level of analysis, the two determinants indicative of a reduction in harmful behaviours are the product type available, within the theme of 'Market characteristics and availability', and being part of a marriage or partnership, within the theme of 'Social structural factors'. The first of these determinants exerts its affect at the population level, where a restriction of the availability of product types associated with the most harm, such as a restriction in the availability of high alcohol content products, or an increase in the range of products available to include an increased number of products which are associated with less harmful use, such as increased levels of low alcohol products available, will result in a change of availability to all users, both those who engage in harmful use and those who do not. This is perceived as a method for reducing harmful use without stigmatising individuals, and which also allow affect for those individuals who may not recognise that their behaviours lead to harm or those who experience silent harms, such as the development of liver disease over a period of time, and thus might not participate in more directed harm reduction strategies (58-60).

The second determinant common to a reduction in harmful use across all substances and gambling is that of marriage or partnership for the user. This determinant is present within both the theme of 'Social structural factors' at the social environmental level and 'Life circumstances' at the individual level. This factor demonstrates the important influence that close relationships may have upon an individual's behaviour, and the adaptations which may take place in response to the behaviour of those around them, this may operate through a conscious effort to reduce harmful usage to maintain a close relationship such as a partnership, or without any conscious intention on the behalf of the user, whereby the association with a spouse or partner who engages in less harmful use the individual shifts their behaviour too to create a reduction in harmful use (76, 105, 109, 113).

Despite the lack of determinants common to all models, some are common to the majority. Examples of this include pregnancy or parenthood being a determinant of a reduction in harmful use across all substance use models, but not in gambling (79, 105). This may reflect a lack of research around this determinant for gambling, or the difference in gambling behaviour compared to substance use, whereby parenthood does not modify gamblers' behaviour in the same manner as for substance users. Pregnancy or parenthood may act to reduce harmful substance use by increasing a users' responsibilities and limiting the available financial resources to engage in such activities, as they are committed to taking care of one's children. Furthermore, the social perception of a good parent does not include a harmful substance user, and such social conventions may play a part in reducing one's harmful use, in much a similar manner as it may do in marriage. Such determinants as parenthood and marriage, generally occur during the life phase whilst individuals are transitioning to adulthood, and thus may exert their influence through the natural recovery process of 'maturing out' of harmful substance use and gambling; a set of socially and biologically determined factors that combine to influence people to reduce such harmful usage during their twenties (76, 77, 105, 109, 110, 113).

Prohibition is a determinant common to all our models except tobacco. The reduction of harmful use associated with prohibition is associated with the limited availability of products and the potential for criminal sanctions against individual users. The ineffectiveness of the alcohol prohibition in the early twentieth century resulted from an increased level of crime to supply the black market demand for such products and the lack of dedicated law enforcement to deal with such issues. Despite this increase in crime, the health effects of limiting alcohol use in this manner were overwhelmingly positive with a two-third reduction in liver cirrhosis (194). The lack of inclusion of this determinant within the tobacco model is associated with the lack of an historical prohibition on tobacco.

The lack of common determinants across models reflects the lack of determinants available from the literature regarding natural recovery. The predominant focus of the research literature regarding an exit from addiction, or a reduction in harmful use is concerned with formal treatment regimens observing patient populations, with very little known regarding natural recovery, despite this being

the most common form of behaviour cessation. At the biological level there are no determinants common to all models, demonstrating our lack of understanding at a molecular level of the determinants which may lead to a reduction in harmful substance use or gambling. Knowledge regarding the determinants which may give rise to a reduction in harmful use is imperative in directing policy and clinical initiatives to aid individuals in such behaviour modifications.

One implication of the lack of common determinants of a reduction in harmful use across the substance and behaviour models displayed here is that each of the addictive behaviours operate within their own parameters or boundaries of influence. As such, it is important to continue researching and treating each behaviour as a separate issue, recognising that we cannot group all addictive behaviours into one common condition with common underlying causes and solutions.

3.3 Multidisciplinarity within the model

Research within the addiction field has long been fractured, with knowledge from across the disciplines being brought together all too rarely. It has been compared to 'The tale of the elephant and the blind men', where each man touches and describes one part of the animal, but none can describe the whole beast. ALICE RAP seeks to advance multidisciplinary addiction research and our models highlight potential areas for work which can improve our current understanding and highlight new solutions to societal problems.

One key challenge in developing a model for a reduction in harmful substance use and gambling was illustrating the state of knowledge. In presenting the model clustered around themes, we have masked some of the additional learning around the multidisciplinarity of research of the determinants of risky substance use and gambling. As such, here we present an alternative version of the model, targeted towards researchers and policy makers with an interest in the multidisciplinarity of research on risky substance use and gambling.

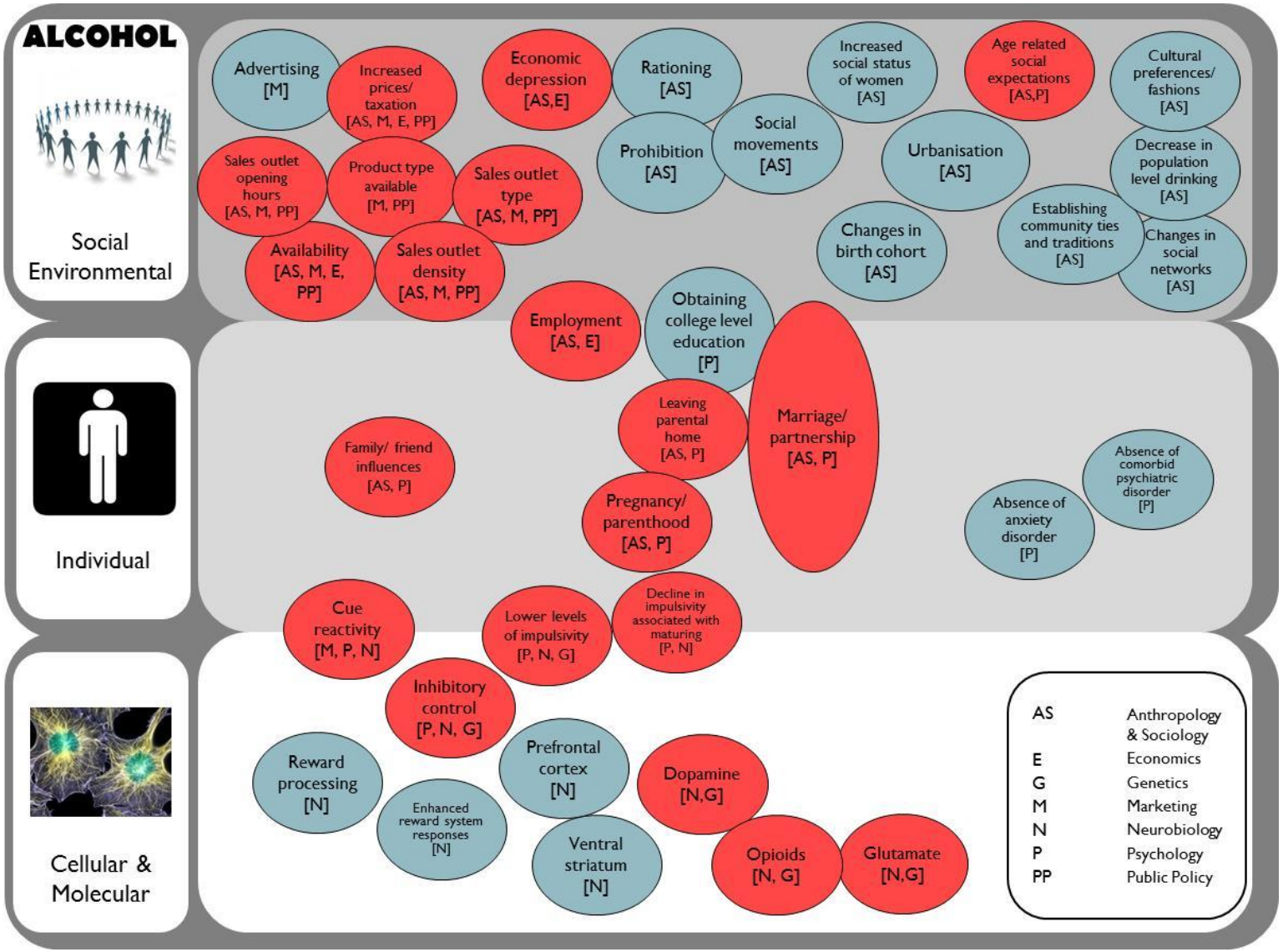
3.3.1 Example: the multidisciplinarity of alcohol research

Figure 9 (below) presents a variation on the alcohol model described in Section 3.1 (p.13). The same determinants are illustrated within both models, but rather than clustering determinants into broader themes, each determinant is a stand-alone bubble in Figure 9. The lighter, blue circles indicate determinants that are researched by a single discipline whilst the darker, red circles show determinants that are researched within two or more disciplines. Within each circle, the square brackets indicate the disciplines that have contributed to research on that determinant.

The model illustrates that over half of the identified determinants of a reduction in harmful alcohol use were researched by more than one discipline. Of the multidisciplinary determinants within the alcohol model, over half show research contributions by the disciplines of anthropology and sociology, demonstrating the increased research into reductions in harmful use and natural recovery by these disciplines, and thus our enhanced understanding of these issues at this level.

Within our working group we were unaware of previous multidisciplinary research projects concerning the reduction of harmful substance use or gambling in non-treatment populations. The determinants that show research overlap across multiple disciplines in the model may represent starting points for future multidisciplinary research. Indeed, where determinants show research input from multiple disciplines this tends to involve disciplines within the same level of analysis, (i.e. cellular and molecular, individual, social environmental), which therefore may have more common research approaches and practices that may facilitate multidisciplinary working. Research working across epistemological backgrounds to understand addiction is rare in the literature to date.

Figure 9: Alcohol model with multidisciplinary emphasis



Thus, to further our understanding of the determinants of addiction we should encourage researchers to work across disciplines and particularly across epistemologies in developing future addictions research. Policy makers and funding bodies should be aware that they might greatly further knowledge by supporting multidisciplinary research around the determinants of harmful substance use and gambling. Such multidisciplinarity and cross-epistemological research could enhance our understanding of substance use and gambling by drawing on learning from different disciplinary approaches in larger, co-ordinated multidisciplinary projects to aid in the design of effective intervention strategies to prevent harmful addictive substance use and harmful gambling.

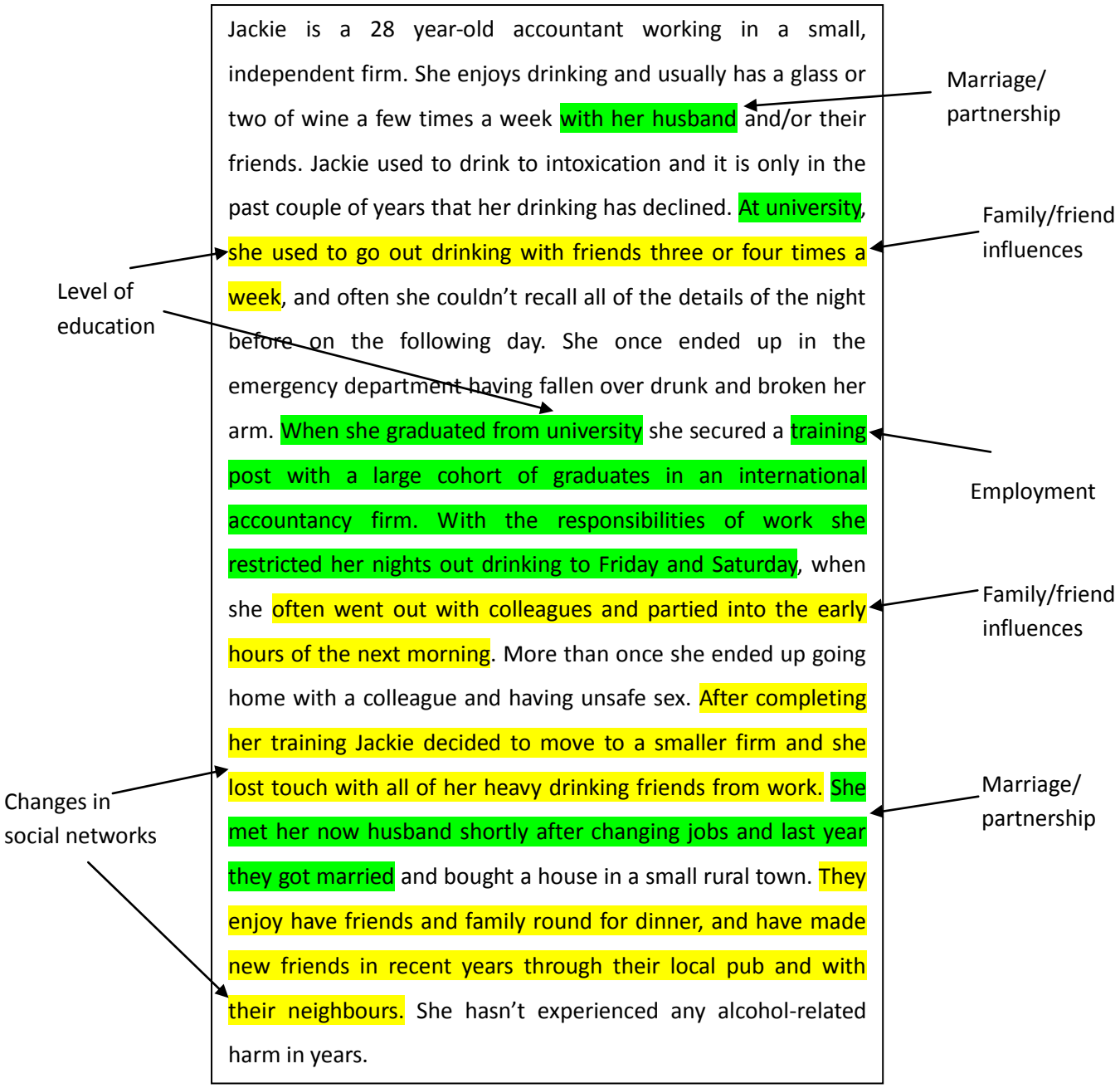
3.4 Case Studies

To illustrate how the models depicted above can be used to further understanding of the determinants of a reduction in or the cessation of harmful substance use or gambling, we have produced two illustrative case studies. These case studies relate to a reduction in harmful alcohol consumption and are plausible but fictional scenarios designed to show how different determinants work together within different individuals and dependent upon the social context of both the user and, more specifically, the use of the substance. They also illustrate that not all determinants influence the reduction of harmful use in all individuals engaging with a particular substance; some individuals might have four or five determinants of a reduction in use whilst another has fourteen or fifteen. The case studies are not exhaustive but seek to highlight a range of potentially relevant determinants.

For each case study, we present the scenario in three different ways: firstly as a stand-alone brief text-based description, secondly as a brief text-based description with commentary, and finally within the alcohol-specific model, where relevant determinants are highlighted in black and the remaining determinants not relevant to the case study are shown in grey.

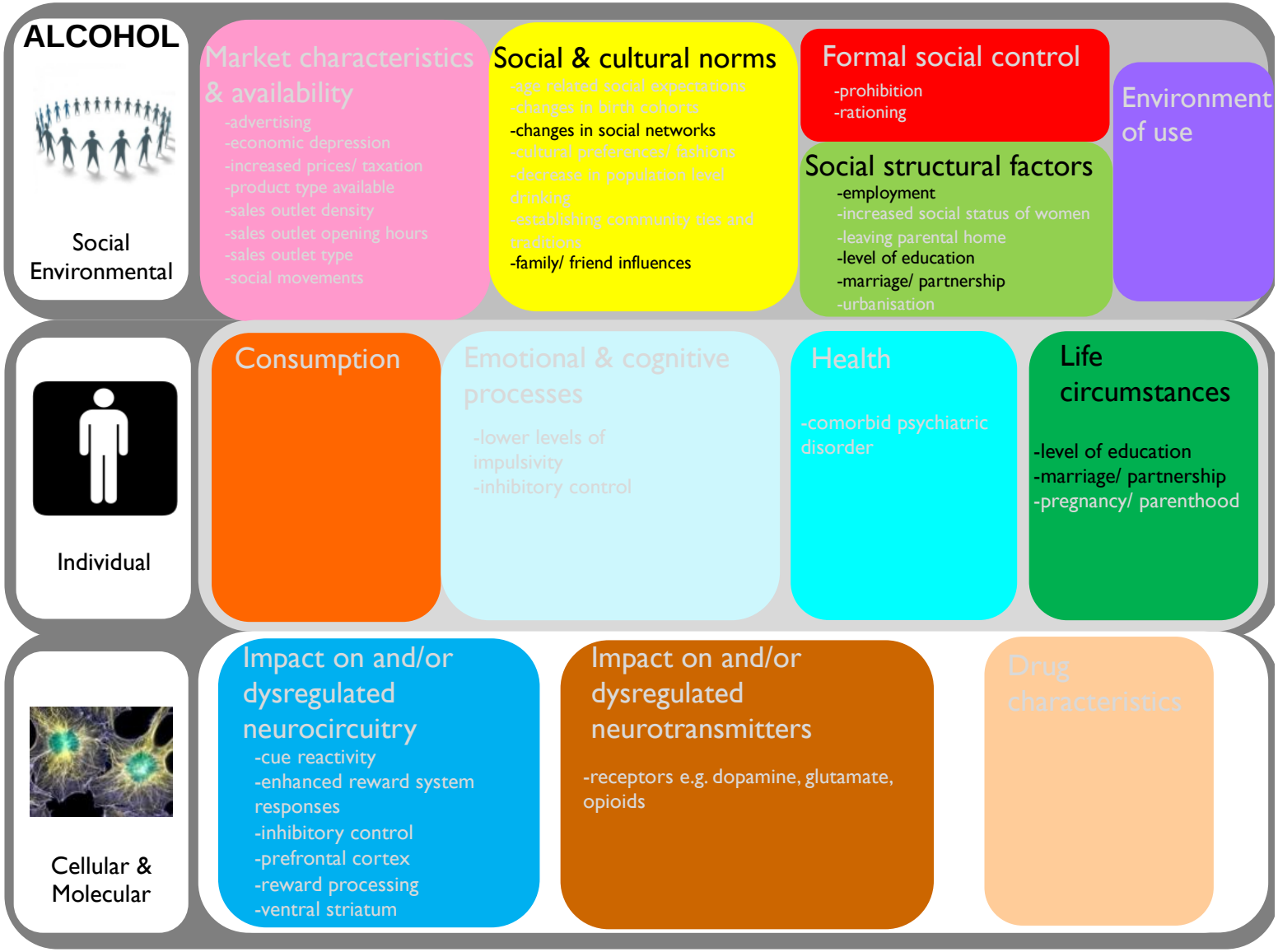
Case study 1: Jackie

Jackie is a 28 year-old accountant working in a small, independent firm. She enjoys drinking and usually has a glass or two of wine a few times a week with her husband and/or their friends. Jackie used to drink to intoxication and it is only in the past couple of years that her drinking has declined. At university, she used to go out drinking with friends three or four times a week, and often she couldn't recall all of the details of the night before on the following day. She once ended up in the emergency department having fallen over drunk and broken her arm. When she graduated from university she secured a training post with a large cohort of graduates in an international accountancy firm. With the responsibilities of work she restricted her nights out drinking to Friday and Saturday, when she often went out with colleagues and partied into the early hours of the next morning. More than once she ended up going home with a colleague and having unsafe sex. After completing her training Jackie decided to move to a smaller firm and she lost touch with all of her heavy drinking friends from work. She met her now husband shortly after changing jobs and last year they got married and bought a house in a small rural town. They enjoy having friends and family round for dinner and have made new friends in recent years through their local pub and with their neighbours. She hasn't experienced any alcohol-related harm in years.


Jackie is a 28 year-old accountant working in a small, independent firm. She enjoys drinking and usually has a glass or two of wine a few times a week with her husband and/or their friends. Jackie used to drink to intoxication and it is only in the past couple of years that her drinking has declined. At university, she used to go out drinking with friends three or four times a week, and often she couldn't recall all of the details of the night before on the following day. She once ended up in the emergency department having fallen over drunk and broken her arm. When she graduated from university she secured a training post with a large cohort of graduates in an international accountancy firm. With the responsibilities of work she restricted her nights out drinking to Friday and Saturday, when she often went out with colleagues and partied into the early hours of the next morning. More than once she ended up going home with a colleague and having unsafe sex. After completing her training Jackie decided to move to a smaller firm and she lost touch with all of her heavy drinking friends from work. She met her now husband shortly after changing jobs and last year they got married and bought a house in a small rural town. They enjoy have friends and family round for dinner, and have made new friends in recent years through their local pub and with their neighbours. She hasn't experienced any alcohol-related harm in years.
Marriage/ partnership
Family/friend influences
Level of education
Employment
Family/friend influences
Changes in social networks
Marriage/ partnership

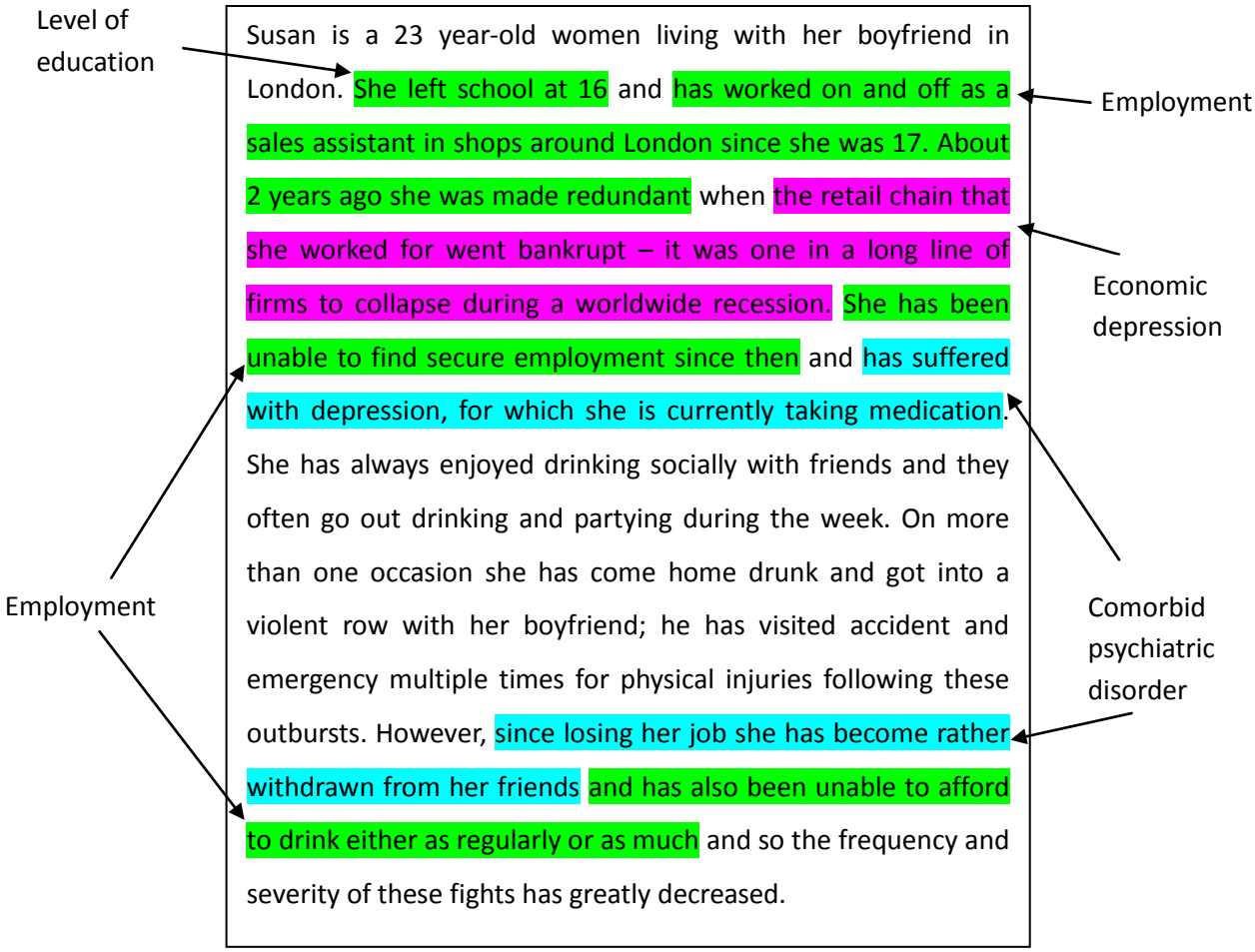
Case study 1: Jackie

(Relevant determinants in black text)



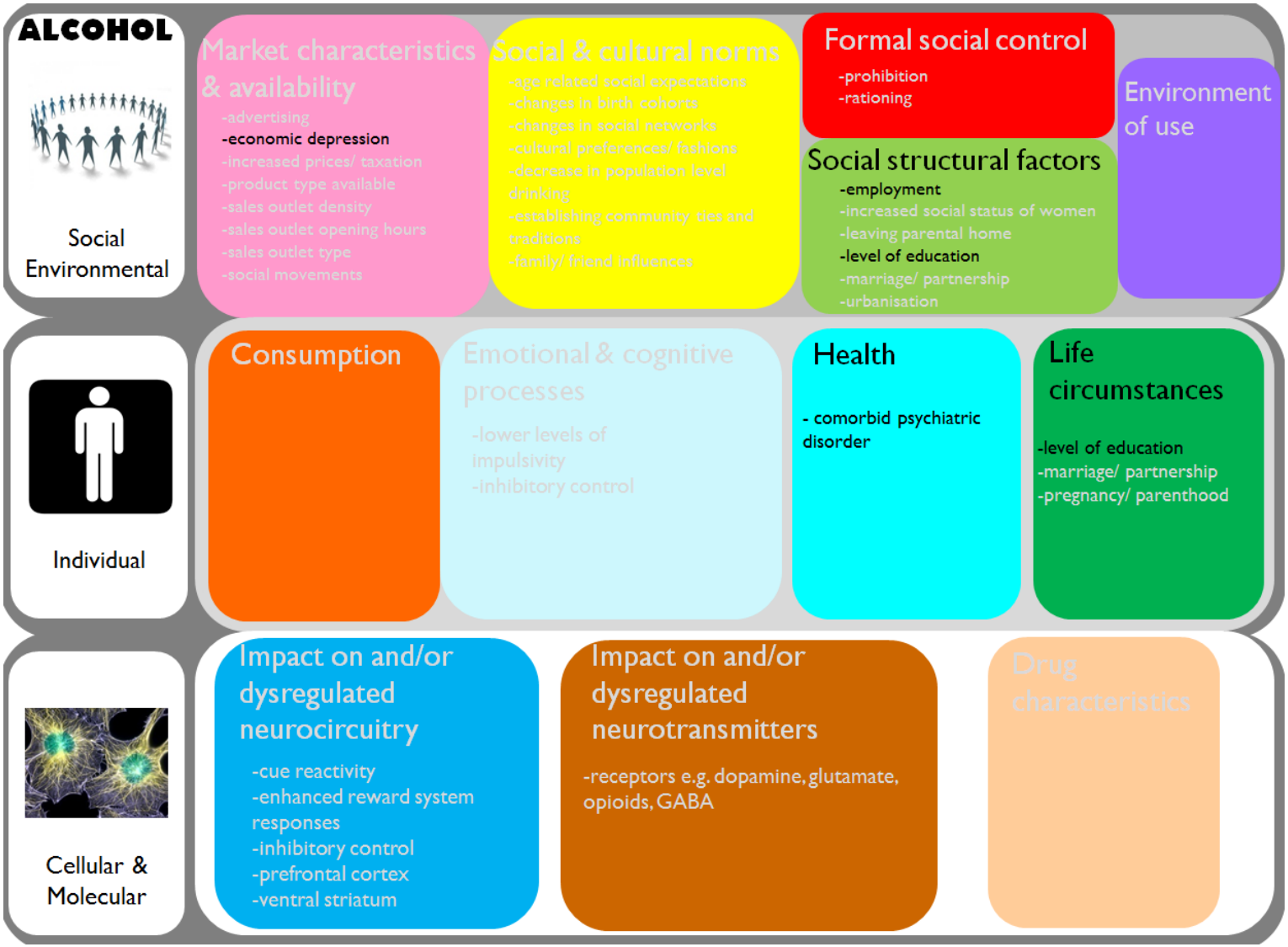
Case study 2: Susan

Susan is a 23 year-old women living with her boyfriend in London. She left school at 16 and has worked on and off as a sales assistant in shops around London since she was 17. About 2 years ago she was made redundant when the retail chain that she worked for went bankrupt – it was one in a long line of firms to collapse during a worldwide recession. She has been unable to find secure employment since then and has suffered from depression, for which she is currently taking medication. She has always enjoyed drinking socially with friends and they often go out drinking and partying during the week. On more than one occasion she has come home drunk and got into a violent row with her boyfriend; he has visited accident and emergency multiple times for physical injuries following these outbursts. However, since losing her job she has been unable to afford to drink either as regularly or as much and so the frequency and severity of these fights has greatly decreased.



Case study 2: Susan

(Relevant determinants in black text)



3.5 Transition probabilities

3.5.1 Transition probabilities

The annual transition probabilities for the four-state model and the respective 95% CIs are shown in Table 4. The highest probabilities were observed for staying in one state: for abstinence, use, and risky use the respective probabilities lied roughly between 70% and 80%. The only exception was the probability of about 13% for staying a harmful user. Harmful users had a probability of 79% to be a categorized as a user in the following year. The lowest transition probabilities were observed for transitioning to abstinence (<5% for all states) as well as transitions from abstinence to risky or harmful use (<3%). The probability of becoming a user within one year from being an abstainer was about 19%.

Table 4: Annual transition probabilities in % between all four drinking states and respective 95% confidence intervals (CI). Transition probabilities in each row sum to 1. Figures in bold face indicate transitions to a more severe drinking state, figures in the diagonal reflect probability to stay in one use state.

	Abstinence	CI	Use	CI	Risky use	CI	Harmful use	CI
Abstinence	78.3	76.8-79.8	**18.8**	17.4-20.4	**1.0**	0.8-1.1	**1.9**	1.1-2.5
Use	4.1	3.5-4.7	77.8	76.4-80.5	**7.5**	6.5-8.5	**10.6**	7.6-11.8
Risky use	0.7	0.6-0.9	26.6	22.8-31.6	69.9	64.9-74.1	**2.8**	1.6-3.6
Harmful use	3.1	1.8-4.0	78.5	57.5-80.1	5.8	3.3-7.2	12.6	10.1-37.3

3.5.2 Covariates, age, gender and SES

For the allowed transitions (see Q-matrix reported above) HRs were calculated for the covariates age, gender, and SES (operationalized as self-rated financial situation; see Table 5).

For age, conform to our hypothesis, all investigated transitions except of risky use to use showed significant HRs, indicating lower transition probabilities when getting one year older. As hypothesized we found significant HRs for gender for the 'early' transitions with males being more likely to transition to use and less likely to transition back to abstinence. Furthermore a significant HR for harmful use to use indicated that females are more likely to transition to use when being a harmful user. As hypothesized SES showed significant HRs in transitions relating to use (use to risky as well as to harmful use, harmful use to use). Persons with a higher SES (self-rated financial situation) were less likely to transition to risky patterns of use and more likely to transition to use when being a harmful user. Against our expectations persons with a higher SES were more likely to become a harmful user when being a user.

Table 5 Hazard ratios and their 95% confidence interval for the covariates age, gender and SES, for all allowed transitions.

		Gender		Age		SES	
Transition		HR	CI	HR	CI	HR	CI
Abstinence	→ use	0.82*	0.71-0.95	0.93*	0.91-0.95	1.00	0.90-1.10
Use	→ abstinence	1.93*	1.46-2.55	0.93*	0.89-0.97	0.87	0.72-1.05
Use	→ risky use	0.76	0.56-1.03	0.92*	0.88-0.96	0.77*	0.64-0.94
Use	→ harmful use	0.71	0.27-1.87	0.71*	0.59-0.86	2.32*	1.29-4.17
Risky	→ to use	0.95	0.66-1.36	1.00	0.95-1.06	0.88	0.71-1.10
Harmful use	→ use	2.61*	1.02-6.68	0.83*	0.68-1.00	2.58*	1.46-4.55

* Significant, α=5%; HR hazard ratio; CI 95% confidence interval

3.5.3 Simulations

The simulations of prevalence (proportions) based on age- and gender-specific transition probabilities are shown in Figure 10. Graphs for abstention, risky and harmful use show a clear gender gap and a stabilization of the prevalence over age in the early twenties. Stabilized prevalence of abstainers was around 10% in males and 30% in females. The proportions of risky and harmful use (past 12 month) peak around the age of 20 with a prevalence of about 20% in men (risky and harmful use) and 17% (risky use) and 7% (harmful use) in women and slowly decrease afterwards.

3.5.4 Sensitivity Analyses

Analyses based on the expanded datasets (expansion with wt * 10 and wt * 100) with SE correction replicated the findings based on the original dataset without weighting. The simulations for both expansions are shown in the Appendix. In comparison with the simulations based on the unexpanded data, in both expansions the peak around the age of 17/ 18 in harmful use for men is more prominent. For the HRs both versions of expansion exactly replicated the pattern of significances found for the original, unweighted dataset with one exception. In both versions of expansion the HR for gender on the transition harmful use to use was not significant anymore after adjusting the SE.

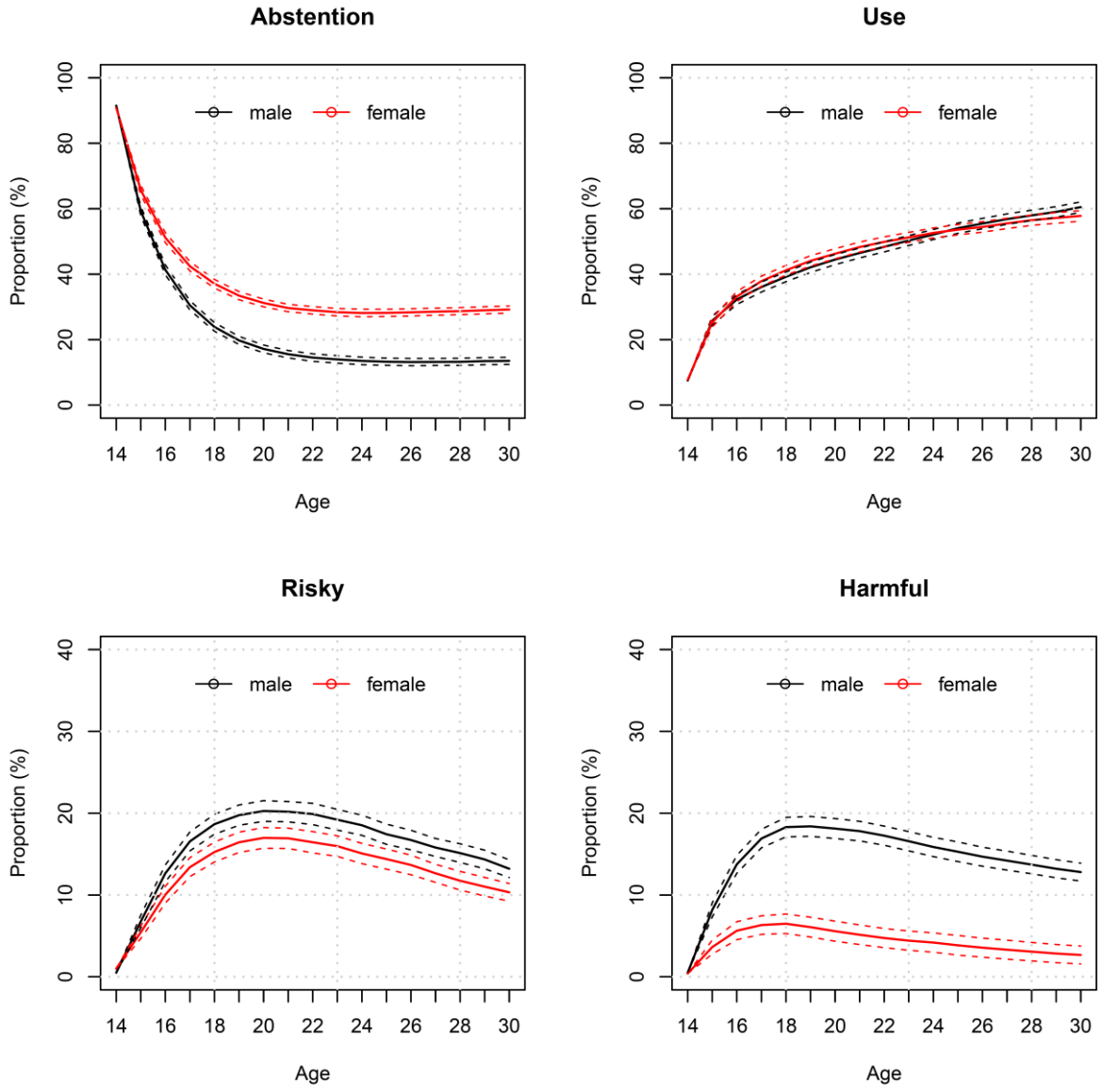


Figure 10: Simulated prevalence of all four use states (abstinence, use, risky use, and harmful use) by age and gender. Dashed lines indicate 95% confidence interval.

4. DISCUSSION

4.1 Models

4.1.1 Key findings

The models presented here for addictive substances and gambling demonstrate a multidisciplinary understanding of the key determinants of the transition from harmful use to a reduction in harmful substance use and harmful gambling. We have grouped these determinants into key themes, which provide easy ways to understand the mechanisms by which these determinants may function and consequently infer possible policy responses and interventions.

The initial finding from our research into the reduction in harmful substance use and gambling in non-treatment populations was that there exists a lack of research into non-treatment populations and reductions in harmful use that may not coincide with the cessation of use. This was particularly evident at the biological level where few determinants were available. Indeed, the model for club drugs shows no known determinants at the cellular and molecular level and no determinants were found to be common to all the models at this level. We have found that whilst there are many reports characterising differences in brain structure and function in addicts compared with healthy controls and how these may be related to behaviour, less is known about resilience. When resilience is described, it is generally in relation to *not* developing abuse rather than recovering or maintaining enduring abstinence. This lack of understanding stemming from a lack of research results in an inability to adequately target policy interventions to reduce harmful substance use and gambling, and thus more research in this area is key to improving future effective policy in the field of substance use and gambling behaviours.

Some of the models contain fewer determinants than others as a result of less research having been carried out in this area. The most under-populated substance model is that of club drugs. This may reflect the more recent history of use of such substances, in comparison to the other models, or the increased level of natural recovery undertaken by users of such substances. Additionally, the illegal nature of such substances make them more difficult to accurately research. However, use of these drugs is increasing within society and thus an understanding of how to reduce harmful use is imperative to prevent future harms.

As our models show that the greatest number of determinants of a reduction in harmful use are present at the social environmental level of use. This offers us a more refined understanding of the factors influencing reductions in harmful use at this level. Additionally, analysis of the different contributing disciplines to the different determinants (Figure 9, p.34) highlights the high number of determinants which are encompassed within the research of the disciplines of anthropology and sociology, with over half the determinants for a reduction in harmful alcohol use having been researched by these disciplines. This may indicate that policy interventions to promote a reduction in harm may be most effective at this level, as our nuanced understanding affords a more targeted approach.

Within the gambling model there exists the theme of ‘Game characteristics’ at the cellular and molecular level of analysis (Figure 7, gambling, p23). Though the determinants within this theme do not directly refer to factors at this level of analysis this theme was felt by the expert panel to represent analogous factors to those found within the similar theme of ‘Drug characteristics’ of the different substance models, with slower games with a lower jackpot size being similar to drugs with a slower mechanism of action and ultimately less addictive. The difference in the titles of these themes between the gambling and substance models however, highlights an important finding from this work which is also represented in Figure 8 (All substances, p.31); that a reduction in harm from the different addictive behaviours is governed by different factors in each case, and thus we cannot group addictive behaviours together *and* effectively tackle the myriad of different underlying causes.

It is possible to draw together some of the different important factors which appear most often within the different models influencing reductions in harmful usage. Determinants such as marriage/ partnership, pregnancy/ parenthood, employment at the social environmental level, lower levels of impulsivity at the individual level and inhibitory control at the cellular and molecular level all act within the key developmental process of change of ‘maturing out’. This theory involves the transition to from childhood to adulthood, and is associated, in Western societies, with a period of experimentation, including harmful substance use and gambling behaviours. As individuals progress to adulthood social expectations revolve around reducing such harmful behaviours and taking on

more responsibilities, such as marriage, parenthood and employment (105, 109, 113). At the biological level this age-related transition occurring in the mid-twenties, is associated with the development of the prefrontal cortices that are responsible for inhibitory control over the earlier developed striatal circuits, which are responsible for reward processing. This later adaptation of cognitive control therefore acts to inhibit impulsive behaviours such as substance use and gambling within individuals (114, 115). However, it is important to note that each of these determinants may also operate outside of the process of 'maturing out' to effect reductions in harmful substance use and gambling.

We have presented here our findings concerning the determinants of reductions in harmful substance use and gambling and displayed relationships between such determinants through their inclusion within different themes and at different levels of analysis. Furthermore, we have highlighted potential research foci for future multidisciplinary research (Figure 9, p.34) within this field, in order to address the lack of available knowledge. Such future research is essential to develop our understanding of the determinants of reductions in harmful substance use and gambling in non-treatment populations, and allow the targeting of policy measures to promote such behaviours.

4.1.2 Limitations

We acknowledge that whilst the panel of experts assembled to produce this work covered many disciplines, with opinions sought from additional discipline experts, there are specific influences from certain disciplines that research within the field of addiction that are absent. For example, a medical expert for input on topics such as health, and criminologists for input on the legal and criminal aspects of addictive behaviours. As such, this range of models is specific to the range of disciplines that have contributed to work area 3 of ALICE RAP and the time frame within which it was generated. It would undoubtedly contain different and additional determinants had the panel of experts assembled to carry out the task varied or been broadened. Further, our expert panel from across all the disciplines involved showed a bias towards alcohol research. Consequently, our model of the determinants of reductions in harmful alcohol use shows a greater number of determinants than for many of the other behaviours, in particular, tobacco. Were the research bias in our expert panel weighted differently then perhaps the models presented here would display a different level of understanding concerning the examined reductions in harmful use. Similarly, if these models were to be generated in a decade's time, again the determinants considered important would be different than those highlighted here; as addiction studies move forward key theories and determinants will change in light of new evidence. However, it is important to not only assess our current state of knowledge within the field, of which these models provide an overview for factors contributing to reductions in harmful substance use and gambling, but also to provide workable models for future research to build upon. Our models highlight current knowledge gaps specific to different addictive behaviours, whilst presenting key determinants around which different discipline experts can collaborate to enhance our understanding of this.

In our analysis of reductions in harmful use we have included behaviours such as cessation of use, reductions in an individual's level of usage, changing substances to one that is less harmful e.g. to a lower strength tobacco product or lower strength alcohol, reduction in harms to others, such as family members without affecting the individuals use. With such a broad definition and covering both substances and gambling we were unable to display clearly within our models the different types of harm reduction associated with each of the determinants, and rather than confuse users we opted to eliminate such information from the models presented here. Moreover, the concept of harms to others is not clearly understood within the literature, and further research is required in the addiction field to complete our understanding of the underlying determinants of such behaviour.

In addition to the limitations described above, we are also conscious that in our series of reports on the transition from no use or use to risky use (WP7), from risky to harmful use (WP8), and on the reduction in or cessation of harmful use (WP9) of licit and illicit substances and gambling, we have not developed transition probabilities for gambling or illicit substance use. The reason why we have not developed transition probabilities for gambling or illicit substance use is that, after extensively searching the available European datasets that collate information on addictive behaviours, we have been unable to identify an adequate dataset containing all the information required to allow us to model the probability of transitions for these behaviours. We have, however, been able to identify an appropriate dataset for modelling the probability of transition between different stages in the development of addiction for two of the substances with the highest prevalence of use and a high burden of harm to the individual and society: alcohol and tobacco. To make possible the calculation of transition probabilities for gambling (and other addictive behaviours) in the future, below we summarize the kind of dataset that would be required to model gambling transition probabilities.

Preconditions to final decisions on data requirements are a) clear inclusion criteria for the kinds of gambling that should be included, b) identification of relevant covariates, and c) disjunct operationalisations of abstinence, gambling, risky gambling and harmful gambling. Gambling and addictive behaviours constitute a very heterogeneous phenomenon ranging from gambling in casinos and penny arcades over online gambling to recently sports betting (195). Next to covariates such as age and gender, availability, peer influence, cognitive distortions, comorbidity, and substance use should be considered for inclusion (196-198). In the development of any such survey we would strongly recommend that the work of ALICE RAP Work Area 3, including the synthesis reports and especially the multidisciplinary models, be used to identify appropriate covariates to measure. The operationalisations of different gambling states require knowledge on relative risks for a set of consequences associated with different patterns, kinds and possibly also settings of gambling (195).

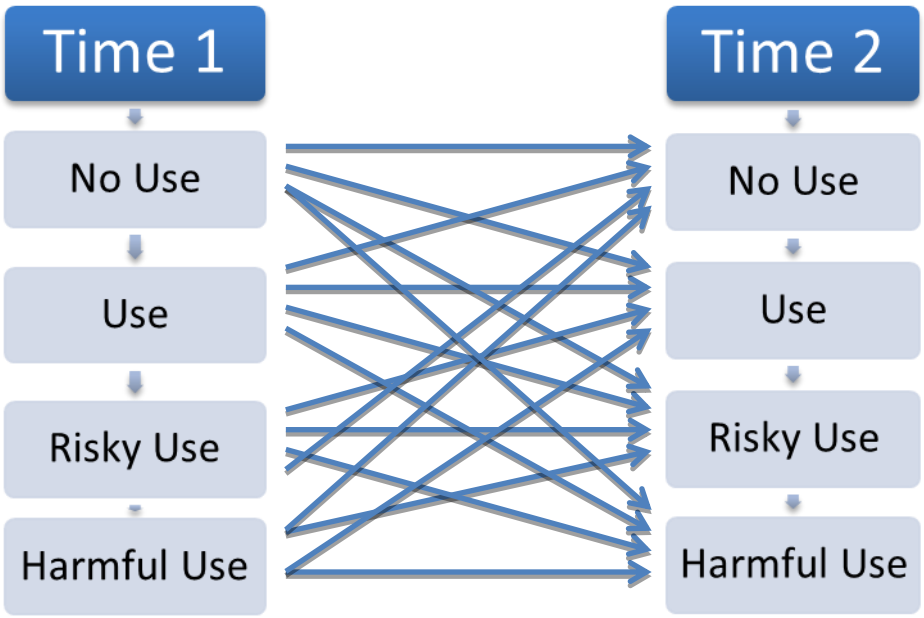
For a dataset allowing the investigation of transition probabilities based on such a conceptual framework, we have identified four requirements.

Firstly, when calculating transition probabilities our aim is to investigate the course of substance-related and addictive behaviours in the general population. We aim to identify the relative importance of covariates (such as age and gender) for different transitions, such as from gambling to risky gambling and from risky gambling to harmful gambling. In order to do this, we require a population-based, representative sample.

Secondly, a mathematical model of transition probabilities for all stages in the development of a non-substance use disorder such as gambling would require the modelling of change between four stages: no gambling (which is important both for modelling the probability of initiation of use and also for remission/cessation of risky or harmful use), non-risky gambling, risky gambling and harmful gambling. In total, 16 transitions (see Figure 11 below) would be modelled between these four stages in the development of harmful gambling use. Thus, the dataset would need to include a nuanced measure of gambling use in order to allow for operationalisation of the four states, for example including a detailed assessment of gambling behaviour and diagnostic criteria on gambling disorders/pathological gambling. We would also require the dataset to measure gambling-related consequences to enable us to classify behaviour as harmful gambling. Lastly, we would need to ensure that the dataset included information on relevant covariates.

Finally, for each of the 16 possible transitions, an estimated minimum of 120-150 observations would be required for the model. This requirement is most crucial for the transitions involving the states of risky and harmful gambling. Respective operationalisations would include gambling disorders and problematic gambling. Given the low 12-month prevalence of gambling disorders and problematic gambling within the general population (0.1–0.8% and 0.1–2.2% respectively) (199), a very large sample size would be required.

Figure 11: 16 changes over time to be modelled



It can be roughly estimated that the sample size required to investigate the twelve transitions related to risky or harmful gambling would need to be at least 20,000 if gambling use was measured at two points in time, or 10,000 if it was measured at three points in time. The inclusion of covariates would further increase the sample size requirements of the dataset, depending on the covariance structure. Of course, if we use populations with higher prevalence of harmful gambling, the sample sizes would shrink, but then we may have biased estimates for the other transitions, i.e., transition probability estimates between abstinence and gambling, which would not correspond to the transitions probabilities in the general population.

To summarise, depending on the conceptual framework applied, a dataset for the calculation of gambling transition probabilities would need to include as a minimum:

- A sample of at least 20,000 people that is representative of a European population
- Data collection at a minimum of two points in time
- Validated operationalisations of risky and harmful gambling
- Appropriate covariates (minimally age and gender)

4.2 Transition Probabilities

4.2.1 Key findings

A four-state Markov model was fitted in order to calculate annual transition probabilities and HRs for the covariates age, gender, and SES. The highest transition probabilities (≥70%) were found for staying on one state (abstinence, use, risky use) and for transitioning from harmful use to use. Lowest transition probabilities were found between abstinence and risky or harmful use and between risky and harmful use (≤6%). The pattern of significant HRs for all three covariates matched

the assumptions of the underlying heuristic model very well. The simulations mirrored the overall picture of alcohol use described in the introduction with respect to prevalence over age as well as gender gaps.

The calculated annual transition probabilities showed that for abstinence, use, and risky use people are most likely not to change their pattern of use within one year. Interestingly, harmful use was the most instable state with only about 13% of harmful users still being harmful users the following year. This contradicts the widely spread image of AUDs as chronic disorders (200), at least for the young sample under investigation. This finding might be related to the assessment of AUDs using the CIDI interview. In a comparison of AUD diagnoses by general practitioners and the CIDI, a clear relationship with the participant's age has been shown. The CIDI tended to identify AUDs in younger patients while general practitioners were more likely to identify more severe cases in older persons (201). One reason might be that a lot of young people recently experienced symptoms as e.g. tolerance when initiating alcohol use. In the ALICE RAP WA3 it was assumed, that risky use is an important pre-state to harmful use, associated with an elevated risk of transitioning to harmful use. However, transition probabilities we found between risky and harmful use were very low, raising the question if risky use really is some kind of relevant pre-state of harmful use.

In simulations we estimated the prevalence of all four drinking patterns, its change trends in youth and young adulthood and gender differences. Taking differences in operationalization into account, the simulated prevalence matched recent findings from a German, representative sample on use, risky use, and AUDs fairly well (202). The main difference was seen in the simulated prevalence of abstainers (past 12 months). The prevalence of abstainers simulated in the present study seems to be a little bit too high. With respect to trends, the strong decrease to a relatively low but stable prevalence of abstainers as well as the early peak in risky and harmful use are conform with the global picture of German and European drinking cultures as described in the introduction. The gender gap in risky and harmful use seems inconsistent with the HRs we found and the hypothesis that gender might influence predominantly 'early' transitions. It should be noted, that the respective HRs for transitioning from use to risky or harmful use showed a trend towards elevated risks for men even if they were not significant. While as expected there was a substantial gender gap in abstinence, simulations did not show a gender gap in user rates. It should be noted that the user rates do not mirror e.g. mean daily consumption but just the fact that someone used alcohol at least 13 times in the past year and was not categorized as risky or harmful user.

Overall the hypothesis derived from the heuristic model were confirmed, indicating high influence of environmental factors on early stages of use and increasing influence of individual and intra-individual factors for later stages of use. Gender was found to be relevant for transitions related to abstinence and use, SES being associated with transitions between use and risky or harmful patterns and decreasing transition probabilities with increasing age for almost all transitions investigated. Inconsistently we found a significant HR indicating an elevated probability for women to transition from harmful use to use, indicating that gender influenced a 'later' transition as well. Sensitivity analysis taking sample weights into account did not confirm this finding. A second result inconsistent with our hypotheses was the elevated risk of more wealthy persons to transition from use to harmful use. It is possible that adolescents from a less wealth background simply did not have the financial resources to engage in harmful use of alcohol compared to their wealthier counterparts. For investigations of covariates relating to later transitions as proclaimed in the heuristic model, the introduction of an intra-individual covariate as genetic vulnerability would have been useful. Jackson et al. (26) investigated the influence of a family history of alcohol dependence in a similar analysis. They found that persons with such a family history had a lower probability to transition out of 'large effect drinking', which is in line with the assumptions of the heuristic model.

4.2.2 Limitations

Overall, the method applied proved useful for the investigation of transition probabilities, testing hypotheses on the relative importance of different covariates for separate transitions, the simultaneous consideration of multiple covariates, as well as the simulation of prevalence in the population. As mentioned above, due to restricted sample size, applying a statistical model required focusing on a small set of covariates and restriction of allowed transitions. In the present study transitions between risky and harmful use as well as between abstinence and risky or harmful use were sparse. This made it necessary to constraint the allowed transitions as described above, since otherwise the model did not converge. For the transitions from abstinence to risky or harmful use this was acceptable since an instantaneous transition is highly unlikely: one would assume that someone experiences at least a very short period of use in between those two states. Transitions from risky and harmful use to abstinence might appear instantaneously in the context of therapy (point-stop method). However, auto-remission for AUDs is very high (203) and in the young sample we looked at, health service use for alcohol related problems was very low (204). Of course this does not rule out the possibility of stopping alcohol consumption instantaneously. The major disadvantage of restricting allowed transitions was that we were not able to investigate covariate influence for the respective transitions. This would have been specifically interesting for the adjacent states risky and harmful use. Overall, a larger dataset would have been useful not only for the investigation of more allowed transitions but also for introducing more covariates.

The introduction of sample weights to ensure representativeness was not implemented in the msm command (32). This issue was addressed by two separate analyses with dataset expansions based on the weight variable. The results replicated the findings of the original, unexpanded dataset.

Generalizability of results is technically limited to Munich and surrounding areas around the turn of the century. Even though drinking cultures in Europe are converging over the past years, there is still variation with respect to choice of beverages, drinking patterns and per capita consumption (205). Within Germany, the area around Munich is a particularly wealthy area, limiting the variance in SES. Overall, generalizability for other European countries is limited due to the variance in drinking cultures and socioeconomic structure of the countries. However, as discussed below, the overall picture matches our knowledge on prevalence, age trends and gender gaps for Europe and Germany in particular fairly well.

4.2.3 Future research

The present study was an example of how knowledge gained from literature reviews can be tested using a modelling approach based on representative panel data. Future research should consider using the same approach on larger datasets and from a variety of different countries. As shown in WA3, many more covariates than just age, gender, and SES may influence transitions in use patterns. Future research should aim at introducing other relevant covariates as comorbidity, age of onset, and (as mentioned) genetic vulnerability (146, 206-208). In the present study the age span was limited to youth and young adulthood (age 14 to 30). Especially in elderly drinking patterns seem to change again as major life changes (e.g. retirement) happen (209). In aging societies, which characterises the population in most European countries (210) transition probabilities and relevant covariates in this age group should receive more attention in future research (211). Furthermore it would be interesting to look at transition probabilities for other substances, too. The heuristic model is not limited to alcohol and could be tested for other substances as well. To facilitate such future undertakings it would be useful to implement a weighting option in the msm package (32).

4.3 Consequences for EU research and health policy

The findings of our work have major implications for future EU research, clinical practice and EU member state health and broader social policy.

4.3.1 Consequences for research

(1) **To increase the research focus across all disciplines into the determinants of reductions in harmful use.** There is very little available research regarding the reduction in harmful substance use or harmful gambling either through a reduction in usage, changes in other behaviours or policy interventions. Further research is required across all disciplines in the field of addiction to increase our understanding of this key transition phase.

(2) **To focus research upon self-change and natural recovery.** The majority of harmful users limit their behaviour, for a larger or shorter period of time, without formal treatment. Despite this being the most common exit route from harmful use it is markedly under-researched, and there exists a need to further our understanding of such processes through increased research.

(3) **To increase the number of longitudinal studies examining the aetiopathogenesis of substance use and gambling including the transition to a reduction in harmful use.** Such longitudinal studies will allow the accurate identification of determinants which promote the transition from harmful substance use or gambling to a pattern of less harm in different individuals. There is a particular need for such studies within the biological field.

(4) **To focus research on multidisciplinary and interdisciplinary studies.** Multidisciplinary work within this field is surprisingly lacking. It is only through working together across disciplines will we develop the level of nuanced understanding required to tackle such complex problems. Moreover, such multidisciplinary work allows the necessary contextualization of determinants, enabling the most accurate and relevant factors to be pinpointed for different individuals.

(5) **To study the commonalities and differences between reductions in harmful substance use and harmful gambling.** There is increasing scientific knowledge in this field that is revealing a pattern of commonalities and differences in the reduction of harmful substance use and gambling, which is at present not well understood. In spite of the big differences underlying the different substance and non-substance use disorders, there are many common factors on both the environmental and individual level, including new biological correlates. But a better understanding of these developments is necessary to be able to target specific interventions and promote harm reduction across all behaviours.

(6) **To promote research on the different aspects of a reduction in harmful use, beyond cessation.** Currently research is focused on the cessation of harmful substance use or gambling, especially via formal treatment. There is not enough knowledge regarding harm reduction beyond a reduction in usage. A better understanding would help to promote the prevention of harms.

(7) **To focus biological research within the addiction field on human studies.** Currently much of our understanding regarding biological determinants is derived from preclinical studies. The analysis of the biological factors at play, in determining a reduction in harmful use, within limited preclinical models does not allow a full understanding of their relevance to the human within different complex environmental settings. An increased level of research

considering human subjects is required to enable the biological determinants identified to be correctly contextualised.

4.3.2 Consequences for health and broader social policy

(8) **To promote the possibility of self-change and natural recovery to reduce harmful substance use and harmful gambling.** Current formal treatment for substance use and gambling is expensive and thus only limited numbers of users may access such services. The promotion of self-change processes to highlight this method of cessation of substance use and gambling offers a cost effective solution, removing the burden on healthcare services, whilst allowing the potential to reach more subjects.

(9) **To target policy intervention at the social environmental level.** We have demonstrated that our understanding of the determinants of reductions in harmful usage is most detailed at the social environmental level. This nuanced understanding allows for an increased accuracy in the targeting of policy intervention. Moreover, as a group we perceived that policy was most effective at the social environmental level, with an increased difficulty associated in targeting policy to the lower levels of analysis. As such we recommend that policy interventions to reduce harmful usage are focused firstly at the social environmentally determined influences of reductions in harmful use.

(10) **To pursue harm reduction strategies.** Harm reduction strategies have been proven to be successful in reducing the harm associated with substance use and gambling. Many countries have already taken steps to reduce the harm from some substance use behaviours, such as injection drug use, and further harm reduction strategies should be pursued to generate further harm reductions.

(11) **To focus not solely on addiction, but also broader social and cultural determinants.** To promote the integration of minority populations, recognizing and allowing for differences and to strengthen communities may prevent marginalization and feelings of dissociation, aiding certain individuals to reduce their harmful substance use or gambling.

4.3.3 Consequences for practice

(12) **To identify individuals capable of natural recovery and promote this method of self-change.** An increased understanding of the drivers that motivate individuals to undergo the transition to a less harmful pattern of substance use or gambling, may offer clinicians the ability to correctly identify those able to benefit from such methods. To highlight natural recovery as a possibility to reduce harmful usage may reduce the burden on healthcare services, reduce the number of individuals undergoing formal treatment and reduce the number of individuals undergoing repeated cycles of treatment.

5. CONCLUSIONS

The major conclusions arising from this work are:

- The determinants underlying the transition from harmful use to a reduction in harm of substances or gambling are complex in nature and span factors from the molecular and cellular through the individual to the environment.
- The influence the environment of an individual plays in the reduction of harmful substance use and harmful gambling is more acutely understood than that of individual characteristics and molecular factors.
- The reductions in harm from substance use and gambling extend well beyond those attributed to the dependent user, and include reduction in harms to others.
- An increased research focus on the different aspects of harmful use reduction is required to increase understanding and produce effective strategies for the prevention of harm to individuals and society.
- An increased research focus on and promotion of self-change strategies, such as natural recovery, is important to increase our understanding of the drivers of such change and reduce the burden on healthcare services through the reduction of individuals undergoing formal treatment for substance use and gambling problems.
- In order to aid a reduction in harmful substance use and gambling society as a whole must work to overcome key issues, for example social and cultural norms, through tackling factors such as the acceptance and the stigmatisation of substance use and gambling, and marketing and other commercial promotion.
- Increased levels of multidisciplinary research within this field are necessary to fill knowledge gaps and highlight possible effective future strategies in dealing with problems of harmful use.

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APPENDIX 1: Glossary of determinants

This glossary includes all the determinants that occur within the model for each different substance and gambling. A number of determinants (listed first below) are not defined because they were deemed self-explanatory:

- Decline in religiosity
- Divorced/ Separated marital status
- Early age at alcohol use onset
- Early age at nicotine use onset
- Early age of onset of cannabis use
- Family history of drinking
- Family history of smoking
- Gambling promotions
- Globalisation of alcohol industry
- High jackpot size
- Low education
- Low income
- Male gender
- Parent/sibling use
- Parental divorce
- Personal alcohol use
- Prior illicit substance use
- Sex
- Stress
- Unemployment
- Unmarried male
- Youth

Accessibility – the extent to which people are able to find an individual or business selling a product, with high accessibility referring to a state in which a product is easy to find.

AChRs – an acetylcholine receptor is an integral membrane protein that responds to the binding of acetylcholine, a neurotransmitter. Acetylcholine receptors are classified according to their sensitivity to different molecules, for example nicotine.

Affordability – the state of being cheap enough for people to be able to buy, with high affordability referring to a price at which many people can afford to buy a product.

Agoraphobia – a fear of being in situations where escape might be difficult, or help wouldn't be available if things go wrong, for example when travelling on public transport or leaving home .

Anxiety disorders – an unpleasant state of inner turmoil, often accompanied by nervous behaviour (e.g. pacing). It is a subjectively unpleasant feeling of dread over something unlikely to happen.

Availability – the extent to which something is easily obtainable and ready for use. Availability and accessibility are often used interchangeably.

Baseline alterations in neurocircuitry – endogenous differences in brain receptors, transporters and neurotransmitters that may confer increased or decreased susceptibility to harmful substance use or gambling.

Bipolar disorder – a condition that effects one's mood, where it can swing from one extreme to the other. Often characterised by episodes of mania and depression.

Branding –the process involved in creating a unique name and image for a product in the consumers' mind. Branding aims to establish a significant and differentiated presence in the market that attracts and retains loyal customers (such as mild or menthol cigarettes).

Cognitive distortions – exaggerated or irrational thoughts that are believed to perpetuate the effects of certain states such as anxiety and depression.

Coping mechanism – the coping skills or strategies that people use to manage difficult situations.

Criminalisation – the process by which behaviours are transformed into crimes and individuals become criminals.

Cue reactivity – physiological and subjective reactions to presentations of drug-related stimuli (e.g. cigarettes or alcohol bottles) or being in an environment associated with drug use.

Depression – a medical illness that causes a constant feeling of sadness and lack of interest, affecting how a person feels, behaves and thinks.

Descriptive norms – perceptions regarding typical behaviour in given situations, usually based on observations and perceptions of the behaviour of those around you.

Dislocation – a break-down in the psychological integration of individuals within a community, for example as a result of a natural disaster, accident, conflict or violence and economic change. Individuals and groups in society become dislocated or alienated to a greater or lesser extent, with severely dislocated individuals potentially struggling to find psychosocial integration and therefore constructing a lifestyle that substitutes it.

Drinking venue characteristics – for example, designing pub/bar/club layout to minimise violence or encourage drinking.

Drug driving – driving under the influence of illicit substances.

Early positive reactions to use – positive experiences of use early in the use career.

Economic downturn – a general slowdown in economic activity.

Economic upturn – a general upturn in economic activity.

Ethnicity – a socially defined category of people who identify with each other based on a shared social experience or ancestry.

Expectancies – the state of thinking or hoping that something, especially something good, will happen as a result of performing a given behaviour.

Externalising disorders – problem behaviours are directed outwards towards other people, for example through disobedience, aggression and delinquency.

Extraversion – extraversion is manifested in outgoing, talkative, energetic behaviour.

High event frequency – high number of opportunities to gamble within a given time period.

Implicit cognitions – unconscious influences (such as memory or perception) that influence an individual's behaviour.

Implicit memory associations – unconscious recall of memories associated with a behaviour.

Impulsivity – a multi-factorial construct that involves a tendency to act on a whim, displaying behaviour characterized by little or no forethought, reflection, or consideration of the consequences.

Lack of access to drug services – including both the availability of drug services (such as substitute prescribing or residential rehabilitation) in a society and individual difficulties in accessing services those services (e.g. due to geographical location or funding restrictions).

Lack of secure environment for use – absence of environments that reduce harm to illicit substance users, such as needle exchange facilities and supervised injection sites.

Legal limits/legality – the legal status of a substance or behaviour within a society, including the age at which consumption of a particular substance becomes legal. For example, in certain countries alcohol is prohibited whilst in others it is legal to drink above a certain age (e.g. 18 or 21 years).

Light, colour, and sound effects – of gambling machinery.

Low consciousness – a low level of awareness of internal or external stimuli.

Low housing stability – an inability to retain housing, for example due to lack of affordability.

Low level of constraint – inability to say no or stop engagement with a behaviour once started.

Low social class – social class describes people with the same social, economic, or educational status. Low social class therefore describes people with low social, economic or educational status.

Marginalisation – the social process of becoming or being made marginal that can apply to an individual or group within a larger society.

Metabolism – chemical transformations that sustain life within the cells of living organsims.

Mood disorders – a psychological disorder characterised by the elevation or lowering of a person's mood, such as depression or bipolar disorder.

Novelty seeking – a personality trait associated with impulsive decision making, extravagance in approach to reward cue and curiosity and exploratory activity in the face of novel stimuli.

Openness to experience – a global personality trait of habits and tendencies (such as active imagination, attentiveness to inner feelings, preference for variety and curiosity) that may cluster together.

Poor response inhibition – the inability to of an individual to keeps in mind goals and prioritise actions, giving rise to poor impulse control.

Prefrontal cortex – the anterior part of the frontal lobes of the brain. Lying in front of the motor and pre-motor areas, this part of the brain effects our expression of personality, decision making and social behaviours.

Price promotions – offers on a purchase price making products more affordable, for example 'buy one get one free' and '25% off if you buy 6 bottle' deals.

Psychoticism – a personality pattern characterised by aggression and interpersonal hostility.

Receptors –different receptor genes may confer susceptibility to the risky use of substances or gambling (e.g. dopamine, nicotinic, serotonin, opioid, etc.)

Reward processing – the systems within the brain, involved with learning, responsible for positive or negative feedback following certain actions.

Route of consumption/delivery – the method use to ingest a substance (e.g. smoking, snorting or injection).

Sensation seeking – a personality trait defined by the search for experiences and feelings, that are "varied, novel, complex and intense", and by the readiness to "take physical, social, legal, and financial risks for the sake of such experiences."

Short pay out intervals – short time frame between opportunities to win when gambling.

Social acceptance/normalisation – the acceptability of a behaviour within a given culture or society at a given point in time.

Social anxiety – a persistent fear about social situations and being around people.

Specific phobia – a term used to describe any kind of anxiety disorder that is characterised by an unreasonable or irrational fear of specific objects or situations.

Stigmatisation – the process of identifying or highlighting something as bad.

Substance use disorders – the overuse of or dependence on a drug (such as alcohol or an illicit substance) that has detrimental effects on the individual's physical and mental health, or that of other people around them.

Ventral striatum – a part of the brain that facilitates and balances motivation with both higher- and lower-level functions, such as inhibiting behaviour in complex social interactions.

Visible near miss features – A near miss is a failure to reach a goal that comes close to being successful. A near miss may be taken as encouragement that a game strategy is working, raising hopes for future success, even in games of pure chance such as slots or lotteries where strategy does not impact on outcome. Some gambling systems are contrived to present a higher number of near misses than would be seen by chance alone.

APPENDIX 2: Evidence base for the determinants included in the models

Alcohol

Determinants	References
Absence of a comorbid psychiatric disorder	(144-146,212,213)
Absence of anxiety disorder	(214)
Advertising	(43,71)
Age-related social expectations	(79)
Availability	(35)
Changes in birth cohorts	(215-223)
Changes in social networks	(78,224)
Cue reactivity	(157,160,177,225-230)
Cultural preferences/ fashions	(231,232)
Decline in impulsivity associated with maturing	(233-235)
Decrease in population level drinking	(58-60)
Dopamine	(174,175,177,178,229,236-238)
Economic depression	(61)
Employment	(105,106,113,219)
Enhanced reward system responses	(160,225-227,239,240)
Establishing community ties and traditions	(80)
Family/ friend influences	(148,241-243)
GABA	(238,244,245)
Glutamate	(184,185,187-190,238,246,247)
Increased prices/ taxation	(35,37-43,248)
Increased social status of women	(231,232)
Inhibitory control	(136,139,249-251)
Leaving parental home	(105)
Lower levels of impulsivity	(133)
Marriage	(79,105,109)
Obtaining a college level education	(105)
Opioids	(182,237)
Outlet density	(35,56)
Outlet opening hours	(35)
Outlet type	(35)
Prefrontal cortex	(136,139,149-152,157,230,238,250,252)
Pregnancy/ parenthood	(79,105,219)
Product type available	(35)
Prohibition	(64)
Rationing	(253-257)
Reward processing	(136,139,174,229,230,237,250,251)
Social movements	(62-66)
Stress avoidance	(230,258-263)
Urbanisation	(231,232)
Ventral striatum	(136,149-152,249)

Tobacco

Determinant	References
Availability	(46)
Clean air laws	(86,87)
Cue reactivity	(264)
Dopamine	(177)
Employment	(105,106)
Family/friend influence	(148)
Glutamate	(246,247)
High alcohol prices	(55)
Inhibitory control	(136)
Length of abstinence	(265)
Marriage	(105)
Obtaining a college level education	(105)
Plain cigarette packaging	(72)
Prefrontal cortex	(136,149-152)
Pregnancy/ parenthood	(105)
Price	(44-46,48-54,266)
Reward processing	(136)
Quitting cold turkey	(129,130)
Sales outlet density	(46)
Sales outlet location	(46)
Sales outlet opening hours	(46)
Type of product available	(46,73,74)
Ventral striatum	(136,149-152)

Cannabis

Determinants	References
Agency	(131,132,141)
Availability	(267)
Conscious evaluation of pros and cons of use	(132,141)
Cue reactivity	(168)
Employment	(105)
Inhibitory control	(136)
Learning from use	(131,132)
Lower levels of impulsivity	(133)
Marriage	(105)
Obtaining college level education	(105)
Prefrontal cortex	(136,149-152)
Pregnancy/ parenthood	(105)
Price	(54)
Prohibition	(82)
Reduced alcohol prices	(55)
Reward processing	(136)
Social identity	(131)
Social networks	(131,268,269)
Subculture	(131,269)
Type of product available	(267)
Ventral striatum	(136,149-152)

Stimulants

Determinants	References
Absence of chronic mental illness	(108,116)
Absence of domestic violence	(108,116)
Adequate provision of socially perceived necessities	(108,116)
Availability	(267)
Being occupied/ interests	(270)
Brain-derived neurotrophic factor	(271-274)
Conscious evaluation of pros and cons	(141)
Corticotrophin-releasing factor receptor-1	(275)
Cue reactivity	(276-278)
Dopamine	(150,170-173,176,229,238,278-281)
Employment	(105,106,108)
GABA	(238,279,282,283)
Glutamate	(186,238,246,247,279,284)
Inhibitory control	(136,139,153,173,186)
Length of abstinence	(155)
Lower levels of impulsivity	(133)
Marriage	(105)
Needle exchanges	(88-102)
Obtaining college level education	(105)
Opioids	(180,183,282,283,285)
Outreach centres	(117)
Prefrontal cortex	(136,139,149,150,150-152,170,238,284,286,287)
Pregnancy/ parenthood	(105)
Prohibition	(82)
Punishment	(128)
Rationing/prescription	(267)
Reward processing	(136,139,229,288)
Self-care strategies of users	(289)
Serotonin	(286,290)
Shorter time of use	(128)
Social identity	(270)
Social integration	(108,116)
Social networks	(291)
Stress avoidance	(285)
Type of product available	(267)
Ventral striatum	(136,149,150,150-152,170,280,281,288)

Opiates

Determinant	References
Absence of chronic mental illness	(108,116)
Absence of domestic violence	(108,116)
Adequate provision of socially perceived necessities	(108,116)
Agency	(141,143,292)
Availability	(267)
Avoidance of stress	(154)
Being occupied/ interests	(293,294)
Conscious evaluation of pros and cons	(141)
Corticotrophin-releasing factor receptor-1	(275)
Cue reactivity	(295-298)
Dopamine	(177,229,282,298-300)
Employing coping mechanisms	(301)
Employment	(105-108)
GABA	(282)
Glutamate	(246,247,302)
Inhibitory control	(139,154,250,250,296,303)
Lack of coping mechanisms	(294)
Lower levels of impulsivity	(133)
Marriage	(105)
Needle exchanges	(88-102)
Obtaining college level education	(105)
Opioids	(181,282,302)
Outreach centre	(117)
Prefrontal cortex	(139,149-152,250)
Pregnancy/ parenthood	(105)
Prohibition	(82,83)
Rationing	(267)
Reward processing	(139,229,250)
Self-care strategies of users	(304)
Social identity	(305)
Social integration	(108,116)
Social networks	(294,306)
Stress avoidance	(154,307)
Type of product available	(267)
Ventral striatum	(149-152)

Club drugs

Determinant	References
Agency	(118)
Availability	(267)
Conscious evaluation of pros and cons	(118)
Employment	(105,106)
Inhibitory control	(136)
Marriage/ Partnership	(105)
Not taking drugs alone	(118)
Obtaining college level education	(105)
Prefrontal cortex	(136,152)
Pregnancy/ parenthood	(105)
Prohibition	(82)
Reward processing	(136)
Social Identity	(308,309)
Subculture	(308,309)
Type of product available	(267)
Ventral striatum	(136,152)

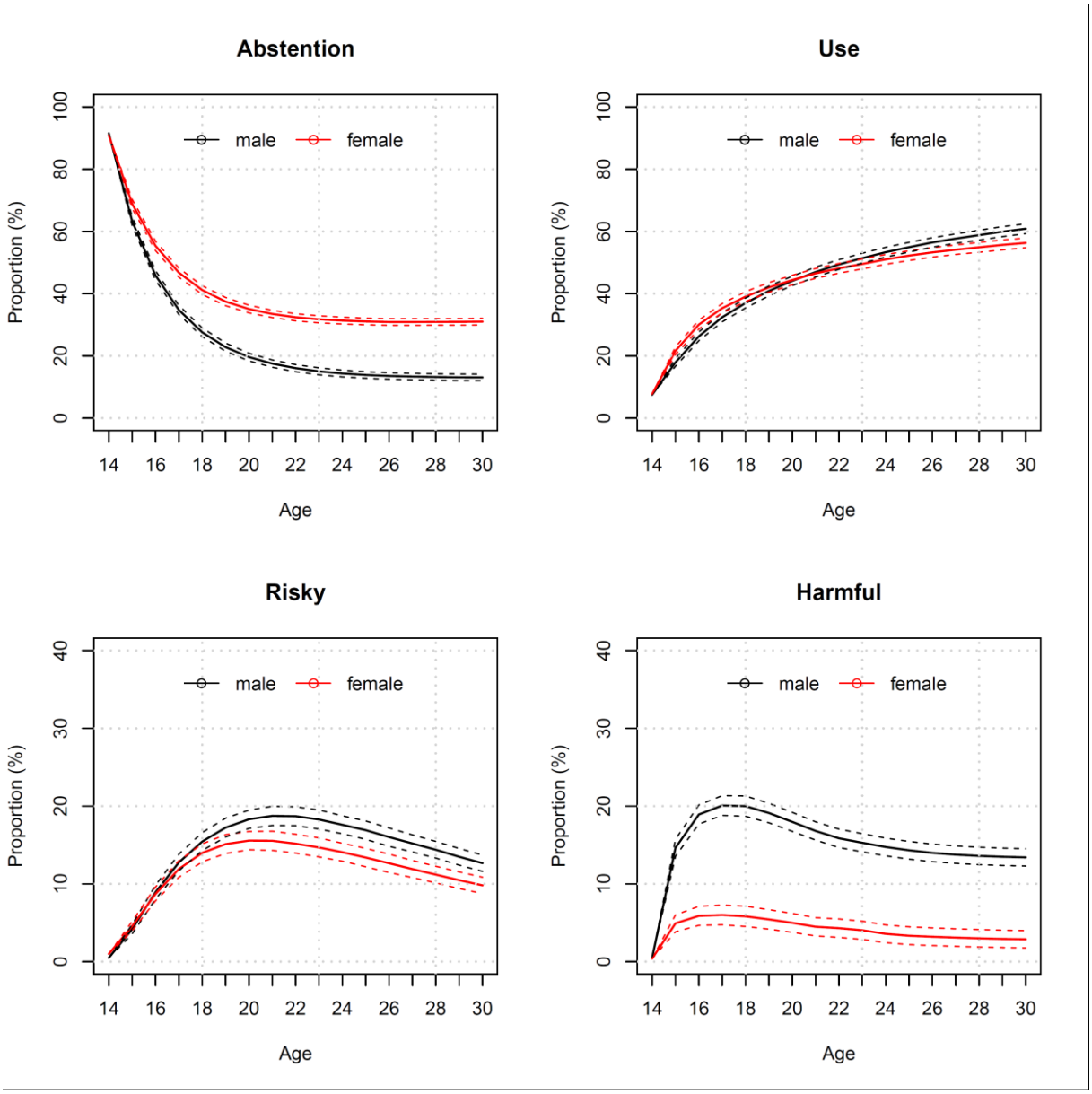
Gambling

Determinant	References
Absence of comorbid psychiatric disorder	(147)
Absence of current anxiety disorder	(147)
Absence of current PTSD	(147)
Accessibility	(123,310,311)
Advertising	(67-70)
Aging	(76)
Availability	(57,312,313)
Change in another addictive behaviour	(77)
Cue reactivity	(264)
Density of EGMs	(119-126)
Family friends minding users	(76)
Family/ friends persuasion/ confrontation	(76,77,127)
Family/ friends taking financial control	(76)
Fewer lifetime psychiatric disorders	(127)
Financial concerns	(76,77,110,314)
Genuine motivation to stop for oneself rather than for others or instrumental reasons	(76)
Incompatibility with self-identity/ self-perception	(76,77)
Inhibitory control	(250,303)
Life events	(76,77,110)
Male	(315)
Married	(76)
Negative emotions	(77,314)
No family member with addictive problems	(127)
Opioids	(302)
Outlet density	(57)
Outlet location	(57)
Outlet opening hours	(57)
Outlet type	(57)
Prohibition	(57,81)
Type of gambling available	(57)

APPENDIX 3: Transition probabilities

Appendix Table 1. Annual transition probabilities in % between all four drinking states and respective 95% confidence intervals (CI), based on weighted data with expansion factor d=10.

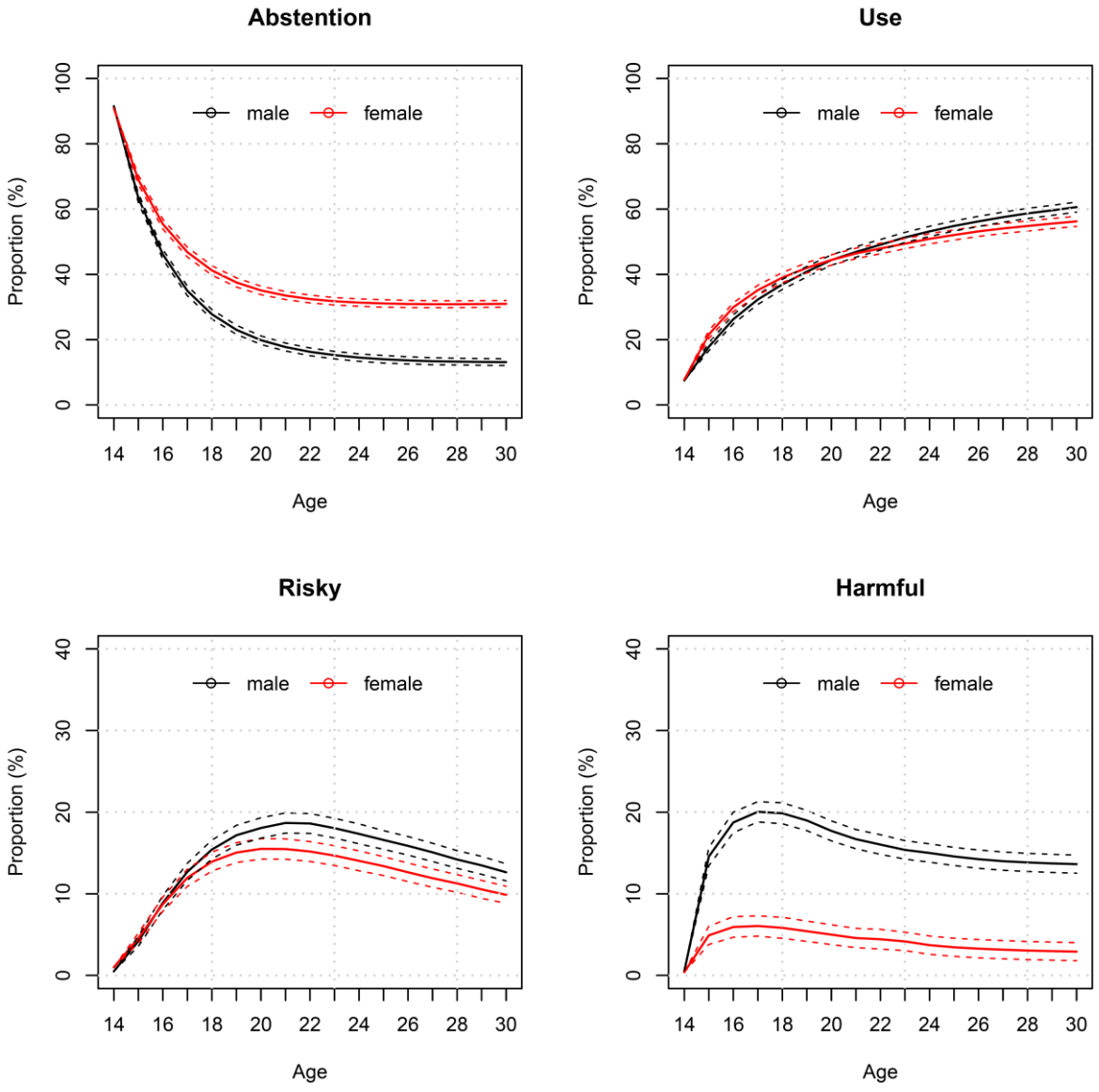
	Abstinence	CI	Use	CI	Risky use	CI	Harmful use	CI
Abstinence	79.7	79.2-80.2	17.6	17.1-18	0.8	0.8-0.9	1.9	1.8-2.1
Use	3.9	3.8-4.1	79.7	79.3-80.2	6.9	6.6-7.2	9.5	9.1-9.8
Risky use	0.7	0.7-0.8	28.2	26.8-29.5	67.9	66.5-69.4	3.1	2.9-3.4
Harmful use	3.7	3.5-3.9	80.3	79.8-80.8	6.5	6.1-6.8	9.5	9.2-10



Appendix Figure 1. Simulations based on weighted data with expansion factor d = 10. Dashed lines indicate 95% confidence interval.

Appendix Table 2. Annual transition probabilities in % between all four drinking states and respective 95% confidence intervals (CI), based on weighted data with expansion factor d=100.

	Abstinence	CI	Use	CI	Risky use	CI	Harmful use	CI
Abstinence	79.7	79.5-79.8	17.6	17.4-17.7	0.8	0.8-0.8	2.0	1.9-2
Use	3.9	3.9-4	79.7	79.5-79.8	6.9	6.8-6.9	9.5	9.4-9.6
Risky use	0.7	0.7-0.8	28.2	27.8-28.6	67.9	67.4-68.4	3.2	3.1-3.2
Harmful use	3.7	3.7-3.8	80.2	80-80.3	6.5	6.4-6.6	9.6	9.5-9.7



Appendix Figure 2. Simulations based on weighted data with expansion factor d = 100. Dashed lines indicate 95% confidence interval.