Only Just Eighteen?

Adolescent alcohol Intoxication: the Dutch policy approach

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Nog maar net achttien?

Alcohol intoxicatie bij jongeren: de Nederlandse benadering van beleid

Loes de Veld

This project has received funding from “Stichting Jeugd en Alcohol”, a Dutch non-profit organisation that aims to prevent direct and indirect harm caused by alcohol usage amond Dutch adolescents.

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Adolescent alcohol intoxication: the Dutch approach to management

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Alcohol intoxicatie bij jongeren: de Nederlandse benadering van beleid

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CONTENTS

INRODUCTION

ADOLESCENT ALCOHOL INTOXICATION: THE DUTCH APPROACH TO MANAGEMENT

SECTION 1

PREVENTION: IDENTIFICATION OF RISK FACTORS AND DETERMINANTS

SECTION 2

ACUTE TREATMENT AND DIAGNOSTICS

SECTION 3

OUTPATIENT FOLLOW-UP

DISCUSSION

APPENDICES

INTRODUCTION

Adolescent alcohol intoxication: the Dutch approach to management

PROLOGUE

Setting the scene

Setting the scene, a doctor's perspective

1. PROLOGUE

SETTING THE SCENE, A DOCTOR'S PERSPECTIVE

It was a rather busy night shift during the COVID-lockdown, when the charge nurse of the emergency department announced the arrival of four ambulances with patients requiring immediate pediatric emergency care. The announcement of four ambulances does not happen to often and therefore astonished me. I asked the charge nurse what the reason of emergency department attendance was. In a split second, some possible reasons passed my mind: carbon monoxide intoxication or acute alcohol intoxication? The charge nurse confirmed my initial thoughts and announced the arrival of four adolescents with acute alcohol intoxication of which one was unresponsive.

The charge nurse triaged the patients and asked me to assess a 14-year old unresponsive male adolescent first. The acute care of an adolescent presenting with alcohol intoxication follows the Advanced Pediatric Life Support guidelines. I started with the assessment of the airway. At first sight, there were no signs of airway problems, by opening his mouth the airway seemed free. However, the level of his consciousness in combination with active gagging contributed to a threatened airway. Insertion of a oropharyngeal airway was considered, but the gagging might have caused trouble in toleration of the oropharyngeal airway and might have increased the risk of aspiration. The vital parameters showed a respiratory rate of 14 breaths per minute with an oxygen saturation of 98%, a mild tachycardia of 110 beats per minute and mild hypotension and hypothermia of 35.0 °C. Besides a minor hematoma on his right knee, no external injuries were observed. The nurse placed a peripheral intravenous catheter and took blood samples. His bedside glucose was within the normal limits. Electrocardiographic evaluation indicated slight QTc-prolongation. I continued with the assessment of his level of consciousness: he opened eyes to pain stimuli (E2), withdrawal to pain stimuli (M4) and moaned in response to pain (V2). Pupils were equal and reactive to light. There were no signs of lateralization. He was admitted to the pediatric department for monitoring of vital functions, received intravenous rehydration and was covered with heated blankets to gradually warm up. The laboratory results showed a blood alcohol concentration of 2.6 g/L and a negative urine drug screening.

About half an hour after the initial assessment, the father of the patient arrived at the emergency department.The father has been woken up in the middle of the night by the police who came to inform him that his son was admitted in the hospital for alcohol intoxication during his sleepover at a friend. When the father saw his son, he was emotionally affected about the state of his son. Cases like these always remind

me why I started this research project: the realization that an admission for acute alcohol intoxication is such an impactful event, both physically and mentally, and overcomes still too many adolescents. A few hours after hospital admission, he became conscious. The relieve caused me to realize what an enormous amount of social costs (rough estimation: 4 ambulances 750 euro each, 3x mild intoxication with emergency department presentation 200 euro each, 1x moderate to severe intoxication with hospital admission for cardiorespiratory monitoring 1300 euro) can be attributable to an adolescent sleepover part.

CHAPTER 1

General introduction

1. ADOLESCENT RISK-TAKING BEHAVIOUR

Adolescents are often stereotyped as self-centered, irresponsible, impulsive, emotionally unstable, self-centered and reckless human beings. If someone would ask you, there would probably pop up a name in mind of someone who got into trouble due to risk-taking behavior in his or her teenage years. A short search on Google provided plenty examples of news articles in which adolescent misadventures left a trail of turmoil: falling through thin ice after jumping on a fresh frozen pond [1,2], being injured after train surfing [3-6], participating in choking games on social media [7-10], dead seeking the perfect selfie or attending virtual raves during the coronavirus lockdown [11-12]. The question why otherwise smart, savvy young people are notoriously prone to unwise and risky actions bothers researchers in the study of adolescent health and development, is proven by the fact that all of the phenomena's above have been addressed in scientific articles. Most children will test their limits, walk closer to the line, see the line of in the distance and stay clear. However, adolescents will walk right up to that line, wrap their little toes around the edge and peer beyond. Some adolescents seem to appreciate that line, while others tight rope it every day and cross the line whenever they can.

A broad range of research led to a complex and nuanced picture to why adolescents are prone to risk-taking behavior. It is just since two decades that we know that the adolescent brain does not fully mature until at least age 25, with the implication that adolescent decision-making and judgement is limited up to this age [13-16]. The maturation of the limbic system is completed a few years before the maturation of the prefrontal cortex.

The maturation of the prefrontal cortex continues in adulthood and is characterized by dendritic pruning and strengthening of connections between neurons. As a result of this asynchronous development of brain regions, it is proposed that adolescents have a structural and functional deficit in the ability to control the overdrive of impulses and emotions spurred by the limbic system (Figure 1). It only requires a little understanding that this inability may lead to self-centered, impulsive and reckless behavior in adolescence.

Consistent with the stereotype on an adolescent, adolescents exhibit heightened attraction to new and exciting experiences despite their evident risks [17-19]. This tendency is known as sensation seeking [20]. Sensation seeking rises rapidly during adolescence and peaks around the age of 16 in females and 19 in males [21]. This patterns is regarded the result of rising dopaminergic activation during adolescence [22]. The dopaminergic system is involved in recognition and anticipation of reward and therefore suggests a biological basis for impulsiveness and reward-seeking.

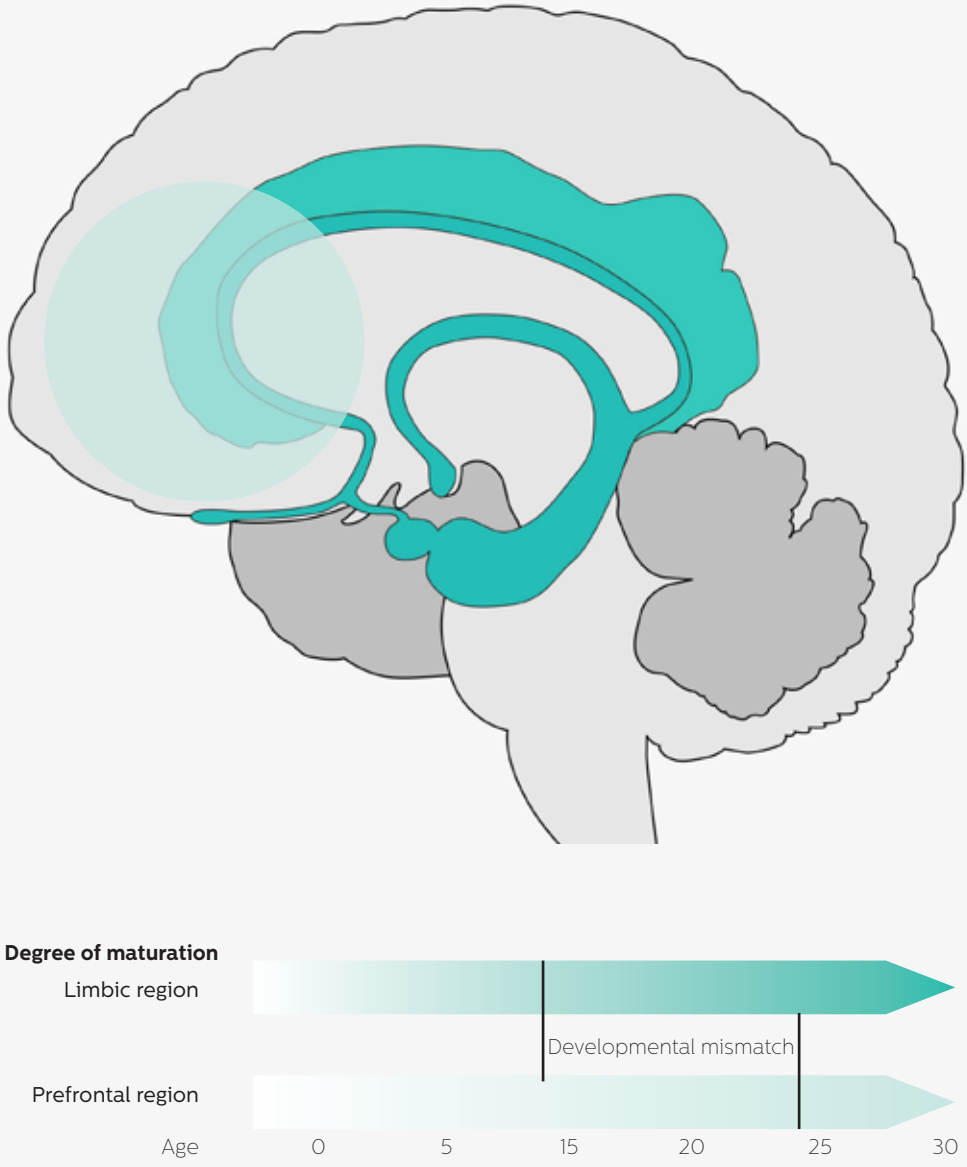


Figure 1: Mismatch in development of brain regions. Based on Giedd, 2016 [15]

So, the stereotyping statement of an adolescent in the first sentence of this general introduction contains at least a grain of truth. What makes the statement a stereotype, a widely held but fixed and oversimplified image of a particular type of person, then? As already suggested in the first paragraph of this general introduction, researchers tend to focus excess levels of maladaptive behavior. For the vast majority of adolescents, this

period of development passes without harmful consequences of risk-taking behavior, such as injury, illicit drug use, teenage pregnancy and sexual transmitted diseases due to sexual risk-taking behavior, homicide or suicide [23]. However, the risks of these negative outcomes are often comorbid with each other [24-26], leaving the average adolescent without great risk of life-altering consequences. Moreover, increasing attention has gained for the necessity of risk-taking behaviour for the transition of adolescence to well-functioning adults.

Yet, it makes perfectly sense that researchers focus on excess levels of risk-taking behaviour. It is widely agreed among experts in the study of adolescent health and development that the greatest threats of well-being of adolescents in high income countries come from preventable causes. Worldwide, 3 out of 5 leading causes of deaths among adolescent were injury-related: motor vehicle accidents (1st), self-harm (3rd) and drowning (5th) [27]. Furthermore, risk behaviours such as smoking, alcohol intake, drug use and physical inactivity are often initiated during adolescence and account for a substantial morbidity throughout life. That is the reason why more focus is has been given by researchers to disentangling individual differences: why are only some teenagers risk-takers? Disentangling individual differences, many hope, could lead to preventive strategies that protect especially those who are at risk of serious harm.

2. ADOLESCENT ALCOHOL CONSUMPTION

Alcohol use and alcohol abuse is of all time. The ability to metabolize alcohol likely predates humanity with primates eating fermenting fruit [28]. The oldest variable brewery has been found in a prehistoric burial site in a cave near Haifa in modern-day Israel [29]. Researchers have found residue of a wheat-and-barley-based alcoholic beer in stone mortars carved into a cave floor. The earliest evidence of wine production dates back to 6000 BC in the northern Zagros mountains of Iran and Georgia [30]. Nowadays, worldwide 37.5% of the population between 15 and 19 years of age has used or is currently using alcohol [31]. The prevalence of adolescent alcohol use is higher in more economically developed regions of the world: Region of the Americas (70.2%), European Region (59.8%) and Western Pacific Region (46.5%).

The high prevalence of adolescent alcohol use in the European Region, might be explained by the finding that alcoholic beverages are perceived to be easy to obtain compared with other substances. The European School Survey Project of Alcohol and Drugs (ESPAD), reported that 80% of the 15- to 16-year-old students stated that they

would find it easy to get to hold of an alcoholic beverage if they wanted to [32]. Of the ESPAD study population, 1 in 3 reported having tried an alcoholic beverage at the age of 13 or younger (33%) and 1 in 15 (6.7%) experienced alcohol intoxication at age 13 or younger. The Health Behaviour in School-aged Children (HBSC) study indicates similar results: 14% of the 11-year-old participants, 32% of the 13-year-old participants and 59% of the 15-year-old participants ever drunk alcohol [33]. One in three participants of the ESPAD study (34%) reported heavy episodic drinking (= binge drinking = five or more glasses of alcoholic beverages on one occasion at least once in the past month [22].

From an international perspective, studying adolescent alcohol use in the Netherlands is an important case study [34]. Whereas adolescents in the Netherlands topped international rankings of alcohol consumption in the beginning of this century [35], in more recent comparisons the Dutch can be found more toward the bottom of these rankings [32]. A recent study among Dutch adolescents indicates a strong decline in adolescent drinking behaviours, such as frequency of lifetime alcohol use, last month alcohol use, early onset alcohol use and early onset drunkenness [34]. Yet, among those that have experience with adolescent alcohol use and reported alcohol use in the last 30 days, a majority (71%) has been binge drinking (consuming more than 5 glasses of alcoholic beverages at 1 occasion) and even 1 in 10 (10%) reported drinking more than 10 glasses of alcoholic beverages on 1 day [36]. Time trends indicate that among adolescents that report last 30 days alcohol use, the proportion of binge-drinking does not show a significant decline [36]. During the last decade, alcohol-related hospital admissions among adolescents between 12 and 18 years old have been showing an increasing trend [37]. Therefore, despite the positive developments, adolescents alcohol use remains an issue of concern.

ACUTE CONSEQUENCES

Direct consequences of adolescent alcohol ingestion, are usually related to the blood alcohol concentration (BAC). Figure 2 displays dose-related symptoms of alcohol ingestion in adults [38, 39]. In children and adolescents these stages are reached at a lower BAC (Table 1). Several factors can influence the extent of acute alcohol intoxication; besides the amount of alcohol ingested, sex, age, individual weight and medication use. Tolerance to alcohol, the percentage of alcohol in the beverage and the period of alcohol ingestion seem to be particularly important [40–42].

During the last decade, the mean BAC of adolescents with an alcohol-related hospital admission in the Netherlands was 1.9 g/L [37]. The Reverse Widmark calculation [43]

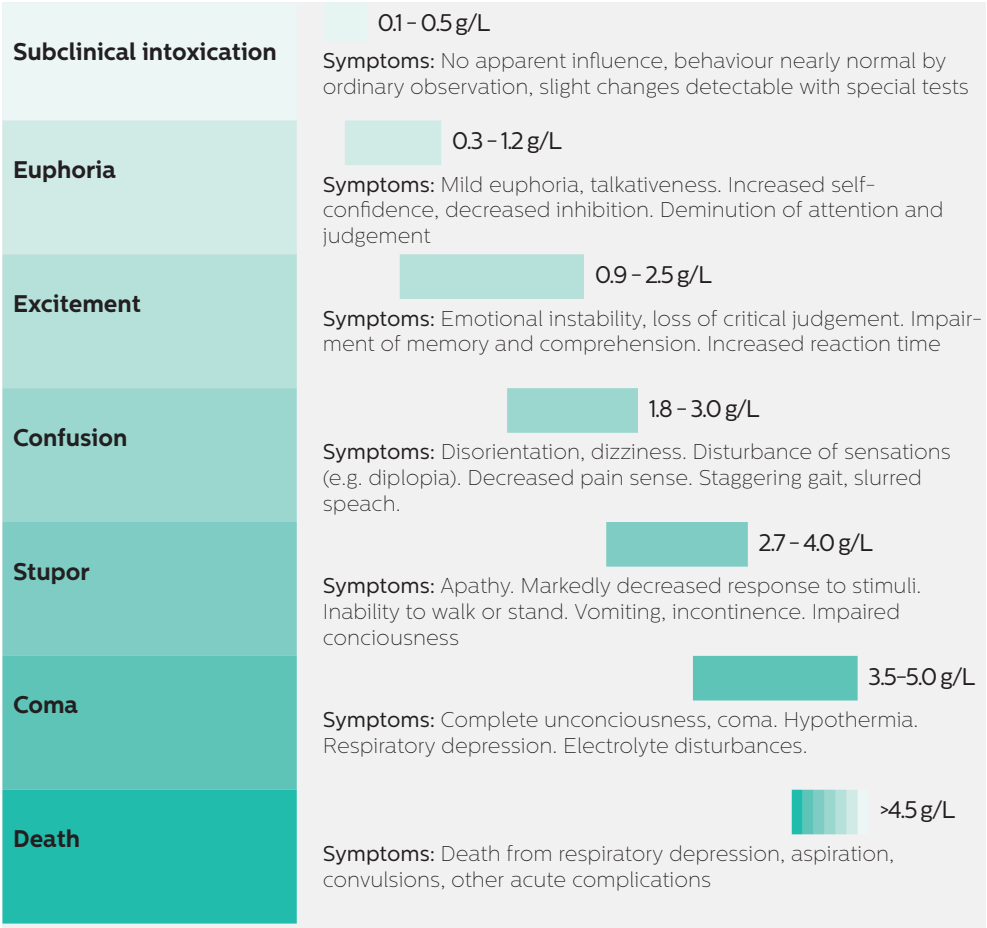


Figure 2: Stages of acute alcohol intoxication in adults. Based on Dubowski, 1977 [35]

allows us to calculate how many units of alcoholic beverages were consumed by an adolescent weighing 60kg: 6.5 alcoholic units for females and 8 alcoholic units for males, taking a delay of 1 hour between the emergency call and blood draw at the emergency department into account. Acute alcohol intoxication among adolescents can be complicated by reduced consciousness [34], hypothermia [44], electrolyte disturbances [44], hypoglycemia [44] and secondary injuries related to acute alcohol intoxication [37].

Besides the direct consequences of acute alcohol intoxication, alcohol consumption by adolescents has numerous indirect health consequences, such as increased risk for motor vehicle accidents, violence and aggression. For example, a study in the United States of America showed that more than a quarter (28.0%) of the motor vehicle accident fatalities of those ≤20 years old were alcohol related [45].

An estimation based on Dutch data showed similar results with 12-23% of the fatal motor vehicle accidents being alcohol related [46]. Of young cyclists between 15 and 19 years old that presented on the emergency department of a Dutch hospital during weekend nightshifts, almost half (49.0%) of the crashes were alcohol-related [46]. Furthermore, alcohol use is a risk factor both for being victimized and perpetrating youth violence [47, 48]. Youth violence takes many forms, including bullying, gang violence, sexual aggression, and assaults [47].

Table 1 BAC and number of alcoholic units (consumed within 2 hours) by sex, age and weight

	Boys			Girls		
Age	Mean weight	n of utits 1.8g/L	BAC at 8 units	Mean weight	n of units 1.8g/L	BAC at 8 units
11 years	35kg	5 (1.9)	3.07	39kg	4 (1.6)	3.25
12 years	39kg	5 (1.7)	2.73	43kg	5 (1.8)	2.92
13 years	45kg	6 (1.7)	2.33	48kg	5 (1.6)	2.59
14 years	52kg	7 (1.7)	1.98	52kg	6 (1.7)	2.37
15 years	57kg	8 (1.8)	1.78	55kg	6 (1.6)	2.22
16 years	61kg	9 (1.6)	1.64	57kg	7 (1.8)	2.13

Based on Jellinek, 2016 [39]

SUB-ACUTE CONSEQUENCES

Adolescent alcohol consumption increases the risk of risk-taking sexual behaviour. Research shows that adolescents who report adolescent alcohol use at a young age, are more likely as their alcohol-delaying peers to have initiated sexual intercourse at a young age [49]. Furthermore, alcohol intoxication has been associated with higher frequencies of unprotected sexual activities [50,51] and consequently higher risks of sexual transmitted disease [52,53] and teenage pregnancies [54,55]. Furthermore, binge drinking predicted alcohol-involved sexual assaults and alcohol-related assaults were more severe than those assaults that did not involve alcohol [56,57]. This association accounts for both victims and perpetrators of sexual assault [56,57]. These associations suggest that adolescent risk-taking behaviour has both negative personal and public health implications.

Secondly, despite the negative consequences of polysubstance use, strong associations between alcohol use, tobacco usage and illicit drug use have been established [58,59]. In Europe, almost all students (87% or more) who used a licit or illicit substance also reported having consumed alcohol, while 93% of students who ever smoked cigarettes also consumed alcohol [60]. Similar associations have been found in the Netherlands, where the prevalence of cannabis use among adolescents who had tried alcohol was

21%, in comparison to 1% among adolescents who had never tried alcohol [61]. A recent review indicates that alcohol and tobacco potentiate each other's rewarding effects, and, hence, that concurrent usage may potentiate their respective negative effects [62].

Thirdly, associations between adolescent alcohol use and school performance have been demonstrated. In a prospective follow-up study, among adolescents who never engaged in binge drinking at baseline, those who reported regular binge drinking at follow-up were relatively less likely to complete their homework, attend class, and value and achieve high grades [63,64]. More frequent binge-drinking at follow-up generally resulting in larger relative risk ratios [64]. These results suggests that students who initiate binge drinking have poor school performance and engagement, which may interfere with achieving their future academic goals. These results have been confirmed by a recent meta-analysis that identified substance abuse, negative attitude towards school, externalizing and internalizing problems of the juvenile and low parent-school involvement as the strongest risk-factors for school absenteeism [65].

TRANSITION TO ADULTHOOD

Besides the acute and subacute consequences, prevention of adolescent alcohol use is important as the persistence of adolescent binge drinking into adulthood is common. Across the world, as in the Netherlands, a key aim of alcohol policy is to postpone the age at which alcohol is first used. The rationale of this policy is based on 2 main reasons: there is substantial evidence for notable cognitive consequences of repeated exposure to alcohol during adolescence [66-68] and there is a substantial evidence for the association between early initiation of adolescent alcohol use and higher alcohol consumption levels and the development of adult alcohol use disorders [69-77].

Evidence suggests that adolescents who exhibited extreme binge drinking (10 drinks or more per occasion at least once over the last 3 months) performed more poorly on short-delay memory tasks and verbal learning in comparison to a non-drinking reference group [77]. The association between the number of drinks consumed during peak drinking episodes was linearly dose-related with these poorer performances is short-delay memory tasks and verbal learning tasks, suggesting that there was no safe drinking level to avoid these impairments [77]. The systematic review by Spear 2018 provides a clear overview of the cognitive and personality variables that for predictors of use vulnerability for adolescent alcohol consumption and consequences of alcohol exposure on cognitive and personality variables [66].

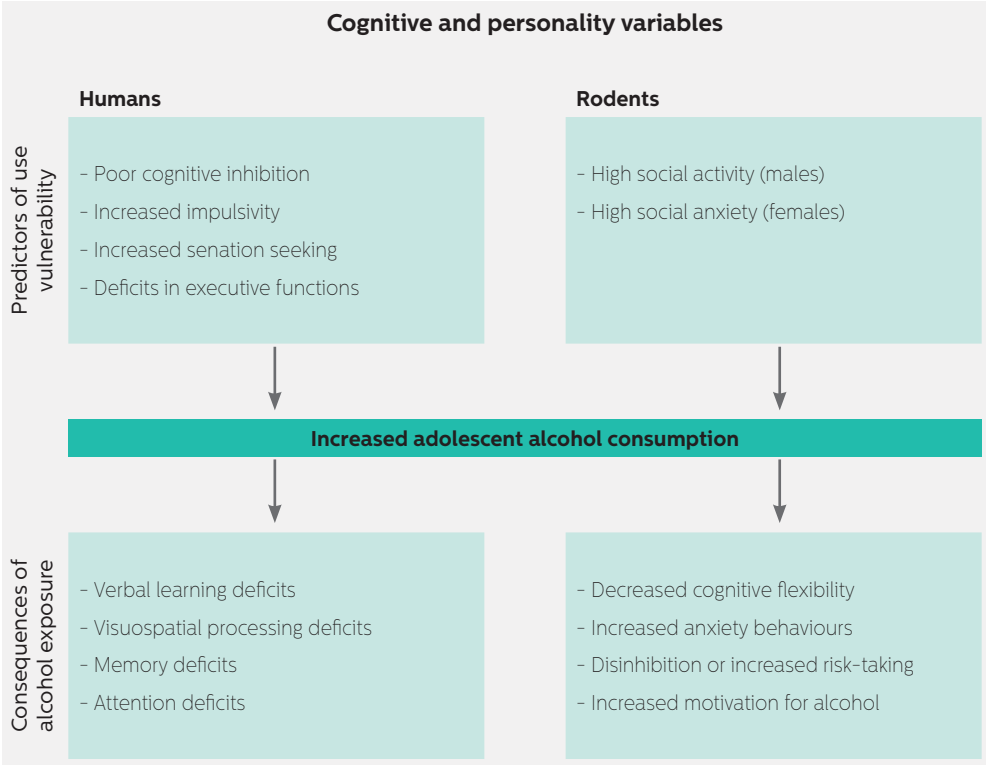


Figure 3: Cognitive and personality variables. Based on Spear, 2018 [63]

Several Magnetic Resonance Imaging (MRI) cross-sectional studies, although they cannot be used to ascertain causality, have showed that the brain of adolescents who have a history of substantial alcohol use differs from those without the exposure. Those who frequently engage in binge drinking exhibit deceases in grey matter volume of the frontal, parietal and temporal cortices, as well as limbic regions such as the hippocampus and the cerebellum [78-81]. Furthermore, adolescent alcohol use was associated with less developmental increase in white matter, disrupted white matter integrity and less connectivity between the prefrontal cortex and the limbic The systematic review by Spear, 2018, also provides a clear overview on the neural alterations that are predictors of use vulnerability and neural alterations as a consequence of adolescent alcohol consumption [66].

LONG-TERM CONSEQUENCES

Worldwide, alcohol was responsible for 5.3% of all premature mortality [27]. People of younger ages were disproportionately affected by alcohol compared to older persons, and 13.5% of all deaths among those who are 20–39 years of age are attributed to alcohol

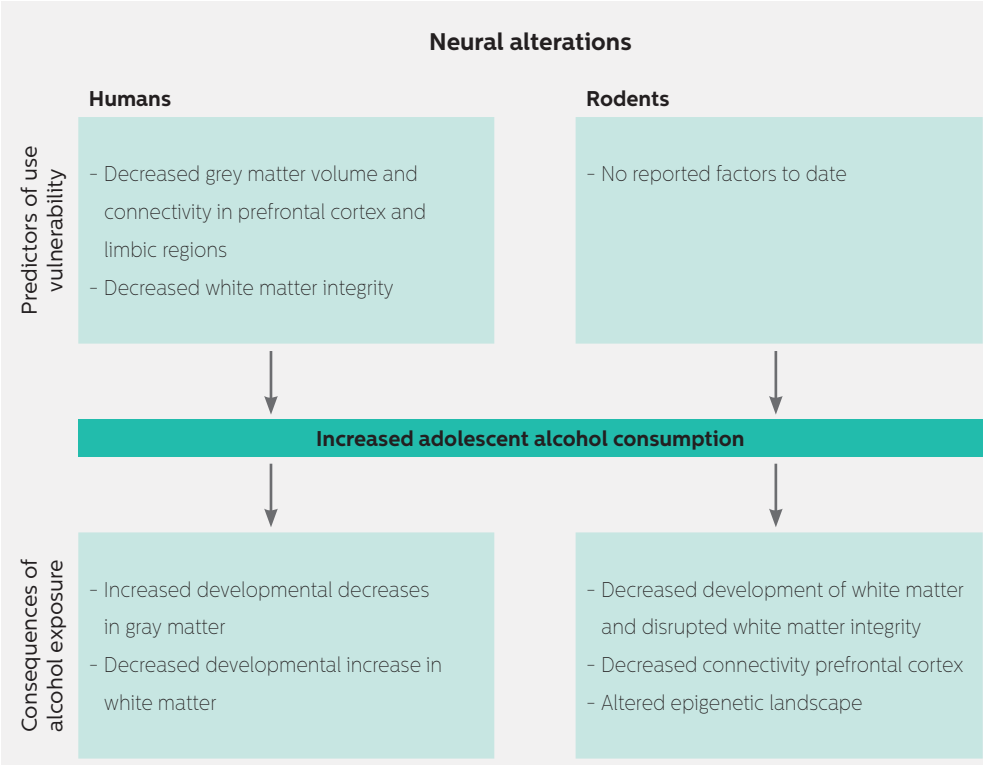


Figure 4: Neural alterations. Based on Spear, 2018 [63]

[27]. Alcohol consumption is a unique risk factor for population health as it affects the risks of approximately 230 three-digit disease and injury codes in the International Statistical Classification of Diseases and Related Health Problems –10th Revision (ICD-10) including infectious diseases, non-communicable diseases (such as cardiovascular diseases, cancers and liver disease) and injuries [79]. The concurrent use of alcohol and tobacco, in comparison to both alcohol use and tobacco use alone, have been associated with supra-multiplicative health risks, such as cardiovascular problems, head and neck cancers, cirrhosis, pancreatitis and psychiatric comorbidity [83-85]. A recent multinational cohort study founded that alcohol-induced consciousness (at any age), irrespective of the overall alcohol consumption, is associated with a subsequent increase in the risk of dementia [86].

For the Netherlands, a social cost-benefit analysis shows that if all costs and all benefits of alcohol are expressed in monetary terms, the net costs per year ranges between 2.3 to 2.9 billon euro per year [87]. Examples of costs that have been taken into account in this cost-benefit analysis include less productivity at work, costs of police and justice and traffic accidents. Benefits that have been to account in this cost-benefit analysis include tax

income and the feeling of wellbeing that consumers may experience from drinking alcohol. The monetary benefits of alcohol have been subtracted from the costs of alcohol to arrive at a final estimate of the yearly costs for the Dutch society.

3.PREVENTION: IDENTIFICATION OF RISK FACTORS

Prevention of adolescent alcohol-related hospital admissions requires understanding the factors that influence adolescent alcohol consumption. A common used model in public health is the social-ecological model which is based on four influence levels: individual, relationship, community and societal factors. Figure 5 displays the studied risk factors based on the data collection by the Dutch Pediatric Surveillance Unit, a nationwide surveillance system that collected data on adolescent alcohol intoxication between 2007 and 2017. The marked topics will be discussed in the current thesis.

INDIVIDUAL FACTORS

The first level of the socio-ecological model identifies individual factors that influence adolescent alcohol-related hospital admissions. This level focusses on biological and personal history factors. Prior studies based on the data collected by the Dutch Pediatric Surveillance Unit on adolescent acute alcohol intoxication explored some individual factors,

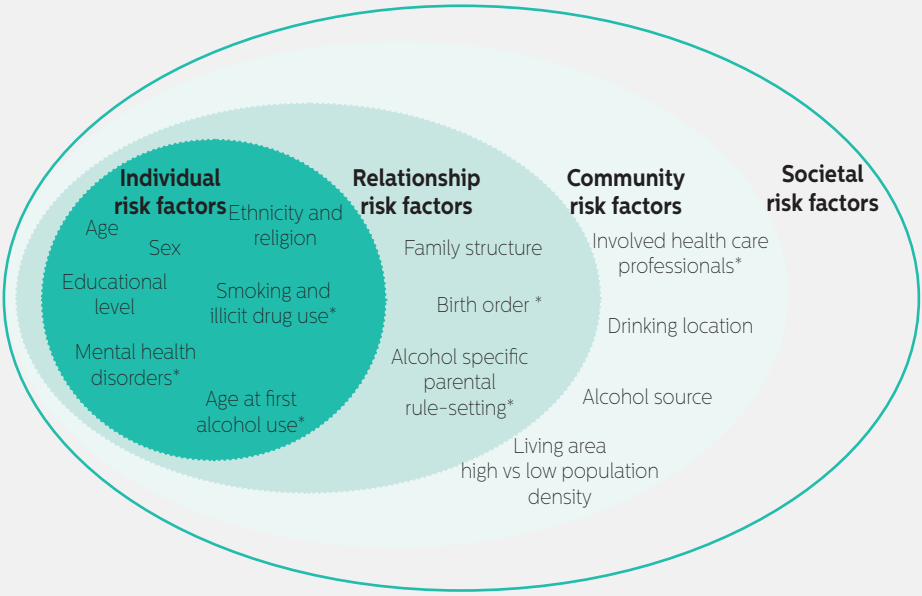


Figure 5: Ecological model adapted to illustrate possible risk factors for adolescent alcohol intoxication studied by the Dutch Pediatric Surveillance Unit data

such as sex [88-92], age [88-92], cultural background [91] and educational level [90, 93]. In this thesis, additional individual risk factors will be studied: the presence of mental health disorders, age at first alcohol use, and the role of smoking and illicit drug use.

RELATIONSHIP FACTORS

The second level examines close relationships that may increase the risk of an alcohol-related hospital admission. A person's closest social circle (peers, partners and family members), influence their behaviour. An example of a relationship risk factor that has been studied based on the data by the Dutch Pediatric Surveillance Unit is family structure [90]. In this study family structure was defined as traditional (living with both biological parents) or non-traditional (e.g. divorced parents, single parent, foster care). In this thesis additional relationship factors will be studies: birth order and alcohol-specific parental rule-setting.

COMMUNITY FACTORS

The third level explores the settings in which social relationships occur and seeks to identify the characteristics of these settings that are associated with adolescent alcohol-related hospital admissions. In prior studies based on the data collection by the Dutch Pediatric Surveillance Unit several community factors were assessed: drinking location [91], source of alcoholic beverages [91] and the living area of adolescents [94]. One of the studies in this thesis explores the presence of co-occurring mental health disorders (individual factor) and the prior involvement of (mental) health care organizations.

SOCIETAL FACTORS

The fourth level looks at broad societal factors that help to create a climate in which adolescent alcohol consumption is encouraged or inhibited. These factors include social and cultural norms that increase the risk of adolescent alcohol consumption. Other large societal factors include the health, economic, educational, political and social policies that contribute to prevention by reducing accessibility, acceptability and affordability of alcoholic beverages [95].

5. ASPECTS OF ALCOHOL INTOXICATION MANAGEMENT

To standardize the care given to adolescents with acute alcohol intoxication, a healthcare pathway was developed. The aim of this healthcare pathway is to guide health care professionals in all aspects related to the management of adolescent acute alcohol intoxication: prevention, acute treatment and outpatient follow-up. Figure 6 displays the organization of the health care pathway schematically.

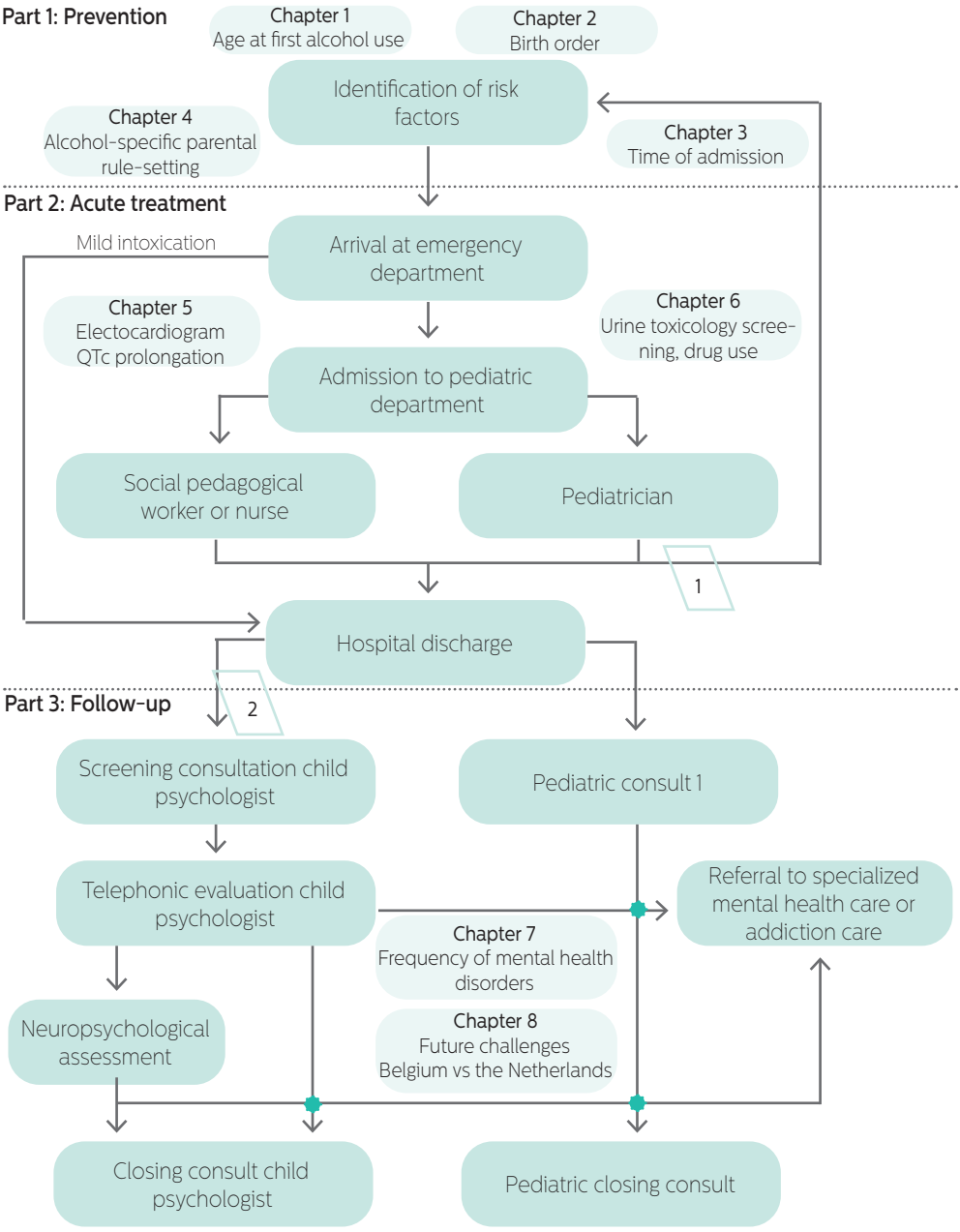
In this thesis, we aim for providing answers on three key topics:

- What are major risk factors for adolescent acute alcohol intoxication hospital admission?
- What is the clinical relevance of diagnostic procedures, such as an electrocardiogram and urine toxicology screening, during the initial assessment of a patient with acute alcohol intoxication?
- What are the results of ten years of follow-up at the 'Outpatient Department for Adolescents and Alcohol'?

In **part 1** of this thesis we focus on the prevention of acute alcohol intoxication by the identification of risk factors. Part 1 consist of four chapters. Each chapter focusses on a different potential risk factor for acute alcohol intoxication: age of first alcohol use (*Chapter 2*), birth order (*Chapter 3*), time of admission *(Chapter 4)* and alcohol-specific parental rule-setting (*Chapter 5*).

In **part 2** we assess the clinical value of 2 diagnostic procedures which are frequently performed upon emergency department presentation. First, we will evaluate the results of ten years of electrocardiogram registrations and determine the prevalence of QTc-prolongation in patients with acute alcohol intoxication (*Chapter 6*). Secondly, we will evaluate the results of urine toxicology screening as the results of urine drug toxicology are relevant for both the acute treatment and outpatient follow-up (*Chapter 7*).

Part 3 ends with two studies about outpatient follow-up and bridges to potential further research. The first study evaluates the follow-up program at the 'outpatient department for adolescents and alcohol' and aims to identify the prevalence of mental health disorders among adolescents admitted for acute alcohol intoxication (*Chapter 8*). Finally, the last chapter will review remaining challenges in the outpatient follow-up and prevention of adolescents with acute alcohol intoxication and highlights future perspectives (*Chapter 9*).



1 Questionnaire Dutch Pediatric Surveillance System
2 Health Behaviour Checklist (CBCL), Teacher's Report Form (TRF), Youth Self-Report (YSR)
Decisions based on multidisciplinary meetings

Figure 6: Health care pathway for adolescents with acute alcohol intoxication

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SECTION 1

Prevention: **identification of risk factors and determinants**

CHAPTER 2

Age at first alcohol use

Age at first alcohol use as a possible risk factor for adolescent acute alcohol intoxication hospital admission in the Netherlands

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ABSTRACT

Background The primary objective of this study is to determine whether age at first alcohol use is a determinant for adolescent acute alcohol intoxication characteristics, such as age at first acute alcohol intoxication and blood alcohol concentration (BAC) at hospital admission. Around the world, as in the Netherlands, a key aim of alcohol policy is to postpone the age at first alcohol use. This is based on cohort studies that indicate a relationship between a younger age at first alcohol use and subsequent adult alcohol use disorders.

Methods This study was conducted using a cohort of data comprising individuals under 18 years of age. Data were collected between 2007 and 2017 by the Dutch Pediatric Surveillance System (NSCK) in order to monitor trends in admissions for acute alcohol intoxication. Multivariate linear regression analyses were used to determine the association between age at first alcohol use and acute alcohol intoxication characteristics, such as age at first acute alcohol intoxication and BAC at admission.

Results This study indicates that among adolescents admitted for acute alcohol intoxication, adolescents who started drinking at ≤14 years of age are significantly more often female, lower educated, and raised in nontraditional family structures than adolescents who started drinking between 15 and 18 years of age. Multiple linear regression analyses indicated that age at first alcohol use, corrected for covariates, significantly predicted the age at acute alcohol intoxication and BAC at admission. The association between age at first alcohol use and age at intoxication was also found to be clinically relevant.

Conclusions Although causation cannot be implied based on the results of these analyses, the results of this study suggest that interventions delaying the age at first alcohol use could be successful in increasing the average age that adolescents are admitted to the hospital for acute alcohol intoxication.

Keywords*: Adolescents, acute alcohol intoxication, age at first alcohol use*

1. INTRODUCTION

BACKGROUND

According to the World Health Organization, more than half (59.8%) of the European population between 15 and 19 years of age has used or is using alcohol [1]. Although adolescents drink less often than adults, they consume higher quantities of alcohol per occasion [2]. Adolescent drinking has been associated with numerous negative health risks, as well as social and economic consequences [3]. Prevention of adolescent drinking is a relevant topic, as adolescent drinking impacts not only the user but also society as a whole.

The prevention of underage drinking requires a comprehensive approach that should include but should not be limited to alcohol policy, limiting the marketing of alcoholic beverages and increasing awareness among adolescents by education [4]. Alcohol policy is based on three factors: reducing availability, reducing affordability and reducing acceptability [5]. Across the world, as in the Netherlands [6], a key aim of alcohol policy is to postpone the age at which alcohol is first used.

The rationale of this policy is based on cohort studies that indicate a relationship between a younger age at first alcohol use and adult alcohol use disorders [7–11]. The age at first alcohol use is a frequently studied risk factor not only for alcohol use disorders but also for alcohol consumption levels among adult general drinking population [12–14]. The age at first alcohol use has been associated with not only negative health outcome measures such as alcohol use disorders later in life but also negative economic and social parameters, such as delinquency, poverty and broken family structures [14].

RESEARCH QUESTION AND OBJECTIVES

Although many cohort studies suggest a causal relationship between age at first alcohol use and adult drinking problems, a recent systematic review based on prospective follow-up cohort studies did not provide evidence for this causal relationship [15]. This review suggests that policy makers should concentrate on minimizing acute and short-term harms associated with drinking among children rather than focusing on uncertain long-term harms and suggests that more research is needed to address this relationship. The current study adheres to this recommendation by investigating whether the age of drinking onset is a risk factor for acute alcohol intoxication in adolescence. In the Netherlands, it is unknown whether age at first alcohol use is also associated with acute alcohol intoxication parameters, such as age of intoxication, BAC and duration of reduced consciousness as a result of acute alcohol intoxication.

The primary objective of this study is to determine whether age at first alcohol use is a determinant for adolescent acute alcohol intoxication characteristics, such as age at intoxication and blood alcohol concentration at the time of admission. This study was conducted using a cohort of data comprising individuals under 18 years of age. Data was collected between 2007-2017 by the Dutch Pediatric Surveillance System (NSCK) in order to monitor trends in admissions for acute alcohol intoxication.

2. MATERIALS AND METHODS

STUDY DESIGN AND STUDY POPULATION

To explore the potential relationship between age at first alcohol use and acute alcohol intoxication among Dutch adolescents, a retrospective cohort study was conducted. The study was based on a nationwide cohort of adolescents younger than 18 years of age who were treated in a pediatric department for a positive blood alcohol concentration. Between the years of 2007 and 2017, a total of 6,828 cases of acute alcohol intoxication were reported to the Dutch Pediatric Surveillance System. During the admission, various characteristics of the acute alcohol intoxication event, patterns of prior substance use and social demographics were registered in the system. Cases where patterns of prior substance use were unknown (n=1,916) were excluded from analyses, leading to 4,912 useable registrations for the current investigation. The cutoff value for age at first alcohol use was set on 5 years based on the definition of the parameter and in order to reduce the effect of outliers.

DATA COLLECTION

Data collection had been previously performed by the Dutch Pediatric Surveillance System (NSCK). The details of data collection based on this study population have been described in several prior articles [16-18]. The NSCK is a nationwide surveillance system used to obtain data to support research on diagnostics, treatment, and prognosis of 10-12 predetermined diseases, disorders or syndromes. In 2007, the rising trend of admissions for acute alcohol intoxication observed by pediatricians was the reason that acute alcohol intoxication was added to the system [18].

All Dutch pediatric departments in the Netherlands cooperate to report cases of underage alcohol intoxication. The reports are based on data obtained by a questionnaire. The questionnaire is used to obtain data on general characteristics (e.g. age at first acute alcohol intoxication and sex), demographic characteristics, substance use patterns (e.g., age at first alcohol use, smoking, and substance use) and intoxication characteristics (e.g.,

blood alcohol concentration and duration of reduced consciousness). The questionnaire is completed by a member of the pediatric team who uses medical records, lab results, and self-reported information from the patient.

MEASURES

The primary measure for this specific study was the age at first alcohol use. There are various ways to define first alcohol use. Some studies define the age at first alcohol use as the first alcohol intoxication (e.g. first time drunk) [10,12]. Other studies define the age at first alcohol use as the age of ingesting the first alcoholic unit (e.g. age at first glass) [8,9,11,13,14]. In the current study, the age at first alcohol use was defined as the age of drinking the first glass of alcohol. In the current study, the age at first alcohol use was defined as the age of drinking the first glass of alcohol.

To minimize the risk of recall bias by a too long duration between age at first alcohol use and admission for acute alcohol intoxication by telescoping [19], adolescents with an age of first alcohol use below the age of 5 were excluded. Furthermore, these outliers with a starting age below 5 years would interfere in the regression analysis. Although the age <5 years was chosen arbitrarily, it was based on research that indicates that the mean age of adolescents dates back to when they were 3.5 years old [20]. Research with adults suggests that people can remember childhood memories back only to about age 6 [21]. A reported age of first alcohol use below the age of 5 was considered more likely to be caused by misinterpretation of the question (sip of alcohol instead of glass of alcohol) as a realistic answer.

General characteristics were measured as follows: sex (male/female), educational level (low and middle level/higher level), ethnicity (Dutch/other), family structure (traditional family structure/nontraditional family structure) and reason for hospital admission (reduced consciousness, accident, aggression, or other). Acute alcohol intoxication characteristics were measured as follows: age of admission in years, blood alcohol concentration in g/L and duration of reduced consciousness in hours.

DATA ANALYSES

For all statistical analyses, SPSS for Windows (version 25) was used. Continuous variables are expressed as the means and standard deviations. For each continuous variable, normality was assessed using the Kolmogorov-Smirnoff test. Nominal variables were expressed as frequencies (percentages) with 95% confidence intervals (CI).

The determinant of interest, age at first alcohol use, was measured in years. For the first analysis, this continuous variable was recoded into a new categorical variable consisting of 2 categories using a median split: age at first alcohol use ≤14 years and age or of first alcohol use between 15 and 18 years of age. Pearson's chi-squared tests were used to analyze categorical variables including sex, educational level, ethnicity, family structure and reason for admission. For numerical variables, an independent samples t-test or a Mann-Whitney U test (performed on age at first acute alcohol intoxication, BAC and duration of reduced consciousness) was performed. The significance level for all statistical tests was set to alpha = 0.05

Multivariate linear regression analyses were used to determine whether an association existed between age at first alcohol use and acute alcohol intoxication characteristics, such as age at first acute alcohol intoxication and blood alcohol concentration at admission. The risk factor age at first alcohol use was identified as the independent variable and the earlier mentioned outcome variables were dependent variables. Covariates included for this analysis were sex, educational level, ethnicity, family structure and reason for admission. For the regression analysis on blood alcohol concentration, age at first acute alcohol intoxication was also included as covariate.

3. RESULTS

STUDY PARTICIPANTS

Out of the 6,828 participants in the study cohort, 4,941 participants completed the section of the survey assessing patterns of prior substance use. An additional 29 participants were excluded because the reported age at first alcohol use was 5 years or younger. Therefore, 4,912 participants were included in this study. In this study population, 50.4% of the adolescents started drinking at ≤14 years of age, while 49.6% started drinking between 15 and 18 years of age.

GENERAL CHARACTERISTICS

Baseline characteristics were analyzed for the 2 groups: age at first alcoholic drink ≤14 years or age at first alcoholic drink between 15 and 18 years of age. The results of these general characteristics are displayed in Table 1. The percentage of female patients admitted for acute alcohol intoxication was higher among the group that started drinking alcohol before the age of 15 (X^2 (1, N = 4,879) = 50.44, p <.001). The educational level was higher in children who started drinking alcohol at the age of 15 than those who started drinking alcohol at an age younger than 15 (X^2 (3, N=4,596) = 12.10, p <.001). Among

Table 1. General characteristics age of first alcohol use

	Age ≤14 years n = 2,477 (50.4%)	**Between 15 and 18 years** n = 2,435 (49.6%)	**p-value***
Sex			p < .0001
% Male	48.0% (CI 46.0 - 50.0%)	58.2% (CI 56.2 - 60.2%)	
% Female	52.0% (CI 50.0 - 54.0%)	41.8% (CI 39.9 - 43.8%)	
Educational level			p < .0001
% Low and middle level	80.9% (CI 79.2 - 82.4%)	76.7% (CI 74.9 - 78.4%)	
% Higher level	19.1% (CI 50.0 - 54.0%)	23.3% (CI 21.6 - 25.1%)	
Ethnicity			p = .91
% Dutch	88.7% (CI 87.3 - 89.9%)	88.8% (CI 87.4 - 90.0%)	
% Other	11.3% (CI 10.1 - 12.7%)	11.2% (CI 10.0 - 12.6%)	
Family structure			p < .0001
% Traditional	62.9% (CI 61.0 - 64.9%)	71.7% (CI 69.8 - 73.5%)	
% Non-traditional	37.1% (CI 35.1 - 39.0%)	28.3% (CI 26.5 - 30.2%)	
Reason of admission			p = .91
% Reduced conciousness	89.0% (CI 87.7 - 90.2%)	87.8% (CI 86.4 - 89.1%)	
% Accident	8.0% (CI 6.9 - 9.1%)	9.4% (CI 8.2 - 10.7%)	
% Agression	2.0% (CI 1.5 - 2.7%)	2.1% (CI 1.6 - 2.8%)	
% Other reason	1.1% (CI 0.7 - 1.6%)	0.7% (CI 0.4 - 1.2%)	

* Chi-squared test

the group that started drinking at ≤14 years of age, the percentage of children living in nontraditional family structures was significantly higher than in the group that started drinking later (X^2 (1, N = 4,743) = 41,51, p <.001). There was no difference in reason for hospital admission (X^2 (3, N = 4,677) = 4.32, p = .23) or ethnicity (X^2 (1, N = 4,688) = 0.01, p=.91) between the 2 created research groups.

ACUTE ALCOHOL INTOXICATION CHARACTERISTICS

The acute alcohol intoxication characteristics are displayed in Table 2. A statistically significant difference (z = -36,86, p <.01; Mann-Whitney U test) was found between age of admission for acute alcohol intoxication, with adolescents who started drinking at ≤14 years of age having a lower mean age of admission (M = 14.8) than adolescents who started drinking between 15 and 18 years of age (M = 16.0).

Although the absolute difference between blood alcohol concentrations was only 0.1 gram/liter, statistical testing indicated that adolescents who started drinking at ≤14 years of age were admitted with a significantly lower blood alcohol concentration than adolescents who started drinking between 15 and 18 years of age (z = -5,73, p <.01; Mann-Whitney U test).

Table 2. General characteristics age of first alcohol use

	Age ≤14 years n = 2,486	Between 15 and 18 years n = 2,422	p-vaiue*
Age at hospital admission *years*	14.8 (SD 1.2)	16.0 (SD 1.2)	p < .0001
Blood alcohol concentration *g/L*	1.88 (SD 0.56)	14.97 (SD 0.53)	p < .0001
Reduced conciousness *hours*	3.0 (SD 2.5)	3.2 (SD 3.2)	p = .56

*Mann-Whitney U Test

AGE AT FIRST ALCOHOL USE AS PREDICTOR

Regression analysis was used to investigate whether age at first alcoholic drink is significantly associated with the age of admission for intoxication, blood alcohol concentration and duration of reduced consciousness. The results of multiple linear regression analysis are displayed in Table 3.

Table 3. Multiple regression analyes

	B	SE_B	β	p-value
Age at hospital admission				
Intercept	+8.896	0.203		
Age at first alcohol use	+0.468	0.012	+0.525	p < .001
Sex	−0.278	0.030	−0.120	p < .001
Educational level	+0.025	0.037	+0.009	p=.51
Ethnicity	−0.124	0.049	−0.034	p = .011
Family structure	+0.110	0.033	+0.044	p = .001
Reason of admission	+0.132	0.033	+0.053	p < .001
Blood alcohol concentration				
Intercept	+1.047	0.142		
Age at first alcohol use	+0.021	0.008	+0.051	p =.008
Sex	−0.096	0.018	−0.088	p < .001
Educational level	+0.111	0.022	+0.084	p < .001
Ethnicity	−0.051	0.028	−0.030	p =.07
Family structure	−0.011	0.019	−0.010	p =.55
Reason of admission	−0.115	0.019	−0.097	p < .001
Age at hospital admission	+ 0.052	0.009	+0.111	p < .001

B = unstandardized regression coefficient, SE_B = standard error of regression coefficient, β = standardized coefficient

The initial multiple regression analysis was run to explore the relationship between age at first alcohol use and age at intoxication. Age at first alcohol use, sex, family structure and reason of admission significantly predicted age at first acute alcohol intoxication ($F(6, 4141) = 299.53$, $p < .001$). In this model, the slope coefficient for first alcohol use

was 0.47 and statistically significant. Among adolescents admitted for acute alcohol intoxication, a 1 year increase in age at first alcohol used was associated with a 0.47 year increase of age at admission for acute alcohol intoxication.

A second multiple regression analysis was run to examine the association between age at first alcohol use and BAC. The model significantly predicted blood alcohol concentration. Although the slope coefficient for age at first alcohol use significantly predicted the blood alcohol concentration at admission, ($F(7, 3688) = 27.50$, $p < .001$), the effect size was minimal.

4. DISCUSSION

MAIN RESULTS

In the Netherlands, the efforts of national policies to increase the age at first alcohol use have been successful. After 2014, when the minimum legal purchase age was increased from 16 for beverages with <15% alcohol (e.g., beer, wine), and 18 for spirits above 15% alcohol to 18 years for all alcohol beverages, the percentage of adolescents who ever used alcohol before the age of 18 showed a declining trend [16]. Despite this reduction in general alcohol use among Dutch adolescents, the number of admissions for acute alcohol intoxication showed a rising trend [16].

The relationship between age at first alcohol use and adolescent alcohol intoxication is unknown in the Netherlands. Age at first alcohol use is a commonly studied risk factor, and therefore the current study extends and adds to prior research. Specifically, this study examined the relationship between the age at first alcohol use and adolescent alcohol intoxication parameters as opposed to previous studies examining outcomes in adulthood.

Our study indicates that among adolescents admitted for acute alcohol intoxication, adolescents who started drinking when they were ≤14 years of age are significantly more often female, lower educated and raised in nontraditional family structures than adolescents who started drinking between 15 and 18 years of age. Multiple linear regression analyses indicated that age at first alcohol use, corrected for covariates, significantly predicted age of acute alcohol intoxication and blood alcohol concentration at admission. The association between age at first alcohol use and age at first acute alcohol intoxication is also clinically relevant. Among adolescents admitted for acute alcohol intoxication, a 1 year increase in age at first alcohol use was associated with a 0.47 year increase in age at first acute alcohol intoxication.

LITIMATIONS

One of the disadvantages of a retrospective study design is the influence of recall bias. In the follow-up after acute alcohol intoxication, adolescents were required to recall the age at which they first used alcohol. Although self-reported measures of alcohol use are generally considered to be reliable and valid [22-23], there is some evidence that the age at first alcohol use is influenced by recall bias. However, the comparison of the two groups as performed in this study is relevant since this bias occurred in both groups.

The longer the time interval between the age at first alcohol use and reporting it is, the higher the risk of recall bias and telescoping forward (report a later age at first alcohol use) [19]. However, the interval between the age at first alcohol use and the age at admission for acute alcohol intoxication is shorter in this study than in studies on the age at first alcohol use and the development of alcohol disorders.

5. CONCLUSION

IMPLICATIONS FOR MEDICAL PRACTICE

Although causation cannot be inferred based on the results of these analyses, the results of this study suggest that interventions that are successful in delaying the age at first alcohol use could be successful in increasing the average age that adolescents are admitted for acute alcohol intoxication. In adolescents admitted for acute alcohol intoxication, the group that started drinking before the age of 14 years was admitted at a younger age. Thus, aiming for abstinence from alcohol for as long as possible will increase the age at first alcohol use and the risk of young admission for acute alcohol intoxication, a finding that is consistent with studies associating a delay of first alcohol use with reduced levels of alcohol consumption later in life [12-14].

FUTURE RESEARCH

The results of this study suggest an association between age at first alcohol use and age of admission for intoxication. However, it remains unclear whether this association is based on a causal relationship or is the result of confounding factors. A currently planned longitudinal neuroimaging study examining the effects of delaying binge drinking on adolescent brain development may strengthen the hypothesis of a causal relationship [24].

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CHAPTER 3

Birth order

The relationship between birth order and acute alcohol intoxication among Dutch adolescents

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ABSTRACT

Background Prior research demonstrated the relationship between birth order and adolescent risky behavior. The possible connection between the presence of siblings and birth order and underage alcohol abuse is unknown.

Methods Our study involves 10 years of data collection on underage alcohol intoxication in Dutch hospitals. A total of 2,234 patients were included in the current study.

Results Adolescents treated for alcohol intoxication less often have no siblings (6.7%) than the population has (14.8%). Furthermore, middle and youngest children are overrepresented in the patient population.

Conclusions The presence of older siblings is a risk factor for acute alcohol intoxication.

Keywords*: adolescent, acute alcohol intoxication, birth order, siblings*

1. INTRODUCTION

BACKGROUND

The adolescent brain is not a larger variant of a child's brain, but the result of a unique process in the formation of a complex network of interconnecting neurons. This process is characterized by dendritic pruning, as well as by the strengthening of connections between neurons [1,2]. Genetic factors, as well as environmental factors such as birth order, play a key role during this process [3]. During this process, the adolescent brain is prone to risk-taking behavior. This behavior is of all time, can be found in all cultures, and from a sociological, as well as an evolutionary perspective, can be seen as very useful. Risk-taking drives the growth of independence from parents and allows teenagers to make enormous progress in socialization. On the other hand, this risk-taking behavior puts adolescents at risk for health hazards.

The emergence of hazardous risk-taking behavior arises from an asynchronous development of brain regions. It starts with the maturation of networks in the limbic system where emotions arise and impulsive response initiates and ends with the maturation of networks in the prefrontal cortex where impulses are controlled and judgment is promoted [2]. This asynchronous development of brain regions puts adolescents at risk for health hazards, such as motor vehicle accidents, unintentional sport injuries, and teenage pregnancy [4]. Furthermore, adolescence is a time that can be marked by the emergence of harmful health behaviors, such as smoking, binge drinking, gambling, and substance use [5,6]. Prevention of hazardous risk-taking behavior, such as alcohol use, requires awareness of both risk factors and protective factors.

In the Netherlands, this awareness has led to the development of national preventive strategies regarding underage drinking and eventually resulted in a decline in regular alcohol use among the general Dutch population between ages 12 and 16 years old [7]. Although there has been a decline in regular alcohol use among Dutch adolescents, adolescent drinking behavior remains a subject of concern for parents, doctors, and politicians. The rising trend of admission to Dutch pediatric departments seen in the past decade increases this concern [8]. Hospital admissions are associated with serious complications, such as reduced consciousness, hypothermia, and electrolyte disturbances [9].

The increase in hospital admissions for alcohol intoxication has prompted the addition of acute alcohol intoxication to the Dutch Pediatric Surveillance System (NSCK). In doing so, risk factors for high blood alcohol concentration (BAC) at admission have been identified: older age, male sex, and higher educational level [10]. Further identification of protective

factors and risk factors remains necessary for the renewal of preventive strategies regarding acute alcohol intoxication. Birth order is considered to be an influential environmental factor and might be related to acute alcohol intoxication. In prior research, birth order has already been associated with both the useful, and the hazardous, aspect of risk-taking behavior.

Several studies have associated birth order with the useful aspects of risk-taking behavior. One study associated birth order with traveling to distant destinations. Compared to firstborns, youngest children are more attracted to traveling to unfamiliar places [11]. Another study among brothers playing major league baseball found that younger brothers were more likely to attempt the high-risk activity of base stealing and more likely to steal bases successfully [12].

Birth order has also been associated with the hazardous aspects of risk-taking behavior. Research among participants in extreme sports shows that ordinal position in the family predicted perception of health-related risks [13]. Furthermore, prior research has shown that younger siblings of children displaying risky behavior are at increased risk of displaying that behavior themselves [14]. This association has been found for risky sexual behavior [15], delinquent [16], and smoking and drug use [17]. It is known that regular drinking by an older sibling is associated with a higher risk of regular drinking for the youngest sibling [18]. It is, however, unknown whether the presence of siblings and birth order also influences excessive alcohol consumption.

This study aims to explore the relationship between birth order and the characteristics of acute alcohol intoxication. First, the study determines whether the absence or presence of siblings is associated with acute alcohol intoxication. Second, the study examines whether the distribution of firstborn, middle, and youngest children in the group of admitted intoxicated adolescents with siblings differs from the expected distribution in the general Dutch population ages 12 to 17 years old with siblings. In other words, is birth order associated with acute alcohol intoxication among Dutch adolescents? Finally, this study aims to analyze whether birth order and the presence of siblings are associated with a higher BAC at admission, corrected for the known covariates [10].

2. METHOD

DATA COLLECTION PROCEDURE

Since 2007, the NSCK has been collecting data from Dutch adolescents admitted to a pediatric department of a Dutch hospital with a positive BAC. Pediatricians from Dutch

hospitals have been asked to report admissions to the NSCK and subsequently complete a questionnaire containing questions regarding sociodemographic characteristics of the child admitted, current intoxication and treatment data, and past substance (ab)use. All the data are collected in a national database. For the current analysis, patients admitted primarily because of alcohol intoxication were selected. Patients without known sibling status as well as patients without known position in the family were excluded from analyses.

The study population was compared to the general population of Dutch adolescents 12 to 17 years old. Characteristics of this reference group were extracted from data collected by the Dutch Centraal Bureau voor de Statistiek [19]. CBS data were available from 2007 to 2016. The extracted data are displayed in Tables 1 and 2.

Table 1 Expected proportion of sibling status and birth order Dutch population 12-17 [19]

Year	Sibling status			Birth order			
	% only child	% siblings	Weight *n* = 2,394	% lastborn	% middle child	% firstborn	Weight *n* = 2,2129
2007	13.55%	86.45%	0.076	35.08%	21.34%	43.57%	0.073
2008	13.98%	86.02%	0.104	35.40%	20.98%	43.62%	0.103
2009	14.30%	85.70%	0.151	35.65%	20.76%	43.59%	0.143
2010	14.56%	85.44%	0.190	35.77%	20.57%	43.66%	0.193
2011	14.65%	85.35%	0.010	35.70%	20.66%	43.64%	0.010
2012	14.83%	85.17%	0.080	35.70%	20.48%	43.82%	0.080
2013	15.10%	84.90%	0.084	35.80%	20.33%	43.87%	0.088
2014	15.42%	84.58%	0.103	35.96%	20.12%	43.92%	0.103
2015	15.68%	84.32%	0.089	36.10%	20.07%	43.83%	0.093
2016	15.58%	84.42%	0.056	36.58%	20.11%	43.31%	0.057
2017	16.02%	83.98%	0.057	36.44%	19.82%	43.73%	0.058
Total	14.78%	85.22%	1.000	35.79%	20.51%	43.70%	1.000

MEASURES

The questionnaire contained two questions that were crucial for the current research question. The first was a multiple-choice question in order to determine the presence of siblings: “Do you have siblings?” Answer A: yes, brothers. Answer B: yes, sisters. Answer C: yes, brothers and sisters. Answer D: no, I am only child. The second multiple-choice question determined birth order when siblings were present: “What is your position in the family?” Answer A: youngest. Answer B: oldest. Answer C: in between.

Additional data obtained by the questionnaire that were used for this study included general characteristics (age and sex), educational level (low, middle, high), religion

(religiously unaffiliated, Christian, Muslim, other), and intoxication characteristics (blood alcohol content in gram/liter).

PARTICIPANTS

Between 2007 and 2017, a total of 6,416 underage adolescents were identified with a positive BAC during treatment in Dutch hospitals, and 77 of them were identified as recidivist alcohol-intoxicated adolescents. Of the 6,339 other cases, the question determining the presence of a sibling was answered in 2,394 cases (37.8%). Among adolescents with a sibling (N = 2,234), 2,129 (95.3%) answered the question regarding birth order.

DATA ANALYSES

All data were analyzed using SPSS for Windows, version 22. Frequencies are expressed as percentages with 95% confidence intervals (CI). Continuous variables, such as age and BAC, are presented as the mean and standard deviation (SD).

For the analyses, a new variable, presence of siblings, was created by pooling the answers brothers, sisters, and both brothers and sisters. Furthermore, statistics for missing years in the CBS data were estimated using the function replace missing values by linear trend at point. Weighted averages, with counts of study participants per year as weight, were used to determine expected frequencies of firstborn, middle, and youngest children. Using weighted averages also resulted in the correction of changes in the distribution of firstborn, middle, and youngest children over time. Throughout the past decade, the proportion of firstborn children remained stable (43%), but the proportion of middle and youngest children changed along with declining family sizes.

The aim of the first analysis was to compare the proportion of children without siblings in the study population to the proportion of children without siblings in the general Dutch population between 12 and 17 years. The chi-square goodness-of-fit test was used to determine how well the theoretical distribution (expected distribution extracted from CBS data) fits the empirical distribution found in the study population [20].The significance level for this study was set to 5%.

The same statistical method was used for the second analysis of birth order. The distribution of birth order (firstborn, middle, and youngest child) in the study population was compared to the distribution in the general Dutch population ages 12 to 17 using Pearson's chi-square goodness-of-fit test with a significance level $p<.05$. In the case of significant results, post hoc analysis was conducted to determine which categories deviate

significantly from expected proportions. The post hoc analysis was performed using a chi-square test for each category versus the sum of the other categories. The Bonferroni correction was used to correct for multiple comparisons, resulting in a significance level of p equals 0.017 (three categories).

Finally, firstborn, middle, and youngest children were compared in terms of BAC, as well as only children versus children with siblings. Multivariable regression was used with BAC as an independent variable. The dependent variables used were birth order (using dummy variables) and known covariates (sex, age, and educational level). Univariate analyses were used to determine differences in sex distribution, age, and educational level among firstborn, middle, and youngest children. For nominal variables, chi-square tests were used, and for continuous variables, independent-samples t-tests or analysis of variance (ANOVA) with post hoc Bonferroni was used.

CONFOUNDING FACTOR: RELIGION

Religion should be considered a confounding factor, as it may influence both the exposure variable (position in the family) and the outcome variable (admissions due to acute alcohol intoxication) indirectly. Therefore, religious differentials may interfere in the association between birth order and acute alcohol intoxication.

Table 2 Religious demographics Dutch population 15-18 [19]

Year	Religiously unaffiliated	Christian	Muslim	Other	Weight *n* = 3,997
2007	46.7%	36.9%	8.0%	5.7%	0.036
2008	47.8%	38.4%	8.2%	5.6%	0.047
2009	48.9%	37.1%	8.3%	5.7%	0.075
2010	49.0%	37.0%	9.0%	5.0%	0.094
2011	52.0%	35.0%	8.0%	5.0%	0.113
2012	53.0%	34.0%	8.0%	5.0%	0.091
2013	53.0%	32.0%	9.0%	6.0%	0.104
2014	55.0%	30.0%	9.0%	6.0%	0.131
2015	55.0%	31.0%	9.0%	5.0%	0.162
2016	56.7%	28.5%	9.1%	5.7%	0.079
2017[a]	57.8%	27.3%	9.2%	5.7%	0.068
Total	52.9%	32.9%	8.7%	5.5%	1.000

[a] Estimated using replacing missing value for trend at point

Religious differentials have been associated with differences in fertility rates expressed as the average number of children per woman [21]. The fertility rate is the highest among Muslims (2.1), followed by Christians (1.6) and the religiously unaffiliated (1.4) [22]. Therefore, religion is indirectly related to the proportion of adolescents being in the middle of

the birth order. Religion might also influence the outcome variable indirectly, because religious norms regarding alcohol use vary among different religions. Therefore, religiously unaffiliated adolescents might be overrepresented in the study population.

3. RESULTS

First, the results of the analysis on sibling status are presented. Second, the results of the analysis on birth order are discussed. Finally, the study population is compared to the general population in terms of religion.

DISTRIBUTION OF ABSENCE/PRESENCE OF SIBLINGS

In the study population, 160 (6.7%) adolescents were only child and 2,234 adolescents (93.3%) had siblings. Given the national statistics of the past 10 years, the expected proportion of being an only child in the general population ages 12 to 17 was 14.7%. These percentages are displayed in Figure 1.The results of the chi-square goodness-of-fit test are presented in Table 3. The test indicated that the proportion of adolescents who were only children was significantly lower in the study population than in the full Dutch adolescent population ($X^2(1, N = 2{,}394) = 124.60$, $p<.001$).

Figure 1. Sibling status

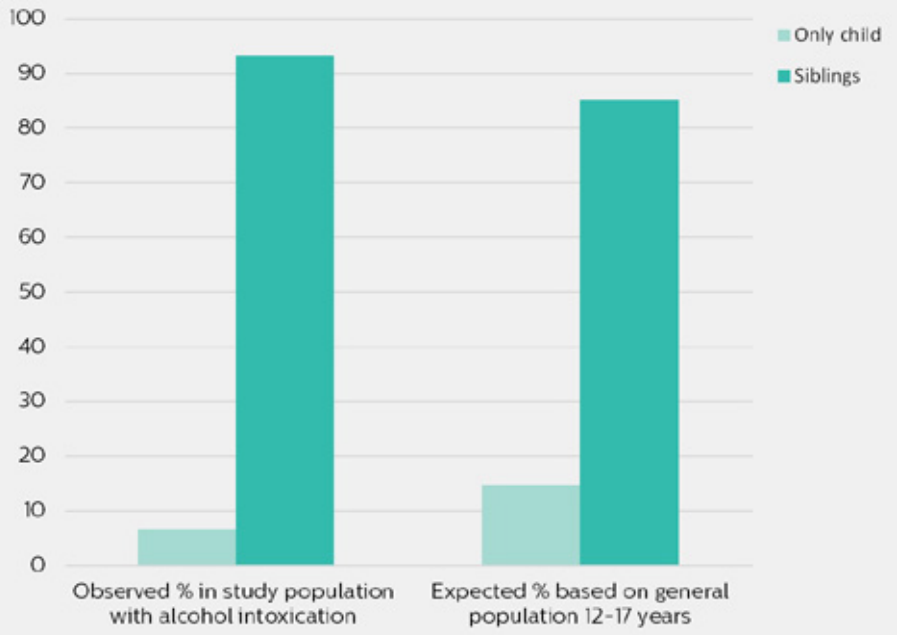


Table 3 Chi-square goodness-of-fit sibling status		
	Measured distribution Alcohol intoxication	Expected distribution General population
Only child	6.7% *(n = 160)*	14.8%
Siblings	93.3% *(n = 2,234)*	85.2%

The characteristics of acute alcohol intoxication are displayed in Table 4. An independent-sample t-test was conducted to compare average age between adolescents who had siblings and adolescents without siblings (p = 0.48). These results suggest that the presence of siblings is not associated with the average age at admittance. Chi-square tests indicated that both gender (p = 0.91) and distribution of educational level (p = 0.60) were equal among both groups. BAC was slightly higher among adolescents without siblings, but correction for known covariates (gender, age, and educational level) by multivariable regression analysis resulted in a non-significant association between BAC and sibling status (p = 0.09).

Table 4 Sibling status related to age, BAC, sex and educational level			
	Only child	**Siblings**	**p-value**
BAC g/L (SD)	1.91 (0.71)	1.87 (0.55)	0.09[a]
Age years (SD)	15.2 (1.2)	15.3 (1.2)	0.48[b]
Sex			
Male	51.8%	53.9%	0.091[c]
Female	48.2%	46.1%	
Educational level			
Low	48.3%	44.7%	0.060[c]
Middle	28.6%	29.7%	
High	23.2%	25.6%	

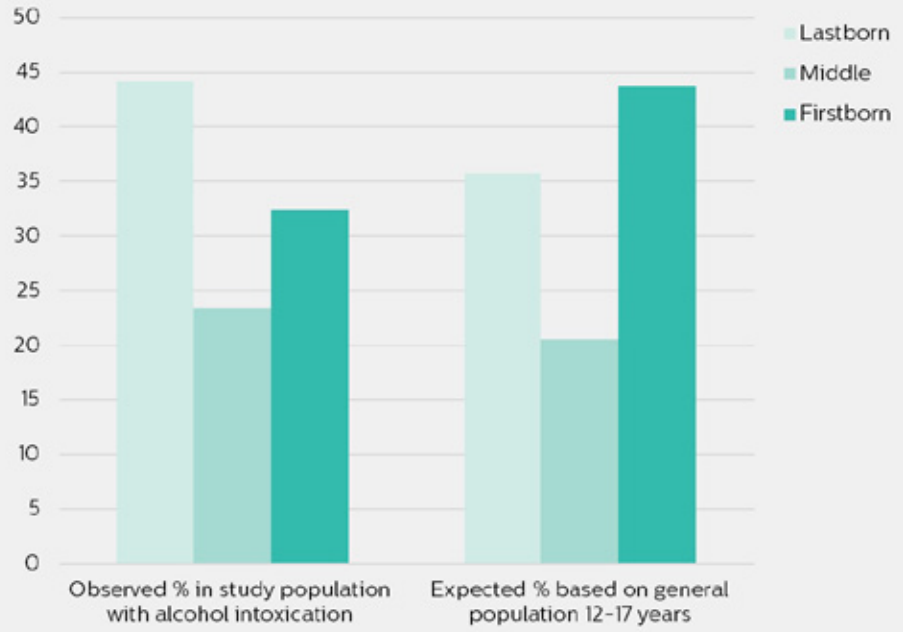
[a] Multivariable linear regression with correction for age, sex and educational level. [b] independent sample t-test. [c] Chi-square test

DISTRIBUTION OF BIRTH ORDER: FIRSTBORN, MIDDLE, LASTBORN

Of the 2,129 participants with siblings and known birth order, 689 (32.4%) were firstborn children, 498 (23.4%) were middle children, and 942 (44.2%) were youngest children. The expected proportions of firstborn, middle, and youngest children in the general Dutch adolescent population were derived from data of the Central Bureau of Statistics (Table 1). The expected distribution was 43.7% firstborn children, 20.6% middle children, and 35.8% youngest children. The expected distribution in the reference population and the observed distribution in the study population is displayed in Figure 2.

The results of the chi-square goodness-of-fit test are displayed in Table 5. The chi-square goodness-of-fit test indicated that the observed numbers of study participantswho were

Figure 2. Birth order



firstborn, middle, and youngest children were significantly different from the expected numbers according to the proportions found in the general population ($X2(2, N = 2,129) = 113.74$, $p<.001$). Post hoc analysis revealed that firstborn children were significantly underrepresented in the study population compared to the general Dutch population ages 12 to 17. The middle and youngest children in the family were overrepresented in the study population compared to the general Dutch population ages 12 to 17.

Table 5 Chi-square goodness-of-fit birth order

	Measured distribution Alcohol intoxication	Expected distribution General population	**p-value post hoc test**
Lastborn	44.2%	35.8%	p<0.001
Middle	23.4%	20.6%	p<0.001
Firstborn	32.4%	43.7%	p<0.001

Table 6 displays acute alcohol intoxication characteristics of firstborn, middle, and youngest children. Youngest children in the family were slightly younger (15.26 years) than firstborns (15.37 years), but one-way ANOVA indicated that average did was not significantly associated with birth order ($p = 0.14$). Chi-square test showed that the proportion of females was significantly higher in youngest children in the family than in middle children

and firstborn children (p = 0.023). Educational level did not differ significantly between the groups (p = 0.08). Multivariate regression showed that BAC, corrected for age, gender, and educational level, was not significantly associated with birth order (p = 0.65–0.87).

Table 6 Sibling status related to age, BAC, sex and educational level

	Lastborn	Middle	Firstborn	p-value
BAC g/L (SD)	1.88 (0.56)	1.87 (0.56)	1.87 (0.56)	L vs M = 0.87[a] M vs F = 0.65[a] F vs L = 0.73[a]
Age years (SD)	15.3 (1.2)	15.3 (1.2)	15.4 (1.1)	0.14[b]
Sex				
Male	48.1%	54.5%	53.9%	0.02[c]
Female	51.9%	45.5%	46.1%	
Educational level				
Low	50.9%	47.6%	44.7%	0.08[c]
Middle	28.8%	27.0%	29.7%	
High	20.2%	25.4%	25.6%	

[2a] Multivariable linear regression with correction for age, sex and educational level. [b] independent sample t-test. [c] Chi-square test. L = lastborn, M = middle child, F = firstborn

CONFOUNDING FACTORS: RELIGION

As mentioned in the methodology section, religion should be considered a confounding factor. Therefore, the proportion of adolescents with a Dutch background in the study population of adolescents with acute alcohol intoxication was compared to the proportion of adolescents with a Dutch background in the general population of Dutch adolescents. For this analysis, the entire database was used.

Table 7 Chi-square goodness-of-fit regligious distribution

	Religiously unaffiliated	Christian	Muslim	Other
Study population Alcohol intoxication	63.5%	27.1%	3.2%	6.2%
Reference population General population	52.9%	32.9%	8.7%	5.5%

In the general population of Dutch adolescents, 48.4% consider themselves religiously unaffiliated, 34.1% are Christian, and 8.6% are Muslim (Table 2). This distribution differs significantly from the study population of adolescents with acute alcohol intoxication ($X2(3, N = 3997) = 269.9, p<.001$). Religiously unaffiliated adolescents were overrepresented in the study population, and those who consider themselves to be Muslim or Christian were relatively underrepresented in the study population (Table 7).

4. DISCUSSION

This retrospective study expands on prior research on the effect of birth order on risky adolescent behavior by examining the relationship between birth order and admissions due to acute alcohol intoxication. Compared to the proportion in the general Dutch population of adolescents, the proportion of adolescents who were the oldest in the family is lower in the study population of adolescents with acute alcohol intoxication. This result is consistent with prior research on the association between birth order and risk-taking adolescent behavior as mentioned in the introduction.

Sex distribution was unequal among firstborn, middle, and youngest children admitted for acute alcohol intoxication. The proportion of girls was significantly higher among youngest children. This result suggests that girls might be more influenced by the presence of older siblings than boys are. This result is in line with prior research in which peer pressure was more positively associated with drinking in girls than in boys [23].

Although birth order had a significant effect on the number of admissions due to acute alcohol intoxication, the severity of intoxication measured by blood alcohol concentration did not differ significantly among firstborn, middle, and youngest children. Furthermore, age at admission did not differ among the groups. Youngest children in the family were not significantly younger than firstborns in case of admission. Similar results were seen in the analysis of sibling status. The proportion of adolescents who had siblings was significantly higher in the study population than in the general population. Differences in age and BAC were non-significant.

The results of this study should be considered in the context of certain limitations of the design. First, the presence of siblings and position in the family were known in approximately 40% of the cases. Missing data can be explained by the usage of various versions of the questionnaire. Questions about sibling status and position in the family were excluded in the online shortened version. Recall bias and response/nonresponse bias are unlikely, given the demographic nature of the questions. The low response rate can be compensated for by the strength of this study, which is the large number of patients included. The group was still sufficient in size to perform the analysis.

Second, this study did not examine the specific reasons why being an only child or being the firstborn child are protective factors. A possible explanation might be that firstborn children are raised more rigorously than their younger siblings. Prior research shows that certain parenting strategies, such as disapproval of adolescent drinking, general discipline,

and rules about alcohol, result in delayed alcohol initiation and reduced levels of later drinking by adolescents [24]. Hypothetically, being consistent in enforcing rules might be more difficult for younger siblings than for firstborn children. Furthermore, drinking by an older sibling (at legal age) can be imitated by younger siblings. Birth order is not significantly associated with blood alcohol concentration, because being a firstborn, middle, or younger child does not influence the exposure to social pressure from society to continue drinking once started.

The strength of this study is that religion as a possible confounding factor has been considered, as it may interfere with the association between birth order and acute alcohol intoxication. Certain factors, such as religion, influence family size and therefore the proportion of firstborn, middle, and youngest children. In the study population, religiously unaffiliated adolescents were overrepresented compared to the general Dutch population. Being religiously unaffiliated is associated with lower fertility rates, smaller families, and therefore a lower percentage of middle children. Instead, the results indicated that the percentage of middle children was higher in the study population than in the general Dutch adolescent population. Therefore, the association between birth order and acute alcohol intoxication might be underestimated in this study. Furthermore, relative underrepresentation of firstborn adolescents and overrepresentation of youngest children in the family cannot be explained by religion or other factors influencing family size and drinking norms.

5. CONCLUSION

Prior research indicated an association between birth order and risky behavior by adolescents. However, further research is needed to explore the relationship between birth order and admissions due to acute alcohol intoxication. This study shows that acute alcohol intoxication occurs more frequently in adolescents who have an older sibling. Therefore, being an only child or the firstborn child should be considered protective factors for acute alcohol intoxication. In contrast, middle and youngest children are at increased risk of acute alcohol intoxication.

6. PRACTICAL IMPLICATIONS

Making parents aware of differences between their children and targeting preventive strategies to those most at risk for acute alcohol intoxication may lead to a reduction in hospital admissions due to acute alcohol intoxication. Special attention should be given to girls with older siblings, as they are more influenced by the presence of older siblings than boys are.

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CHAPTER 4

Time of admission

Time of day as indicator of adolescent alcohol intoxication emergency department presentations

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RESEARCH LETTER

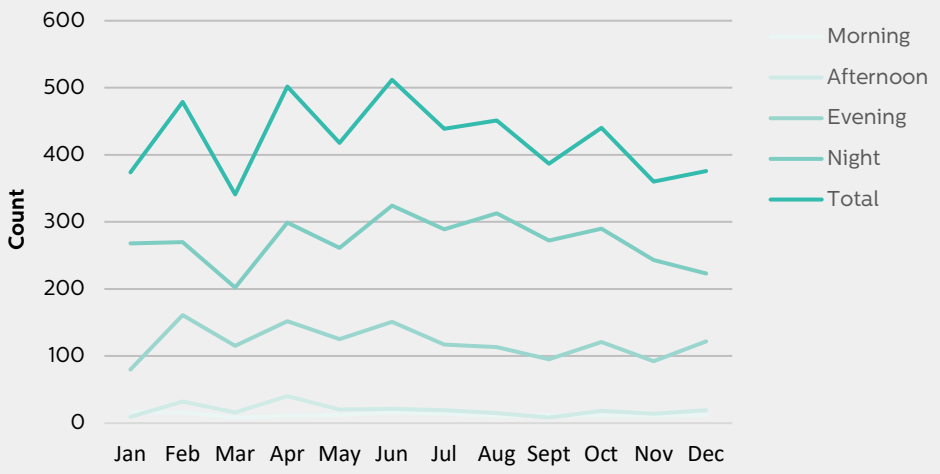
In line with other countries from wealthier parts of the world, the Netherlands show clear trends of less alcohol use and less binge drinking by youth since the millennium shift [1]. Contrary to these trends, the number of underage patients that are admitted to a hospital with alcohol intoxication characteristics, is an ongoing and stable health concern in the country [2].

Knowledge about what time of day patients are brought into the hospital, is important for the development of efficient prevention policies. The primary aim of this repeated cross-sectional study was to investigate how time of day variation (morning, afternoon, evening and night) was associated with patient and intoxication characteristics in Dutch adolescents admitted for alcohol intoxication. Furthermore, we also examined how alcohol intoxication hospital admission times trends developed between 2007 and 2017. In this repeated cross-sectional study the contents of 5,511 patient files were analysed.

During the data collection period (2007 – 2017), paediatric doctors reported cases of alcohol intoxication to the Dutch Paediatric Surveillance Unit (NSCK), a nationwide surveillance system, with around 95% participation grade. Time of day for admittance was one question on the questionnaire with four answering options: morning (6:00 – 11:59), afternoon (12:00 – 17:59), evening (18:00 – 23:59) and night (00:00 – 5:59).

Our study shows that adolescent hospital admissions for alcohol intoxication are most frequently seen during the night (64.6%), followed by evening (28.0%), afternoon (4.7%)

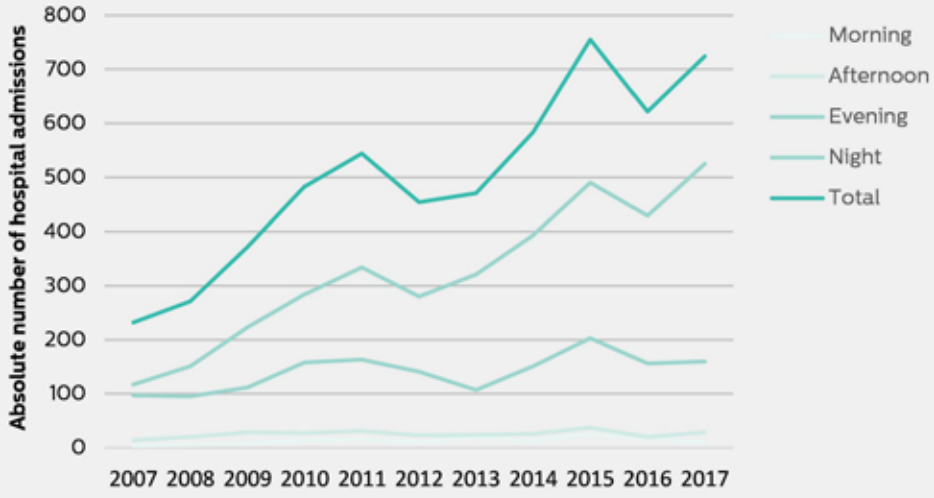
Figure 1. Time of year variation per month during 2007-2017



and morning (3.0%). This pattern is rather stable over the months, with a slight increase in the periods of warmer outdoor temperatures (April–August) as well as a peak in February (Figure 1).

Over the years (2007-2017) the number of admissions during the morning and afternoon is stable, but there was a strong increase in nighttime admissions, and a mild increase in evening admissions. The latter two time frames also caused an overall increase in alcohol intoxication treatments in the Netherlands in the decade from our data collection (Figure 2).

Figure 2. Trends in time of day variation in number of admissions



Our analyses further show that during morning and afternoon admission, the propensity for male patients is higher. Children from parents who disapprove alcohol consumption are most likely to drink at afternoons and evenings, while children who are (partially) allowed to drink have the biggest chance to end up in a hospital during nighttime (Table 1). The group who is admitted during afternoon hours turns out to be the youngest (Table 2).

Table 1 Hospital characteristics by admission time

	Morning	Afternoon	Evening	Night	p-value
Mean BAC g/L (SD)	1.87 (0.7)	1.86 (0.6)	1.90 (0.6)	1.92 (0.5)	0.24
Mean core temperature °C (SD)	35.9 (1.0)	35.8 (0.8)	35.7 (1.5)	35.7 (1.2)	0.69
Length of admission days (SD)	0.90 (1.0)	1.00 (0.5)	0.94 (0.5)	0.89 (0.6)	*<0.05*

Note: p-value calculated using one-way ANOVA

Table 2 Patient characteristics by admission time

	Morning	Afternoon	Evening	Night	p-value
Mean age years (SD)	15.9 (1.0)	14.8 (1.3)	14.9 (1.2)	15.6 (1.1)	*<0.001*^{F}
Sex					*<0.001*^{X2}
Male	63.2%$_{a}$	59.3%$_{a}$	49.6%$_{b}$	53.7%$_{a}$	
Female	36.8%$_{a}$	40.7%$_{a}$	50.4%$_{b}$	46.3%$_{a}$	
Residential area					*<0.001*^{X2}
High density (Randstad)	54.0%$_{a,b}$	55.8%$_{b}$	52.4%$_{b}$	47.3%$_{a}$	
Low density (Regio)	46.0%$_{a,b}$	44.2%$_{b}$	47.6%$_{b}$	52.7%$_{a}$	
Educational level					*<0.001*^{X2}
Low (VMBO)	53.7%$_{a,b,c}$	63.3%$_{c}$	52.8%$_{b}$	48.7%$_{a}$	
Middle (HAVO)	23.5%$_{a}$	15.3%$_{b}$	24.4%$_{a}$	25.7%$_{a}$	
High (VWO)	14.8%$_{a,b}$	16.5%$_{a,b}$	16.8%$_{b}$	20.1%$_{a,b}$	
Other*	8.1%$_{a}$	4.7%$_{a}$	5.9%$_{a}$	5.5%$_{a}$	
Season					*<0.001*^{X2}
Spring	20.1%$_{a,b}$	37.1%$_{c}$	28.6%$_{b}$	24.9%$_{b}$	
Summer	28.3%$_{a}$	21.9%$_{a}$	25.6%$_{a}$	28.2%$_{a}$	
Autum	21.4%$_{a,b}$	16.8%$_{b}$	21.6%$_{a,b}$	24.2%$_{a}$	
Winter	30.2%$_{a}$	24.2%$_{a}$	24.2%$_{a}$	23.8%$_{a}$	
Parental rule-setting					*<0.001*^{X2}
Zero-tolerance	44.4%$_{a}$	62.7%$_{b}$	66.2%$_{b}$	45.5%$_{a}$	
Partial permission	28.6%$_{a}$	21.7%$_{a,b}$	17.6%$_{b}$	24.9%$_{a}$	
Approval	27.0%$_{a}$	15.7%$_{b,c}$	16.2%$_{c}$	29.7%$_{a}$	
Reason of admission					*<0.001*^{X2}
Reduced conciousness	80.8%$_{a}$	88.3%$_{a,b}$	92.2%$_{a}$	86.6%$_{a}$	
Injury/accident	12.2%$_{a}$	7.5%$_{a}$	5.2%$_{b}$	9.3%$_{b}$	
Agression/violence	5.1%$_{a}$	1.3%$_{b}$	1.6%$_{b}$	3.0%$_{a,b}$	
Other**	1.9%$_{a}$	2.9%$_{a}$	1.0%$_{a,b}$	1.1%$_{a,b}$	
Place of consumption					*<0.001*^{X2}
At home	7.8%$_{a}$	10.9%$_{a}$	9.5%$_{a}$	9.6%$_{a}$	
House of others	42.2%$_{a,b}$	16.1%$_{c}$	37.4%$_{b}$	48.8%$_{a}$	
In the streers	13.0%$_{a}$	46.8%$_{b}$	34.9%$_{c}$	15.4%$_{a}$	
Public place (bar, etc)	22.7%$_{a}$	7.7%$_{b}$	8.1%$_{b}$	15.9%$_{c}$	
Other***	14.3%$_{a,b}$	18.5%$_{b}$	10.1%$_{a}$	10.3%$_{a}$	

F = one-way ANOVA, ^{X2} = chi-square test. Each subscript letter denotes a subset of time of day categories whose collumn proportions do not differ significantly form each other at p=0.05

* Defines as working, special-needs education or other, not further specified.
** Including suicide attempts, vomiting or miltiple reasons.
*** Including vacation, at work, at school and other's places

Prevention of adolescent alcohol intoxication in the Netherlands should be specifically targeted at adolescents at risk of nighttime admissions. Afternoon admissions require special attention as these adolescents were younger and more frequently showed rule-breaking behaviour. Future research will also focus on the possible role of national (holidays, carnival) and local (fairs) events in relationship to alcohol intoxication in minors.

Children from parents who disapprove alcohol consumption are most likely to drink at afternoons and evenings, while children who are (partially) allowed to drink have the biggest chance to end up in a hospital during nighttime (Table 2).

Prevention of adolescent alcohol intoxication in the Netherlands should be specifically targeted at adolescents at risk of nighttime admissions. Afternoon admissions require special attention as these adolescents were younger and more frequently showed rule-breaking behaviour. Future research will also focus on the possible role of national (holidays, carnival) and local (fairs) events in relationship to alcohol intoxication in minors.

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APPENDIX A: FULL MANUSCRIPT

Objective Adolescent alcohol consumption remains a substantial health concern. Knowledge about time of intoxication is important for the development of efficient prevention policies. The primary aim of this repeated cross-sectional study was to investigate how time of day variation (morning, afternoon, evening and night) was associated with patient characteristics in Dutch adolescents presented for alcohol intoxication. The study also examined how time trends in emergency department presentations developed between 2007 and 2017.

Design and study population This repeated cross-sectional study analyses data of 5,511 cases of alcohol intoxication reported to the Dutch Paediatric Surveillance Unit (NSCK), a nationwide surveillance system, between 2007 and 2017.

Results In the Netherlands, adolescent hospital emergency department presentations for alcohol intoxication are most frequently seen during the night (64.6%) and evening (28.0%). Time of day variation was associated with patient characteristics, such as education level, residential area and drinking location. Time trend analyses (2007-2017) indicated that a rapid increase in nighttime emergency department presentations specifically contributed to the absolute increase in hospital emergency department presentations for alcohol intoxication.

Conclusions Prevention of adolescent alcohol intoxication in the Netherlands should be specifically targeted at adolescents at risk of nighttime emergency department presentations. Afternoon emergency department presentations require special attention as these adolescents were younger and more frequently showed rule-breaking behaviour. .

Keywords*: adolescent, acute alcohol intoxication, time of admission*

1. INTRODUCTION

In line with other countries from wealthier parts of the world, the Netherlands show clear trends of less alcohol use and less binge drinking by youth since the millennium shift [1]. Contrary to these trends, the number of underage patients that are admitted to a hospital with alcohol intoxication characteristics, is an ongoing and stable health concern in the country [2].

It is of great importance to understand the underlying processes and patterns which encourage minors to consume alcohol and how they lead to alcohol intoxication. Binge drinking (defined as consuming ≥ 5 drinks per occasion for male and ≥ 4 drinks for female adolescents) has been identified the most common pattern of alcohol consumption among adolescents [3]. This binge pattern can lead to alcohol intoxication and significantly increase the risk of the development of alcohol use disorders in later life [4,5].

Underage alcohol consumption may not only lead to serious health issues for the consumer but may also have a great impact on society as a whole. Alcohol consumption among 10-24 year olds is the main cause of incident disability-adjusted life years in this age group [6]. Moreover, harmful personal and social consequences of adolescent alcohol consumption may include an increase in (violent) assault, risky sexual behaviour and mental health problems [7-11].

Several studies have reported demographic statistics on alcohol-related adolescent attendance of emergency departments [5, 12-18]. Studies performed in various countries show that time of day variation in adolescent alcohol intoxication is country specific. A study performed in a large inner city of northeast England showed that the majority of emergency presentations for alcohol intoxication presented in the early morning hours, with higher rates over the weekend [17]. Similar patterns have been described in Welsh children and adolescents, with a peak in emergency department presentations on Saturday (18). In other places, the vast majority of alcohol-related emergency department presentations were in the evening and nighttime [13-16]. Daytime drinking seems to be 'atypical' behaviour among adolescents in Western Europe [16], while a Polish study showed that the majority of emergency department presentations for alcohol intoxication were in the daytime [19]. In the Netherlands, the association between time of admission and the characteristics of patients presented for alcohol intoxication has not yet been explored.

It is of relevance to obtain knowledge of patterns of hospital admission in underage alcohol intoxication, as it can be used to inform a wide range of interventions aimed to prevent harmful behaviour among young people. Restrictions in temporal access to alcohol have proven to be useful in reducing alcohol-related hospitalisation rates among adolescents because they are more likely to show impulsive behaviour that enhances the spontaneous purchase of alcohol [20,21].

The primary aim of this repeated cross-sectional study is to explore at what time of day (morning, afternoon, evening, nighttime) Dutch adolescents present at emergency departments with alcohol intoxication and how the time of admission is related to key indicators such as age, sex, residential area, time of year (season), blood alcohol concentration (BAC), and mean core body temperature at admission. The secondary aim is to determine time trends in emergency department presentations between 2007 and 2017. Evaluation of the time of admission is of major importance in the development of primary preventive strategies for alcohol intoxication in the Netherlands.

2. METHODS

DATA COLLECTION

In order to explore the time of hospital admission in relation to other characteristics, a repeated cross-sectional study was conducted. We used data on adolescents presented with alcohol intoxication in the Netherlands that had been collected by the Dutch Paediatric Surveillance Unit (NSCK). All Dutch paediatricians were approached to participate in the reporting of underage alcohol intoxication to this system when a patient met the follow two inclusion criteria: blood alcohol concentration > 0.0 gram per litre and age younger than 18 years. This study includes patients in all stages of alcohol intoxication [22]. The data was collected using questionnaires filled in by the patient and the treatment team. The questionnaire includes questions in four different domains: general characteristics (sex, age, date and time of admission), demographic characteristics (post code, family structure, educational level), intoxication characteristics (admission reason, BAC, medical characteristics, location of consumption, parental consent, amount and type of alcohol, combined substance abuse, e.g. drugs) and substance use patterns (smoking, use of medication, age first use, previous incidents). Completing the anonymous questionnaire was voluntary. Specific medical and intoxication characteristics in the questionnaire are completed by paediatricians or paediatric nurses based on the patient's medical record.

MEASURES

In this study, time of hospital admission was the primary study variable. Time of admission was a categorical variable with four categories: morning (06:00–11:59), afternoon (12:00–17:59), evening (18:00–23:59) and nighttime (00:00–05:59) emergency department presentations. The additional variables assessed in this study were general characteristics (sex and age), educational level (low, middle, high), residential area (defined as high versus low population density area), season/year of admission, and blood alcohol concentration (BAC defined as g/l). Sex was defined as either male or female.

The parameter of residential area was defined as a categorical variable dividing patients into those living in a high population density area and those living in a lower density population area [23]. In this study, the first two numbers of the Dutch post code were used to determine whether the patient was living in a high density (post code ≤ 3999) or lower density (post code > 3999) area [24]. The categorical variable of season was derived from date of admission. Four categories were distinguished: spring (March–May), summer (June–August), autumn (September–November) and winter (December–February).

STUDY POPULATION

A total of 6,828 questionnaires were completed between 2007 and 2017. All patients included in the database had a positive blood alcohol concentration (BAC > 0.0 g/l). Patients with an unknown time of hospital admission (n = 1282), unknown sex (n = 25) or unknown age (n = 10) were excluded from the study, which resulted in a total of 5,511 adolescents included in this study.

DATA ANALYSIS

The data was analysed using SPSS for Windows, version 25 (IBM Corp., Armonk NY). Normality was assessed using the Kolmogorov-Smirnoff test. Frequencies were expressed as absolute numbers (N) and percentages. Continuous variables (mean age, BAC, core temperature and duration of admission) are presented as means with the standard deviation (SD). In order to establish the continuous variable of 'trend over time', a correlation ratio was determined using the beta-coefficient. In addition, a polynomial linear ANOVA test was used to investigate the trend. The effect of the categorical variables of age, sex, educational level and residential area were assessed using Pearson's chi-squared tests. A one-way ANOVA test was used to assess the continuous variable of blood alcohol concentration in relation to time of hospital admission. Outcomes with p-values < .05 were considered statistically significant.

CONSENT STATEMENT

The data collection started in 2007 and was approved by the medical ethical commission of the Faculty of Behavioral, Management and Social Sciences of the University of Twente and the ethical board of the Reinier de Graaf Gasthuis Hospital Group. The study procedure follows the Helsinki Declaration on human subjects and testing. Informed consent was provided by all adolescents. For patients younger than 16 years of age, additional parental consent was required.

3. RESULTS

GENERAL CHARACTERISTICS IN RELATION TO HOSPITAL ADMISSION TIME

Baseline characteristics were analysed by dividing the study population of 5,511 cases into four different subgroups based on hospital admission time. Demographic and intoxication characteristics were analysed and the different subgroups compared. The results of this analysis are displayed in Table 2. With a percentage of 64.4% (n = 3547), the majority of hospital emergency department presentations took place at night (between 00:00 and 05:59). A one-way ANOVA test analysing mean age on hospital admission showed significant age differences ($p < .05$) between subgroups, with a higher mean age (in years) among nighttime ($M = 15.61$) and early morning ($M = 15.88$) emergency department presentations in comparison to afternoon ($M = 14.80$) and evening ($M = 14.93$) emergency department presentations.

Chi-square tests with a post-hoc Bonferroni correction on sex, residential area, educational level and seasonal differences in relation to admission times were also conducted. Table 1 reveals a significantly higher proportion ($p < .001$) of males in morning (63.2%), afternoon (59.3%) and nighttime (53.7%) emergency department presentations, while a significantly higher proportion of females (50.4%) was found among evening emergency department presentations ($p < .001$). Moreover, the proportion of patients from high-density population areas was significantly higher among afternoon (55.8%) and evening (52.4%) emergency department presentations, in contrast to nighttime emergency department presentations, during which a significantly higher number of patients came from lower density areas (52.7%) ($p = .001$). Chi-square tests indicated that the time of emergency department presentation is significantly related to the season of emergency department presentation ($x2$ [$n = 5511$, $p < .001$]). Subgroup analysis showed that adolescents presented in the afternoon were significantly more frequently presented in spring, in comparison to nighttime and morning emergency department presentations. However, in both summer and winter, distribution throughout the day was equal.

A majority (50.7%) of the overall study population had a low educational level. Among afternoon emergency department presentations, a significantly higher percentage (63.3%, x2 [n = 150, p < .001]) of low educated patients was found. In the overall study population, 43.9% of participants consumed alcohol at the house of friends or acquaintances and 22% consumed alcohol in the streets. A significantly higher number of alcohol consumption in the streets was seen among afternoon emergency department presentations (46.8%, x2 [n = 116, p < .001]). A significant increase in alcohol consumption in commercial public places such as bars was observed among nighttime (15.9%, x2 [n = 120, p < .001]) and morning (22.7%, x2 [n = 142, p < .001]) emergency department presentations. Adolescents presented at night and in the evening were less frequently raised with strict alcohol-specific parental rule-setting than adolescents presented in morning or afternoon Adolescents presented at night or in the morning less frequently had strict alcohol-specific parental rule-setting than adolescents presented in the afternoon or evening (x2 [n = 2355, p < .001]).

HOSPITAL CHARACTERISTICS

Specific hospital characteristics at emergency department presentation were analysed and are displayed in Table 1. One-way ANOVA tests were used to analyse possible differences in mean blood alcohol concentration (g/L), mean temperature (°C) and mean length of hospital admission (days). Mean BAC (1.91 g/L; ANOVA, n = 4958, p = .237) and mean core temperature (35.7 °C; ANOVA, n = 2935, p = .685) did not differ significantly between the four different subgroups. Adolescents admitted at nighttime had a shorter hospital admission duration (0.89 days; ANOVA, n = 3205, p <.05).

TREND IN TIME – EMERGENCY DEPARTMENT PRESENTATIONS

Figure 1 displays the emergency department presentation numbers over the years, comparing the four different emergency department presentation time subgroups. A specific increase in emergency department presentation numbers between 2007 and 2017 can be seen in the nighttime emergency department presentation group, while emergency department presentation numbers in the remaining groups seem to increase at a slower pace or even to remain stable. Figure 2 displays proportional data rather than count data, which demonstrates that the increase in nighttime emergency department presentations is mainly attributable to a decline in evening emergency department presentations.

4. DISCUSSION

This repeated cross-sectional study was conducted to gain insight into the temporal variations in the emergency department presentation of adolescents for alcohol

intoxication in the Netherlands between 2007 and 2017. The majority of the study population (64%) was found to be presented at night (00:00–05:59), while the increase in hospital emergency department presentations for alcohol intoxication in the period between 2007 and 2017 was found to be mainly contributable to the rapid increase in nighttime emergency department presentations. A predominance of nighttime emergency department presentations has also been observed in Belgium [13] and Australia [15]. Our study found afternoon emergency department presentations to be unusual, with only 4.68% of the adolescents presented between 12:00 and 18:00, which is in line with a study performed in Germany [16]. This is in contrast to a study performed in Poland, where the majority of the alcohol-related hospital emergency department presentations took place during the day time [19]. Another recent study suggests that the time of day variation in emergency department presentations for alcohol intoxication might be related to the differences in endorsements of various alcohol control policies across European regions, with the highest level of support in the Nordic European regions and the lowest in the Eastern regions [25].

The growth of the total number of hospital emergency department presentations for alcohol intoxication during nighttime is a finding which should be taken into consideration in the development of paediatric emergency medicine training programs. In the Netherlands, paediatric residents provide the front line of patient care under supervision of a paediatrician. Therefore, paediatric residents should be, preferably simulation-based, trained in scenarios with adolescent alcohol intoxication with focus on Advanced Paediatric Life Support protocols and the systematic evaluation and re-evaluation of the patient following the ABCDE principles [26].

With respect to the prevention of nighttime emergency department presentations for alcohol intoxication, it is useful to determine patient characteristics of this subgroup. The study found that adolescents presented at night were more frequently male, consumed alcohol at a friend's home and were raised in the absence of alcohol-specific parental rule-setting. The overrepresentation of male adolescents in the nighttime emergency department presentation group might be related to previously described differences between the sexes; that is, males require greater quantities of alcohol to achieve intoxication than do females and males experience a lower blood alcohol concentration in comparison to their female counterparts when given a dose of ethanol that is proportionate to body weight [27,28]. Therefore, the time between the initiation of alcohol use and alcohol intoxication will most likely be longer for males in comparison to females, resulting in an overrepresentation of males in nighttime emergency department presentations.

Almost half of the adolescents presented at night reported drinking at the house of friends or acquaintances. Drinking location has been identified as an indicator of potential alcohol-related harm [29,30]. In order to prevent recidivism in the group of nighttime emergency department presentations, it is important to inform parents that alcohol-specific rule-setting and disapproval of adolescent alcohol consumption have been associated with lower quantities of alcohol use [31–36].

Although the group of adolescents presented in the afternoon was relatively small (4.68%), it is important to realise that this group has various unique characteristics in comparison to the other groups. They include a lower educational level, relatively frequently drinking on the street, being younger and showing rule-breaking behaviour. The overrepresentation of a lower educational level in afternoon emergency department presentations might be related to a higher prevalence of truancy among adolescents in pre-vocational education versus adolescents at higher educational levels [37]. Especially for this subgroup, appropriate outpatient follow-up is important, as all the characteristics – a younger age [38–40], showing rule-breaking behaviour [41] and drinking on the streets [29,30] – have been associated with higher quantities of alcohol use later in life.

Over recent years, the Dutch government has invested in several national media educational campaigns and prevention programmes aiming to lower adolescent alcohol consumption and the overall acceptability of underage drinking [42]. Additionally, the minimum legal age for alcohol purchase in the Netherlands was increased from 16 to 18 years in 2014. Since then, compliance rates among Dutch alcohol vendors with the alcohol age limit policy have increased, and a rise in mean age at emergency department presentation has been noted, from 14.9 years (SD 0.18) in 2007 to 15.5 years (SD 1.10) in 2016 [39,40]. Moreover, the change in the law appears to have also positively affected the attitude of Dutch parents concerning alcohol consumption by their offspring.

While the numbers of morning, afternoon and evening emergency department presentations tend to show a minor increase or even to remain stable, the number of nighttime emergency department presentations showed evidently steeper growth. This is an interesting finding, and it could be hypothesised that a move towards a later start to social events in the evening is a contributing factor. Moreover, a decrease in parental control at night and an increase in mean age at emergency department presentation over the years could contribute to this finding [43]. However, further investigation of time trends is necessary to explore cognitive and behavioural factors in adolescent alcohol consumption over the years.

During the data collection via the Dutch Paediatric Surveillance Unit (NSCK) (2007 - 2017), we have reflected on the reliability of the data collection. Some measures on the questionnaires might suffer from under reporting, such as prior substance use patterns or illicit drug use not tested in the standard urine toxicology screening. Other measures are indicative and not exact, such as the duration of reduced consciousness [44]. In the ten years of the data collection, the questionnaire was expanded once (with some extra questions about alcohol-specific parental rule-setting), the other parts of the instrument were not changed. Based on the registration of other diseases that were included in the NSCK system over the years, we think that it is fair to say that the reliability is good. Over the years, the participation from Dutch paediatricians was stable around 90% [45]. Possible bias related to self-reported data are also stable over the years, and are not relevant for the conclusions from this report.

5. CONCLUSION

A better understanding of the relationship between specific characteristics and time of emergency department presentation derived from this study can be used in daily clinical practice by paediatricians and other health care workers dealing with underage alcohol in emergency and/or outpatient settings. Moreover, and perhaps even more important, the results offer evidence-based support in composing and optimising governmental policies designed to regulate and prevent underage alcohol consumption. Educational programmes for Dutch secondary school students and their parents designed to teach them about the harmful effects of alcohol and the risk factors might also be adapted depending on characteristics of the different target groups.

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CHAPTER 5

Parental rule-setting

Trends in Alcohol-specific Parental Rule-setting among Dutch Adolescents admitted for acute Alcohol Intoxication

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ABSTRACT

Background The role of alcohol-specific parental rule-setting among Dutch adolescents admitted for acute alcohol intoxication has not previously been studied. The primary aim of this study is to explore how alcohol-specific parental rule-setting develops over time between 2011 and 2017, and how this relates to alcohol intoxication characteristics.

Methods A repeated cross-sectional study was conducted using seven years (2011-2017) of data collected by the Dutch Paediatric Surveillance Unit (NSCK), compromising 5,207 alcohol-related emergency hospital admissions in adolescents aged 10 to 17 years in the Netherlands. Time trends in alcohol-specific parental rule-setting (zero-tolerance towards alcohol use, partial permission, full permission) were explored by multivariate logistic regression analyses, controlled for confounding factors such as sex, age, educational level, ethnicity and family structure.

Results Among adolescents admitted for acute alcohol intoxication, the use of a zero-tolerance alcohol-specific parenting strategy increased significantly between 2011 and 2017, while the absence of alcohol-specific parental rule-setting decreased significantly between 2011 and 2017. Zero-tolerance alcohol-specific parental rule-setting was associated with an older age at first alcohol use and a lower number of alcoholic units consumed per day on weekends. Absence of alcohol-specific parental rule-setting was associated with higher odds for tobacco use.

Conclusions This study demonstrates that zero-tolerance parental rule-setting is the most effective in prevention of adolescent alcohol use in early adolescence. Addressing alcohol-specific parental rule-setting is especially important in subgroups with a low prevalence of zero-tolerance, namely adolescents between 15-18 years of age and adolescents with a native Dutch ethnicity.

Keywords*: Adolescence, alcohol intoxication, alcohol-specific parental rule-setting*

1. INTRODUCTION

BACKGROUND

In recent decades, the proportion of non-drinking adolescents has increased in many countries, for example in the United States [1], Australia [2]. and the United Kingdom [3]. In Europe, temporal trends among 15 to 16-year-old students indicate an overall decrease in lifetime and last-30-day use of alcohol between 1995 and 2015, from 89% to 81% and from 56% to 47%, respectively [4]. The prevalence of lifetime alcohol use has decreased sharply in, for example, Iceland, Ireland, the Netherlands, Norway and Sweden [4]. In most of these studies, rates of abstention were found consistently across a wide range of population subgroups defined by demographic, socioeconomic and regional factors.

Despite the increasing proportion of non-drinking adolescents, adolescent alcohol use remains an issue of concern. Cohort studies performed in several countries show an increasing trend in emergency department presentations as well as admissions for acute alcohol intoxication [5–7]. In many countries, alcohol-related concerns have provoked debate focusing on the postponement of the moment of first alcohol use (age of onset) and minimising the negative consequences of adolescent alcohol use. For example, national alcohol policy in Australia [8], the United States (Substance Abuse and Mental Health Services [9] and the Netherlands [10] has gradually changed from harm-minimisation to zero-tolerance strategies. This change implies a switch from measures that focus on prevention of excessive alcohol use to measures against all underage alcohol use (zero-tolerance).

From an international perspective, studying trends in adolescent alcohol use in the Netherlands offers an important case study, as time trends in adolescent alcohol use in the country show paradoxical results. The results from repeated cross-sectional school surveys showed that adolescent alcohol use increased substantially between 1992 and 2003, but decreased sharply thereafter [11]. However, during the last decade, among adolescents who consumed alcohol in the last month, the prevalence of binge drinking did not show a significantly decreasing trend and ranged from 63.7% in 2003 to 72.0% in 2017 [12]. Furthermore, during the last decade, the Dutch Paediatric Surveillance Unit (NSCK) has signalled a rising trend in alcohol-related hospital admissions to Dutch paediatric departments [7]. Trend analyses in patient characteristics of adolescents show that a significant increase in adolescent age, but other parameters such as sex composition, cultural background, educational level and reason of hospital admission remained stable over the last decade.

This rising trend in hospital admissions for acute alcohol intoxication prompted political debate and eventually resulted in the transformation of national alcohol policy from harm-minimisation to zero-tolerance [10]. In 2014, the minimum legal age for the purchase and consumption of alcohol was increased to 18 for all alcoholic beverages. The government also launched a multimedia awareness campaign known as 'NIX 18' (Under 18. No alcohol) to promote the social norm of delaying first alcohol use among adolescents and their parents. At the same time, new legislation was introduced that included higher fines for underage alcohol sales and fines for underage public drinking and alcohol possession. In 2018, a comprehensive strategy (Dutch National Preventive Agreement) was established by the Ministry of Health, Welfare and Sport, with over 70 organizations (including educational, health and commercial institutions) committing to the agreement. A similar shift in national preventive strategies has been observed in other countries, for example in Australia [8] and the United States [9].

The decline in adolescent alcohol use in the Netherlands should be interpreted in this broader context of internationally changing sociocultural norms and the development of national prevention programs. All of these measures might have encouraged stricter parenting behaviours [12–15]. The phenomenal decrease in adolescent alcohol use since 2003 appears to coincide with a substantial increase in strict alcohol-specific parental rule-setting [11] Family factors have been identified as important, having a modifiable influence on adolescent alcohol use [16,17].

Prior longitudinal studies regarding the association between parental alcohol rules and adolescent risky drinking are conflicting. Some longitudinal studies show that approval or permissiveness of alcohol use is associated with a higher likelihood of risky drinking in adolescence [18,19]. This is in line with two cross-sectional studies that show that strict parental rules with a lower likelihood of risky drinking [20,21]. In contrast, other studies show that adolescents are less likely to be involved in risky drinking when they are permitted to drink alcohol at home [22,23]. A recent systematic review and meta-analysis have suggested that parental rules concerning alcohol use may decrease the odds of risky drinking later in life [24].

Alcohol-specific parental rule-setting among Dutch adolescents admitted for acute alcohol intoxication has not previously been studied. Studying the association between alcohol-specific parental rule-setting and acute alcohol intoxication characteristics is important, as the shift seen in the Dutch society might have impact on the characteristics of adolescents admitted for acute alcohol intoxication and on outcome measures of

acute alcohol intoxication. The primary aim of the current study was to explore how alcohol-specific parental rule-setting develops over time and to determine whether these time trends are specific to various sociodemographic subgroups. The secondary aim was to determine whether alcohol-specific parental rule-setting is related to acute alcohol intoxication characteristics (blood alcohol concentration, percentage of combined drug use, drinking location) and characteristics of prior substance use patterns (age at first alcohol use, mean alcohol consumption and tobacco use).

2. MATERIALS AND METHODS

STUDY DESIGN, STUDY POPULATION AND DATA COLLECTION

A repeated cross-sectional study was conducted using seven years (2011-2017) of data collected by the Dutch Paediatric Surveillance Unit, compromising 5,207 alcohol-related emergency hospital admissions in adolescents aged 10 to 17 years in the Netherlands. Each year, the Dutch Paediatric Surveillance Unit collects data for research purposes on a maximum of 12 predetermined diseases in childhood, including infectious diseases, genetic diseases, non-communicable diseases, childhood injuries and mental health conditions. Paediatricians who notified a case were sent the link to a case report form requesting de-identified demographic, clinical laboratory, treatment and outcome data on the case. In 2007, adolescent alcohol-related emergency hospital admissions were added to the system according to the following inclusion criteria: a positive blood alcohol concentration (BAC > 0.0) and age between 10 and 18 years. In the current analysis, recidivists were excluded from analyses.

Data collection started in 2007 and was approved by the medical ethical committee in 2007. The study procedure followed the guidelines of the Helsinki Declaration on research on human subjects. Report to the surveillance system requires informed consent, with additional parental consent required for adolescents younger than 16 years of age. The paediatrician who reports the case is responsible for data collection in three categories: sociodemographic characteristics, intoxication characteristics and substance use patterns. A fourth category, alcohol-specific parental rule-setting, was included in 2011. Therefore, the cases included in this study are from the period 2011-2017. The case report form was completed by the paediatrician, paediatric resident or nurse at the moment of discharge of the alcohol-related hospital admissions and was based on a standardized interview with adolescents (sometimes accompanied by parents) and laboratory results. During the period 2011-2017, a total of 5,207 alcohol-related hospital admissions were reported to the surveillance system. Out of these 5,207 reported hospital admissions,

the mean response rate was 88.7% for demographic variables, 66.0% for intoxication variables, 66.4% for prior substance use patterns and 50.3% for alcohol-specific parental rule-setting. The discrepancy between the response rate of the sociodemographic characteristics and the other sections is most likely related to available time during weekend shifts.

MEASURES

Alcohol-specific parental rule-setting

Alcohol-specific parental rule-setting was defined as a categorical variable with three categories, based on the following question during medical interview: 'How do you define the alcohol-specific parental rule-setting?' Answer A: 'I am not allowed to drink alcohol at all/I have strict parental alcohol rules' (zero-tolerance policy). Answer B: 'There are alcohol-specific parental rules/I have permission to drink alcohol on certain occasions' (partial permission). Answer C: 'I don't have parental alcohol rules/my parents approve alcohol consumption' (approval of adolescent alcohol use). For the statistical analyses, dummy variables were created.

Sociodemographic characteristics

The following variables were considered as subgroups: age, sex, educational level, ethnicity and family structure. To determine whether time trends in alcohol-specific rule-setting were specific to age groups, the discrete variable for age in years was recoded into a categorical variable with three categories: ≤ 14 years of age, 15-16 years, and 17-18 years. Sex was defined as a dichotomous variable: male or female. Educational level was a categorical variable with three categories: low, middle and high. The subdivision was based on the Dutch secondary school system. Pre-vocational education was defined as low; senior general secondary education was defined as middle; and pre-university education was defined as high. The variable of ethnicity was based on two subgroups: native Dutch and other ethnic background (first or second generation immigrant). Family structure was a categorical variable with two categories: traditional family structure (biological mother and biological father) and non-traditional family structure (pooled from various categories, such as divorced, single parent, foster care).

Intoxication characteristics and substance use patterns

The secondary aim of this study was to determine whether alcohol-specific parental rule-setting is related to intoxication characteristics, blood alcohol concentration, combined illicit drug use and drinking location. Blood alcohol concentration was defined as a continuous variable expressed in g/L. Combined illicit drug use was defined as a

categorical variable with two categories: positive urine drug screening or negative urine drug screening. Drinking location was also defined using two categories: private area (e.g. at home or at someone else's home) or public area (e.g. bar, restaurant, on the street).

Substance use patterns were explored based on three variables: tobacco use, age at first alcohol use and mean alcohol consumption per day on the weekend. Tobacco use was defined as a dichotomous variable: smoking or non-smoking. Age at first alcohol use was defined as a continuous variable. Mean alcohol consumption per day on the weekend was defined as the mean number of units consumed on Saturday and Sunday. An alcoholic unit was defined as 1 standard drink.

DATA ANALYSES

Firstly, time trends in alcohol-specific parental rule-setting were displayed in a figure by determination of a three-year moving average. The frequencies and proportion per alcohol-specific parental rule-setting category were determined. Three multivariate logistic regression analyses were run, with one of the alcohol-specific parental rule-settings as dependent variable (dummy variable to make it dichotomous) and survey year, age, sex, educational level, ethnicity and family structure as independent variables. Therefore, time trends were corrected for possible changes in population composition.

To determine whether time trends in alcohol-specific parental rule-setting differed across subgroups, descriptive statistics were used to determine the prevalence of zero-tolerance rule-setting, partial permission and approval of adolescent alcohol use among various demographic subgroups. Due to multiple testing, for each category of alcohol-specific parental rule-setting, a stricter significance level of $p < .001$ was applied. To determine whether differences in time trends were statistically significant, interaction analyses, with the interaction term of demographic factor*survey year, were performed. In these analyses, survey year was included as a continuous variable because using dummies would have resulted in a large number of interaction terms, which increases the risk of overfitting the model.

Secondly, to determine whether alcohol-specific parental rule-setting was associated with intoxication characteristics and substance use patterns, multiple multivariate regression analyses were performed. Multivariate linear regression was performed for the continuous variables (blood alcohol concentration, age at first alcohol use and number of alcoholic units consumed per day on the weekend), while multivariate logistic regression was performed for the dichotomous variables (tobacco use, illicit drug use and drinking location).

3. RESULTS

OVERALL TIME TRENDS IN ALCOHOL-SPECIFIC PARENTAL RULE-SETTING

The characteristics of the study population are displayed in Table 1. Among Dutch adolescents admitted for acute alcohol intoxication, alcohol-specific parental rule-setting changed during the period 2011-2017, as displayed in Table 2. The rising trend in zero-tolerance rule-setting was largely attributable to the decrease in adolescents with parental approval of adolescent alcohol use. Approval of adolescent alcohol use decreased from 68.2% in 2011 (CI 59.4%-75.9%) to 11.4% in 2017 (CI 9.1%-14.2%). Since 2014, in particular, partial permission has been showing an increasing trend. The time trends have been depicted as three-year moving averages in Figure 1. Multivariate logistic regression analyses indicate that rising trends in zero-tolerance rule-setting and partial permission, and the declining trend in parental approval of adolescent alcohol use remain significant after controlling for age group, sex, educational level, ethnicity and family structure.

Table 1 Descriptive statistics of study population by survey year, NSCK 2011-2017

	2011	2012	2013	2014	2015	2016	2017
Sex							
% Male	59.2	57.2	55.0	49.9	53.2	52.1	55.9
Age group							
% ≤ 14 years	20.8	15.4	13.9	25.2	23.7	18.0	20.8
% 15-16 years	60.0	55.4	64.8	55.3	57.2	60.2	58.2
1% 7-18 years	19.2	29.2	21.3	19.5	19.1	21.8	22.3
Educational level							
% Low (VMBO)	48.8	56.0	47.0	48.2	44.7	44.6	43.8
% Middle (HAVO)	29.8	27.3	30.9	31.8	31.0	29.3	32.5
% High (VWO)	21.4	16.7	22.1	20.0	24.3	26.0	23.8
Ethnicity							
% Non-native Dutch	12.3	6.7	5.4	7.2	12.5	11.2	10.4
Family structure							
% Not living with both parents	32.4	35.7	37.3	36.5	39.0	33.2	37.3
Reason of admission							
% Reduced conciousness	89.7	89.1	87.3	89.7	87.7	85.4	89.4
% Injury/accident	4.8	3.6	3.9	6.3	5.1	6.0	4.5
% Other	5.8	7.3	8.8	4.0	7.2	8.6	6.1
BAC							
% 0.1 - 0.9 g/L	3.4	3.9	5.8	1.5	3.4	1.5	2.9
% 1.0 - 1.9 g/L	55.5	47.8	51.6	43.3	49.1	40.9	41.7
% 2.0 - 2.9 g/L	37.0	43.8	39.1	51.1	44.7	55.4	53.0
% 3.0 g/L	4.2	4.5	3.6	2.1	2.8	2.2	2.4
Smoking status							
% Smoking	26.7	30.8	24.4	24.9	18.7	18.8	16.1
Illicit drug use							
% Positive drug screening	6.5	14.1	16.2	13.1	9.8	14.0	12.3

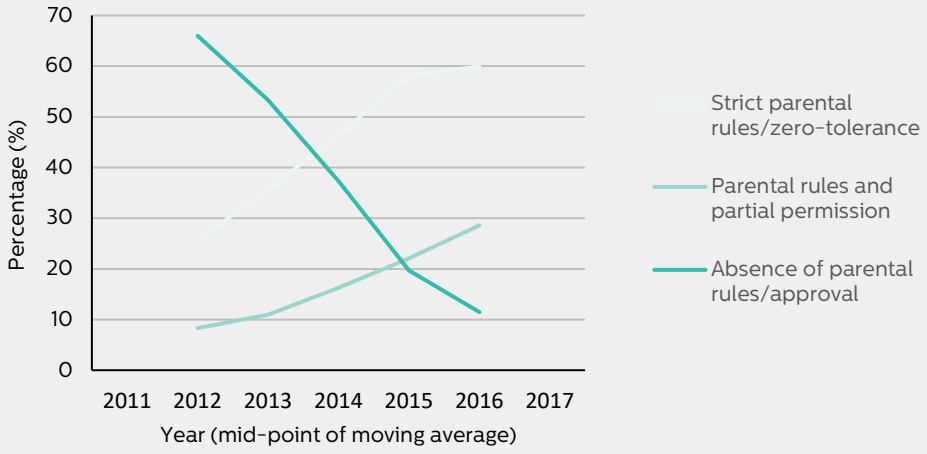
Table 2 Trends in proportion (%) parental rule-setting, NSCK 2011-2017

	2011	2012	2013	2014	2015	2016	2017	Trend
Zero-tolerane policy	25.8	20.5	30.7	49.7	58.9	66.0	54.8	*p*<.001
Partial permission	6.1	12.3	6.6	14.2	28.1	23.9	33.8	p<.001
Parental approval	68.2	67.2	62.7	36.1	13.0	10.1	11.4	*p*<.001

Note: trend analyses were corrected for sex, age group, educational level, family structure and ethnicity

The proportion of adolescents with zero-tolerance rule-setting increased from 25.8% in 2011 (CI 18.7%-34.2%) to 54.8% in 2017 (CI 50.9%-58.8%). The rising trend in zero-tolerance rule-setting was largely attributable to the decrease in adolescents with parental approval of adolescent alcohol use. Approval of adolescent alcohol use decreased from 68.2% in 2011 (CI 59.4%-75.9%) to 11.4% in 2017 (CI 9.1%-14.2%). Since 2014, in particular, partial permission has been showing an increasing trend. The time trends have been depicted as three-year moving averages in Figure 1. Multivariate logistic regression analyses indicate that rising trends in zero-tolerance rule-setting and partial permission, and the declining trend in parental approval of adolescent alcohol use remain significant after controlling for age group, sex, educational level, ethnicity and family structure.

Figure 1. Three-year moving average of alcohol-specific parental rule-setting, NSCK 2011-2017



SUBGROUP-SPECIFIC TRENDS IN PARENTAL RULE-SETTING

Table 3 (and appendix A) indicate whether the observed trends in alcohol use differed according to adolescent sex, age, educational level, ethnicity and family structure.

Alcohol-specific parental rule-setting differed among the three age subgroups. The proportion of adolescents with zero-tolerance alcohol-specific parental rule-setting was significantly lower among the subgroups of 15-16 year olds (OR 0.23, p < .001) and 17-18 year olds (OR 0.09, p < .001). Adolescents in the subgroups of 15-16 year olds (OR 6.58, p < .001) and 17-18 year olds (46.51, p < .001) more frequently had parental approval for adolescent alcohol use, compared to the subgroup of 14 years and younger. There was a significant interaction effect for partial permission among 15-16 year olds (OR 1.37, p < .001) and 17-18 year olds (OR 2.05, p < .001), indicating that among these subgroups the proportion of partial permission increased more than among the subgroup of 14 years and younger.

Table 3 suggests that female adolescents are more frequently raised with stricter alcohol-specific parental rule-setting than are male adolescents. The odds ratios suggest that female adolescents more frequently have partial permission than do male adolescents (OR 1.71, p = .22) and that female adolescents (OR 0.55, p = .11) are less frequently raised with parental approval for adolescent alcohol use than are male adolescents. However, the difference in alcohol-specific rule-setting was not significant. In both female and male patients, zero-tolerance policy and partial permission showed an increasing trend, while parental approval of adolescent alcohol use showed a decreasing trend. The interaction-terms for sex*survey year were not significant, indicating that trends developed in a similar way for female and male adolescents.

At all educational levels, zero-tolerance parental rule-setting and partial permission showed increasing trends, while approval of adolescent alcohol use showed a decreasing trend. Educational level was not significantly related to alcohol-specific parental rule-setting. Interaction analyses indicated that trends in alcohol-specific parental rule-setting did not vary among different educational levels.

Among native Dutch adolescents, a rising trend in zero-tolerance policy and partial permission was observed, while the trends were not significant in adolescents from other ethnic backgrounds. The absence of a rising trend in zero tolerance among adolescents from a non-native Dutch ethnic background can be explained by the relatively high prevalence of zero tolerance in the initial years (53.5% in 2011 and 41.7% in 2012). The results of the multivariate logistic regression analyses indicate that adolescents from other ethnic backgrounds are more frequently raised with zero-tolerance alcohol-specific parental rule-setting than native Dutch adolescents (OR 3.86, p < .001). Furthermore, adolescents with an ethnic background other than native Dutch are less frequently raised with approval for adolescent alcohol use (OR 0.13, p < .001) than are native Dutch.

Table 3 Results interaction analyses of time x sociodemographic subgroup of parental rule-setting, NSCK 2011-2017

	Zero tolerance OR	Partial permission OR	Parental approval OR
Main effect			
Sex			
Male (ref)	1.00	1.00	1.00
Female	1.00 (0.52-1.90)	1.71 (0.73-4.00)	0.55 (0.26-1.13)
Age group			
14 years (ref)	1.00	1.00	1.00
15-16 years	0.23 (0.10-0.52)**	0.37 (0.14-1.02)	6.58 (2.34-18.49)**
17-18 years	0.09 (0.03-0.29)**	0.04 (0.01-0.23)**	46.51 (11.24-192.51)**
Educational level			
Low (VMBO) (ref)	1.00	1.00	1.00
Middle (HAVO)	1.23 (0.61-2.73)	0.77 (0.28-2.10)	0.96 (0.41-3.24)
High (VWO)	1.08 (0.47-2.53)	0.94 (0.31-2.83)	1.14 (0.43-3.03)
Ethnicity			
Native Dutch (ref)	1.00	1.00	1.00
Non-native Dutch	3.86 (1.18-12.58)*	2.18 (0.52-9.09)	0.13 (0.03-0.55)**
Family structure			
Traditional family structure (ref)	1.00	1.00	1.00
Not living with both parents	1.01 (0.50-2.03)	1.24 (0.51-3.03)	1.09 (0.49-2.45)
Interaction effects			
Sex * survey year			
Male (ref)	1.00	1.00	1.00
Female	1.04 (0.92-1.18)	0.86 (0.74-1.00)	1.16 (1.00-1.36)
Age group * survey year			
14 years (ref)	1.00	1.00	1.00
15-16 years	1.01 (0.86-1.18)	1.37 (1.13-1.65)**	0.99 (0.77-1.26)
17-18 years	1.06 (0.86-1.32)	2.05 (1.53-2.75)**	0.75 (0.55-1.03)
Educational level * survey year			
Low (VMBO) (ref)	1.00	1.00	1.00
Middle (HAVO)	0.95 (0.82-1.09)	1.04 (0.87-1.25)	1.04 (0.87-1.25)
High (VWO)	0.98 (0.83-1.14)	1.02 (0.84-1.24)	0.98 (0.80-1.20)
Ethnicity * survey year			
Native Dutch (ref)	1.00	1.00	1.00
Non-native Dutch	0.91 (0.74-1.14)	0.81 (0.63-1.05)	1.21 (0.89-1.65)
Family structure * survey year			
Traditional family structure (ref)	1.00	1.00	1.00
Not living with both parents	1.00 (0.88-1.14)	0.97 (0.83-1.14)	0.96 (0.81-1.14)

Note: analyses were corrected for sociodemographic characteristics (sex, age group, educational level, family structure and ethnicity). *p<0.01 **p<.0001

In both adolescents with a traditional family structure and adolescents with a non-traditional family structure, the proportion being raised with zero-tolerance alcohol-specific parental rule-setting showed an increasing trend. The odds ratios in the multivariate logistic regression analyses suggest that adolescents with a non-traditional family structure are slightly more frequently raised with partial permission for adolescent

alcohol consumption (OR 1.24, p = .64) or with parental approval for adolescent alcohol use than are adolescents with a traditional family structure (OR 1.09, p = .83), but these differences were not significant.

CORRELATIONS

The results of the analyses investigating the relationship between alcohol-specific parental rule-setting and intoxication characteristics are displayed in Table 3. Linear regression indicated that alcohol-specific parental rule-setting was not significantly related to the mean blood alcohol concentration of adolescents admitted for acute alcohol intoxication.

Table 3 Intoxication charachteristics and substance use patterns among parental rule-setting subgroups, NSCK 2011-2017

	2011-2017	*n*	Beta	p-value
Blood alcohol concentration (BAC)		2451		
Zero-tolerance (ref)	1.95 g/L			
Partial permission	1.97 g/L		-0.010 g/L	p=0.76
Parental approval	1.99 g/L		-0.007 g/L	p=0.82
Age at first alcohol use		2227		
Zero-tolerance (ref)	14.4 years		-0.15 years	p=0.02
Partial permission	14.6 years		-0.28 years	p<0.001
Parental approval	14.6 years			
Units alcohol consumption weekend		1678		
Zero-tolerance (ref)	1.6 units/day		=0.9 units/day	p<0.001
Partial permission	2.8 units/day		+2.1 units/day	p<0.001
Parental approval	4.0 units/day			
Percentage tobacco usage		2466		
Zero-tolerance (ref)	17.5%		OR 1.00	
Partial permission	19.8%		OR 1.01	p=0.84
Parental approval	27.9%		OR 1.59	p=0.003
Percentage positive urine drug test		2488		
Zero-tolerance (ref)	11.8%		OR 1.00	
Partial permission	14.0%		OR 1.10	p=0.63
Parental approval	12.2%		OR 0.99	p=0.96
Public drinking lodation		2425		
Zero-tolerance (ref)	42.8%		OR 1.00	
Partial permission	35.3%		OR 0.82	p=0.10
Parental approval	34.5%		OR 0.78	p=0.04

Note: analyses were corrected for sociodemographic characteristics (sex, age group, educational level, family structure and ethnicity).

However, alcohol-specific parental rule-setting was significantly related to mean age at first alcohol use. Adolescents raised with partial permission and adolescents raised in with parental approval were significantly younger at first alcohol use than adolescents raised with zero-tolerance alcohol-specific rule-setting, at 0.15 years and 0.28 years,

respectively. Furthermore, alcohol-specific parental rule-setting was significantly associated with the mean number of units consumed per day on the weekend. Partial permission was associated with an increase of 0.9 units per day on the weekend in comparison to zero-tolerance, while parental approval was associated with an increase of 2.1 units per day on the weekend in comparison to zero-tolerance alcohol-specific parental rule-setting.

Alcohol-specific parental rule-setting was also associated with current tobacco use. Adolescents raised with parental approval had significantly higher odds for smoking (OR 1.59, p = .003) than adolescents raised with zero-tolerance alcohol-specific rule-setting. Illicit drug use was not associated with alcohol-specific parental rule-setting. Alcohol-specific rule-setting was significantly associated with the drinking location. Adolescents raised with parental approval of adolescent alcohol use less frequently drank in a public location (OR 0.78, p = .04), compared to adolescents with zero-tolerance alcohol-specific rule-setting.

BIAS

Appendix B displays a table of patient characteristics of adolescents that completed the section of the questionnaire about alcohol-specific parental rule-setting and those that did not completed the section about alcohol-specific parental rule-setting. Both groups did not differ in terms of sex, age, educational level, ethnicity, reason of admission and illicit drug use. Adolescents that responded to the question were slightly more frequently admitted with a BAC between 2.0 and 2.9 g/L than adolescents that did not respond to the question. Among those that did not responded to the question about alcohol-specific parental rule-setting, the proportion of current smokers was slightly higher than among those that did answer the question. Another aspect of the design that might have caused response bias as the presence of parents during medical interviews. In this study, no data has been collected on whether parents of adolescents were present or absent during the medical interview.

4. DISCUSSION

The main objective of this study was to explore how trends in alcohol-specific parental rule-setting developed over time among adolescents admitted for acute alcohol intoxication, and how these parental rules relate to alcohol intoxication characteristics. Studying trends in alcohol-specific parental rule-setting is relevant to the field, as prior research has identified family factors as important, having a modifiable influence on adolescent alcohol use [16,17]. A more recent systematic review and meta-analysis found

that parental alcohol rules were negatively associated with adolescent risky drinking and alcohol-related problems [24].

In the Netherlands, trends in adolescent alcohol use have been linked with alcohol-specific parental rule-setting [11]. Similar to the general Dutch adolescent population, this study among adolescents admitted for acute alcohol intoxication demonstrates an increasing trend in zero-tolerance alcohol-specific rule-setting and a decrease in parental approval for adolescent alcohol use. The trends are promising and seem to reflect changes in the general Dutch adolescent population. Although both adolescents with a zero-tolerance rule-setting (and thus showing rule-breaking behaviour when admitted) and adolescents with approval are admitted, zero-tolerance rule-setting was associated with favourable outcomes. Studying these trends are the first step in exploring the possible association between alcohol-specific parental rule-setting and acute alcohol intoxication, however, based on the current study it is impossible to determine whether there is a causal factor between alcohol-specific parental rule-setting and hospital admission. At the outpatient department for adolescents and alcohol in our hospital, some parents express concerns over a zero-tolerance rule-setting due to the forbidden fruit effect and decreased tolerance. Although the rising trend of hospital admissions might be related to alcohol-specific parental rule-setting, it is more likely that the increase can be explained by improved awareness, than in decreased tolerance. Decreasing tolerance would lead to admissions at a lower BAC (with correction for confounders), which is not the case [7].

Alcohol-specific parental rule-setting was significantly associated with the age of the adolescent. The proportion of zero-tolerance alcohol-specific rule-setting was significantly lower among the subgroups of 15-16 year olds and 17-18 year olds, compared to the younger age groups. Furthermore, partial permission showed a stronger increasing trend among 15-16 year olds and 17-18 year olds. A similar association between alcohol-specific parental rule-setting and age was found in a representative sample of the general Dutch adolescent population [12-15]. Moreover, according to a qualitative study performed in the United States of America among 44 parents, the decision to approve adolescent alcohol use was either based on deliberate reasons or spontaneous reasons [25]. Deliberate reasons mentioned included an eagerness to pass on the norm of responsible drinking, to stimulate appreciation of alcohol usage and to demystify alcohol consumption. Spontaneous reasons for approving alcohol consumption included pressure from other parents, fear of harming their relationship with the adolescent and the belief that underage drinking is inevitable. Considering the reasons mentioned for

the approval of adolescent alcohol use on either an occasional or regular basis, it is understandable that parental tolerance increases in late adolescence. Therefore, the prevention of adolescent alcohol use should be aimed at subgroups with a relatively low prevalence of zero-tolerance alcohol-specific rule-setting (15-16 year olds, 17-18 year olds and native Dutch adolescents).

In the study population of adolescents admitted for acute alcohol intoxication, zero-tolerance alcohol-specific rule-setting was associated with older age at first alcohol use (age of onset) and a lower number of alcoholic units consumed per day on the weekends. These findings are in line with prior studies that associated strict parental rules with a delay in first alcohol use [26], while parental approval was associated with higher quantities of alcohol consumption [27,28]. It is worth investigating whether broader societal implementation of a strict zero-tolerance approach, for example in school education or mass media campaigns, would strengthen the effects. In contrast, parental disapproval was associated with lower levels of alcohol consumption during adolescence [29,30]. Monitoring children's behaviour and the consistent enforcement of consequences for a violation of rules have been related to a decrease in adolescent alcohol consumption [31,32]. An Australian systematic review of 12 different family factors identified parental monitoring, limiting availability and disapproval of adolescent drinking as predictive factors for reduced levels of adolescent drinking [16]. This systematic review was followed by a Delphi consensus study in which a comprehensive set of parental strategies for preventing and reducing adolescent alcohol consumption was developed [17]. According to this consensus study, parents should be aware that they can teach responsible drinking without allowing the adolescent to drink, and they should also be aware that the longer their adolescent delays alcohol consumption, the less likely they are to develop alcohol-related problems.

This raises the question of whether repeat hospital admissions for acute alcohol intoxication might be prevented by addressing the subject of alcohol-specific parental rules. Although this study did not consider recidivism, prior studies suggest that alcohol-specific parental rule-setting remains important, even if the adolescent already consumes alcohol. A Dutch longitudinal study concluded that although parents become somewhat less strict on alcohol-specific rules over time, and that adolescent alcohol use increases over time, alcohol-specific rules were related to less alcohol use between early adolescence and early adulthood. Alcohol-specific rules were even associated with lower alcohol consumption among young adults living by themselves [33]. Several longitudinal studies among college students in the United States have demonstrated the benefit

of strict alcohol-specific parental rule-setting [34,35]. Further research is necessary to determine whether interventions aimed at stimulating strict alcohol-specific rule-setting could prevent repeat hospital admissions for acute alcohol intoxication.

5. CONCLUSION

Among adolescents admitted for acute alcohol intoxication, the use of a zero-tolerance alcohol-specific parenting strategy increased significantly between 2011 and 2017, while parental approval for adolescent alcohol use decreased significantly between 2011 and 2017. Although these trends seem promising, it remains important to address the issue of alcohol-specific parental rule-setting as there is a rising trend in the proportion of adolescents being given partial permission to consume alcohol. Addressing the issue of alcohol-specific parental rule-setting is especially important for subgroups with a relatively low prevalence of zero-tolerance alcohol-specific parental rule-setting, namely adolescents between 15-18 years old and native Dutch adolescents. Informing these parents that, among adolescents admitted for acute alcohol intoxication, stricter alcohol-specific parental rules are associated with lower quantities of alcohol consumption per day on the weekend might motivate them to enforce stricter parental rules. Prior research has shown that strict alcohol-specific parental rule-setting remains associated with lower quantities of alcohol consumption in late adolescence and early adulthood. Therefore, addressing the subject of alcohol-specific parental rule-setting among parents of adolescents admitted for acute alcohol intoxication might be effective in reducing the risk of repeat hospital admissions.

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Appendix A Trends in proportion (%) of parental rule-setting among sociodemogrpahic subgroups, NSCK 2011-2017									
		2011	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Trend**
Age group	***≤14 years***								
	Zero-tolerance	59.3	53.3	79.4	**79.3**	**80.6**	**90.0**	**79.4**	p<0.001
	Partial	18.5	30.0	**2.9**	10.9	16.3	8.9	18.3	p=0.50
	Approval	22.2	16.7	17.6	9.8	**3.1**	**1.1**	**2.3**	p<0.001
	15-16 years								
	Zero-tolerance	19.2	19.4	29.1	**46.0**	**57.5**	**61.5**	**53.1**	p<0.001
	Partial	3.8	**13.0**	8.2	**17.8**	**28.8**	**26.9**	**33.2**	p<0.001
	Approval	76.9	67.6	**62.7**	**36.1**	**13.5**	**11.6**	**13.7**	p<0.001
	17-18 years								
	Zero-tolerance	8.0	5.3	3.8	22.5	**37.5**	**57.8**	**35.7**	p<0.001
	Partial	0.0	**1.8**	3.8	8.5	**40.4**	**28.4**	**50.0**	p<0.001
	Approval	92.0	67.6	92.3	**69.0**	**22.1**	**13.8**	**14.3**	p<0.001
Sex	***Male***								
	Zero-tolerance	24.7	18.0	26.3	**45.1**	**52.6**	**64.0**	**50.4**	p<0.001
	Partial	3.9	11.7	6.8	**14.8**	**31.5**	**28.0**	**39.0**	p<0.001
	Approval	71.4	70.3	66.9	**40.1**	**15.9**	**8.0**	**10.5**	p<0.001
	Female								
	Zero-tolerance	26.4	24.1	35.8	**60.0**	**66.9**	**68.3**	**60.6**	p<0.001
	Partial	9.4	13.3	6.4	14.8	**24.0**	**19.2**	**26.7**	p<0.001
	Approval	64.2	62.7	57.8	**25.2**	**9.1**	**12.5**	**12.6**	p<0.001
Educational level	***Low (VMBO)***								
	Zero-tolerance	31.7	22.6	38.8	**60.0**	**62.4**	**68.0**	**63.3**	p<0.001
	Partial	4.9	19.0	**3.5**	14.8	**26.9**	**20.0**	**29.5**	p<0.001
	Approval	63.4	58.3	57.6	**25.2**	**10.8**	**12.0**	**7.1**	p<0.001
	Middle (HAVO)								
	Zero-tolerance	32.0	19.5	32.1	47.2	**59.7**	**69.6**	50.6	p<0.001
	Partial	4.9	2.4	7.1	14.6	**30.2**	19.1	**35.3**	p<0.001
	Approval	63.4	78.0	60.7	38.2	**10.1**	**11.3**	**14.1**	p<0.001
	High (VWO)								
	Zero-tolerance	16.7	28.0	25.0	**42.9**	**66.3**	**61.8**	**54.4**	p<0.001
	Partial	5.6	8.0	15.0	19.6	22.8	**29.4**	**33.3**	p<0.001
	Approval	77.8	64.0	60.0	**41.7**	**10.9**	**8.8**	**12.3**	p<0.001
Etnicity	***Native Dutch***								
	Zero-tolerance	20.6	16.2	28.7	**48.1**	**57.0**	**64.1**	**51.3**	p<0.001
	Partial	5.6	12.6	6.7	**14.6**	**28.6**	**25.4**	**36.3**	p<0.001
	Approval	73.8	71.3	64.6	**37.3**	**14.3**	**10.5**	**12.4**	p<0.001
	Other								
	Zero-tolerance	53.5	41.7	66.7	66.7	62.9	72.2	76.2	p=0.07
	Partial	6.7	16.7	8.3	8.3	**35.5**	20.4	15.9	p=0.68
	Approval	40.0	41.7	25.0	25.0	**1.6**	**7.4**	**7.9**	p=0.003
Family structure	***Both parents***								
	Zero-tolerance	22.7	19.7	33.8	**47.7**	**59.2**	**64.0**	**53.4**	p<0.001
	Partial	9.3	10.3	8.1	15.0	**26.3**	**25.0**	**33.8**	p<0.001
	Approval	68.0	70.1	58.1	**37.4**	**14.4**	**11.0**	**12.8**	p<0.001
	Other								
	Zero-tolerance	33.0	26.2	25.0	**53.7**	**55.9**	**66.9**	**56.8**	p<0.001
	Partial	0.0	**16.9**	3.4	**11.4**	**32.8**	**24.5**	**33.9**	p<0.001
	Approval	66.7	56.9	71.6	**35.0**	**11.3**	**8.6**	**9.3**	p<0.001

Note: bold indicated significantly different from reference year 2011

Appendix B Response versus non-response alcohol-specific parental rule-setting, NSCK 2011-2017			
	Response (n=2619)	**Non-response (n=2588)**	**p-value**
Sex			p=0.16
Male	53.9% (CI 52.0%-55.9%)	51.9% (CI 49.8%-54.0%)	
Age group			p=0.32
<14 years	20.4% (CI 18.9%-22.1%)	21.9% (CI 20.3%-24.0%)	
15-16 years	58.2% (CI 56.3%-60.1%)	58.0% (CI 56.0%-60.0%)	
17-18 years	21.4% (CI 19.9%-23.0%)	20.1% (CI 18.5%-21.8%)	
Educational level			p=0.14
Low (VMBO) (ref)	46.2% (CI 43.4%-48.4%)	46.9% (CI 44.4%-49.4%)	
Middle (HAVO)	30.8% (CI 28.8%-32.9%)	28.0% (CI 25.9%-30.3%)	
High (VWO)	25.1% (CI 21.1%-24.9%)	25.1% (CI 23.0%-27.3%)	
Ethnicity			p=0.28
Non-native Dutch	9.9% (CI 8.8%-11.2%)	10.9% (CI 9.6%-12.4%)	
Family structure			**p=0.003**
Not living with both parents	36.4% (CI 34.5%-38.3%)	32.1% (CI 30.1%-32.2%)	
Reason of admission			p=0.27
Reduced conciousness	88.1% (CI 86.7%-89.4%)	87.3% (CI 85.7%-88.7%)	
Injury/accident	5.1% (CI 4.2%-6.0%)	4.7% (CI 3.8%-5.7%)	
Other	6.8% (CI 5.9%-7.9%)	8.0% (CI 6.9%-9.3%)	
BAC			**p<0.001**
0.1-0.9g/L	2.8% (CI 2.2%-3.6%)	4.5% (CI 3.6%-5.5%)	
1.0-1.9g/L	45.4% (CI 43.4%-47.4%)	50.1% (CI 47.8%-52.3%)	
2.0-2.9g/L	48.4% (CI 46.4%-50.4%)	42.0% (CI 39.8%-44.3%)	
>3.0g/L	3.4% (CI 2.7%-4.2%)	3.4% (CI 2.7%-4.3%)	
Illicit drug use			
Positive urine tox screening	12.4% (CI 11.2%-13.8%)	12.4% (CI 11.0%-13.9%)	p=0.95
Survey year			**p<0.001**
2011	17.4%	82.6%	
2012	27.0%	73.0%	
2013	42.7%	57.3%	
2014	53.2%	46.8%	
2015	62.9%	37.1%	
2016	636%	36.4%	
2017	78.4%	21.6%	

Note: Chi-square test

SECTION 2

Acute treatment and diagnostics

CHAPTER 6

Urine toxicology screening

The role of tobacco smoking and illicit drug use in adolescent acute alcohol intoxication

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ABSTRACT

Background This study aims to determine the prevalence of tobacco smoking and illicit drug use among Dutch adolescents admitted to hospital for acute alcohol intoxication treatment. Furthermore, socio-demographic predictors for smoking and illicit drug use in the sample population will be studied. The relationship between illicit drug use and specific characteristics of intoxication, such as blood alcohol concentration (BAC) and duration of reduced consciousness is also investigated.

Methods The national Dutch Paediatric Surveillance Unit was used to prospectively register cases of acute alcohol intoxication from 2007 through 2017. Cases were included if they met the following inclusion criteria: BAC > 0.0 g/L, aged between 10 to 18 years old and requiring hospital treatment due to reduced consciousness. Questionnaires were sent to paediatricians to obtain clinical information.

Results During the period 2007-2017, 5322 cases that met the inclusion criteria were reported. In this patient group, the prevalence of tobacco smoking was 22.2% (CI 21.0%-23.5%), while the prevalence of illicit drug use was 11.8% (CI 10.9%-12.7%). The predictors for smoking were the absence of alcohol-specific parental rule-setting, lower educational level, non-traditional family structure and positive drug screening. The predictors for illicit drug use were the absence of alcohol-specific parental rule-setting and smoking. Illicit drug use was also associated with a lower BAC at the time of admission.

Conclusions Assessing smoking and illicit drug use among adolescents admitted for acute alcohol intoxication is important in acute cases of intoxication, for outpatient follow-up and for the purposes of prevention. The relationship between simultaneous illicit drug use and a lower BAC is of relevance for paediatricians' attempts to diagnose acute intoxication. With respect to outpatient follow-up and preventive measures, it is important to be aware that adolescents' alcohol consumption, tobacco and illicit drug use are related and, ultimately, increase the odds of using other substances.

Keywords*: adolescence, alcohol intoxication, combined illicit drug use, cannabis, tobacco use*

List of abbreviations*:* blood alcohol content (BAC), Dutch Paediatric Surveillance Unit /Nederlands Signalerings Centrum Kindergeneeskunde (NSCK), 3,4-Methylenedioxy-methamphetamine (MDMA), gamma-Hydroxybutyric acid (GHB).

1. INTRODUCTION

BACKGROUND

Harmful health behaviours, such as smoking tobacco, consuming alcohol and using illicit drugs typically commence during adolescence [1-3]. Several studies suggest that the initiation of sensation-seeking and risk-taking behaviour is triggered by tension between, on the one hand, the early development of subcortical regions that express exaggerated reactivity to motivational stimuli, and, on the other, the later maturation of the prefrontal regions which are associated with regulatory control and risk assessment [1,4,5]. This imbalance in the maturation of brain regions is enhanced by peer pressure, which is known to diminish cognitive control and, in turn, lead to adolescents being at increased risk of impulsive behaviour and experimenting with substance use [6-7]. Truancy and runaway behaviour in adolescence have also been identified as predictive factors for binge drinking, alcohol dependence, illicit substance use and poor general life satisfaction in late adolescence and young adulthood [8].

The combined use of alcohol and illicit drugs has been found to be associated with various short-term deleterious health consequences. The use of illicit drugs alone has been associated with increased healthcare engagement, namely in the form of increased emergency department episodes and hospital admissions [9]. The co-ingestion of alcohol and cocaine can potentiate the cardio toxic effects associated with both cocaine and alcohol [10], which serves to increase the risk of immediate death as a result of the hepatic metabolism of cocaethylene [11]. The combined use of (meth)amphetamines and alcohol decreases alcohol-specific feelings of intoxication, such as feeling drunk and sedated, resulting in more severe alcohol intoxications [12]. The combination of alcohol and other sedatives, such as gamma-Hydroxybutyric acid (GHB), increases the risk of reduced consciousness, respiratory depression and admission to an intensive care unit [13, 14]. In adolescents who were not intoxicated, the simultaneous use of cannabis and alcohol was associated with the use of higher quantities of both substances than when either substance was used concurrently or alone [15-17]. Among adolescents, the combined use of alcohol and drugs has also been associated with violence and aggression [18], trauma [19], involvement in cyberbullying [20] and sexual risk behaviour [21].

Preventing combined alcohol and drug use among adolescents is of critical importance in the long-term, due to the fact that the onset of most cases of substance use disorders occurs during adolescence [22,23]. Adolescents who have engaged early in regular smoking and drunkenness-orientated alcohol use, are particularly at risk of developing hazardous

substance use later in life [24–26]. Indeed, a recent review indicates that alcohol and tobacco potentiate each other's rewarding effects, and, hence, that concurrent usage may potentiate their respective negative effects [27]. In adulthood, alcohol and tobacco use are highly comorbid and have multiplicative health risks when used in conjunction with one another. The concurrent use of alcohol and tobacco, in comparison to both alcohol use and tobacco use alone, have been associated with supra-multiplicative health risks, such as cardiovascular problems, head and neck cancers, cirrhosis, pancreatitis and psychiatric comorbidity [28–30]. Another study indicated that from midlife onwards, age-related decline in the global cognitive score was faster in individuals who were smokers and heavy drinkers than in non-smoking moderate drinkers, which suggests that the combined effects of smoking and alcohol consumption are greater than their individual effects [31].

Despite the short- and long-term negative consequences of polysubstance use, strong associations between alcohol use, tobacco usage and illicit drug use have been established [32,33]. In Europe, almost all students (87% or more) who used a licit or illicit substance also reported having consumed alcohol, while 93% of students who ever smoked cigarettes also consumed alcohol [34]. Similar associations have been found in the Netherlands, where the prevalence of cannabis use among adolescents who had tried alcohol was 21%, in comparison to 1% among adolescents who had never tried alcohol [35].

Although prior research has demonstrated the strong associations between alcohol usage and the use of other substances across the general adolescent population in the Netherlands, the simultaneous use of tobacco or illicit drugs by adolescents admitted to hospital for acute alcohol intoxication has hitherto not been explored. This study aims to identify both the socio-demographic predictors and deleterious effects of the combined use of tobacco and illicit drugs among Dutch adolescents admitted to hospital for acute alcohol intoxication. We hypothesized that, just like has been demonstrated in the general adolescent population, smoking and illicit drug use are strongly related and important determinants for each other.

2. MATERIALS AND METHODS

STUDY POPULATION AND DATA COLLECTION

In 2007, the Dutch Paediatric Surveillance Unit (NSCK), which was initiated by the Dutch Paediatric Society, started collecting data on acute alcohol intoxication. The purpose of the surveillance system is to, firstly, gain population-level insights into the prevalence of rare and new diseases among youths (0–18 years), and secondly, to promote scientific

research that addresses the background, nature and prognosis, as well as the treatment and prevention, of these diseases. Approximately 90% of Dutch paediatricians report to the system if they diagnose a disease included in the surveillance system. Data collection by the NSCK was approved by the medical ethical committee of the Faculty of Behavioural, Management and Social Sciences, University of Twente. All adolescents provided their informed consent and additional parental informed consent was obtained for participants younger than 16 years of age. Cases were reported to the system if they met the following two major inclusion criteria: blood alcohol concentration (BAC) > 0.0 g/L and under 18 years of age. With respect to the present study, only those admissions that pertained to reduced consciousness were included (admissions for different reasons, such as aggression, vomiting, suicide attempts and injuries were excluded from the analyses).

OUTCOME MEASURES

This study aimed to determine the prevalence of tobacco smoking and illicit drug use among the study population. Smoking was defined as a dichotomous variable, based on the current smoking status of the participant (either smoking or non-smoking). Due to its availability and societal acceptance, alcohol and tobacco smoking, are the psychoactive substances with the highest consumer rates worldwide [36]. Therefore, alcohol use and tobacco smoking are often classified as separate entities with the psychoactive substances. Illicit drug use was also defined as a dichotomous variable: negative drug screening and positive drug screening. Drug screening was based on self-reported declarations, heteroanamnesis and clinical signs that were suggestive of illicit drug use. According to protocol, admission for acute alcohol intoxication was an indication for a urine toxicology test and the results of those urine toxicology tests were used to confirm self-reported declarations and clinical signs. Illicit drug use was coded in accordance with the categories listed in the routinely used urine toxicology test: cannabinoids, cocaine metabolites, (meth)amphetamines (including 3,4-methylenediocymethamphetamine) and GHB. There was one residual category “other” that pertained to those drugs not in the above groups, such as mushrooms, nitrous oxide and opioids.

COVARIATES

Subsequent to reporting to the surveillance system, paediatricians received instructions and a questionnaire in order to collect data on general patient characteristics (such as age at time of admission and sex), demographic characteristics (such as educational level, ethnicity and family structure), intoxication characteristics (such as BAC and duration of reduced consciousness) and substance use patterns prior to this instance of acute

intoxication (tobacco smoking, alcohol consumption and illicit drug use). Completion of the questionnaire required conducting a standardised interview with the adolescents admitted for acute alcohol intoxication, and gathering details from their patient records, such as laboratory results.

Educational level was defined as a categorical variable comprising three categories, which corresponded to the Dutch secondary school system: low (pre-vocational education), middle (senior general secondary education) and high (pre-university education). Family structure was defined as a categorical variable made up of two categories: traditional family structure (both biological parents) and non-traditional family structure (all other family structures, such as, for example, divorced parents, single-parent households, or foster care). Alcohol-specific parental rule-setting was defined as a categorical variable consisting of the following categories: zero-tolerance rule-setting, partial permission to consume alcohol and the absence of alcohol-specific parental rule-setting (drinking allowed).

STATISTICAL DATA ANALYSIS

IBM SPSS Statistics (IBM Corp. Released 2017/ IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp) was used for all the statistical analyses. Continuous variables were expressed as means and standard deviation. Categorical variables were expressed as frequencies with 95% confidence intervals (CIs).

First, the prevalence of tobacco smoking and illicit drug use were determined via the use of descriptive statistics. A binomial logistic regression was performed to ascertain the effects of age group, sex, educational level, ethnicity, family structure and alcohol-specific parental rule-setting on the likelihood of participants currently smoking or using illicit drugs. A Bonferroni correction was applied using multiple terms in the model.

3. RESULTS

PREVALENCE OF SMOKING AND ILLICIT DRUG USE

During the period 2007-2017, 5322 cases that met the inclusion criteria were reported to the system. Smoking status was reported in 94.7% of the cases, while the drug screening results were reported in 90% of the cases. The mean age of the adolescents admitted for acute alcohol intoxication was 15.4 years (SD 1.2 years). The prevalence of tobacco smoking and illicit drug use is displayed in Table 1.

Table 1. Prevalence of smoking and illicit drug use

	Prevalence 2007-2017 (95% CI)	***n***
Smoking status		4789
% Smoking	**22.2% (CI 21.0%-23.4%)**	1063
Illicit drug use		5041
% Positive	11.8% (CI 10.9%-12.7%)	549
% Cannabis	6.8% (CI 6.1%- 7.8%)	342
% Cocaine	0.3% (CI 0.1%- 0.5%)	13
% (Meth)amphetamine	0.7% (CI 0.5%- 1.0%)	38
% GHB	2.1% (CI 1.7%- 2.5%)	104
% Other type of drug	0.8% (CI 0.6%- 1.3%)	42
% Multiple drugs	1.1% (CI 0.8%- 1.4%)	55

Overall, 22.2% (CI 21.0%-23.45%) of the adolescents admitted for acute alcohol intoxication smoked cigarettes. The prevalence of illicit drug use among adolescents admitted for acute alcohol intoxication was 11.8% (CI 10.9%-12.7%), with cannabis being the most frequently consumed illicit drug.

LOGISTIC REGRESSION MODEL

Table 2 shows the prevalence of smoking and illicit drug use in various demographic subgroups, as well as presenting the results of the logistic regression model.

The logistic regression model for tobacco smoking was statistically significant, X2(12) = 152.6, p < .001. The model correctly classified 83.4% of the cases. Of the predictors, five determinants were statistically significant: educational level, family structure, BAC, illicit drug use and year of diagnosis. Low educational level was associated with an increased likelihood of smoking, in comparison to adolescents with a middle or high educational level. Being raised in a non-traditional family structure increased the odds of smoking by a factor of 1.43 (CI 1.05-1.96, p=.02) in comparison to adolescents raised in a traditional family structure, with both biological parents. Positive drug screenings were associated with 4.26 (CI 2.97-6.13, p<.001) times higher likelihood of tobacco smoking than adolescents who had a negative drug screening. During the study period 2007-2017, the likelihood of smoking decreased each year by a factor of 1.14 (CI 1.04-1.24, p=.007). Increasing BAC at admission was associated with an decreased likelihood of smoking (OR 0.74, CI 0.55-0.98, p=.04).

The logistic regression for illicit drug use was also statistically significant, X2(12) = 102.1, p < .001. The model for illicit drug use correctly classified 88.0% of the cases. Three determinants were statistically significant: family structure, smoking and BAC. The odds of a positive drug screening were 1.42 (CI 1.00-2.02, p =.05) times higher among

adolescents raised in a non-traditional family structure, compared to adolescents raised in a traditional family structure. Among adolescents admitted for acute alcohol intoxication, smoking was associated with 4.21 (CI 2.96-6.06, p<.001) higher odds of illicit drug use than non-smoking. Increasing BAC was associated with a decreased likelihood of illicit drug use (OR 0.59, CI 0.43-0.82, p=.002).

Table 2 Socio-demographic predictors of smoking and illicit drug use

	Smoking		**Illicit drug use**	
	Prevalence	Adjusted OR	Prevalence	Adjusted OR
Demographics				
Age category				
≤ 14 years (ref)	19.9% (CI 17.7-22.4%)	1.00	10.8% (CI 9.2-12.8%)	1.00
15-16	22.1% (CI 20.6-23.7%)	1.26 (CI 0.86-1.86)	11.4% (CI 10.3-12.6%)	1.29 (CI 0.82-2.01)
16-17	25.6% (CI 25.6-28.7%)	1.38 (CI 0.80-2.39)	14.3% (CI 12.1-16.8%)	1.76 (CI 0.96-3.20)
Sex				
Male (ref)	22.5% (CI 20.8-24.2%)	1.00	13.6% (CI 12.3-15.0%)	1.00
Female	21.8% (CI 20.2-23.6%)	0.79 (CI 0.58-1.07)	25.6% (CI 8.8-11.2%)	0.74 (CI 0.52-1.05)
Educational level				
Low (ref)	28.6% (CI 26.5-30.7%)	1.00	12.8% (CI 11.3-14.5%)	1.00
Middle	15.0% (CI 12.9-17.3%)	0.50 (CI 0.35-0.71)[a]	9.7% (CI 8.1-11.7%)	1.11 (CI 0.75-1.66)
High	9.9% (CI 8.1-12.1%)	0.31 (CI 0.20-0.49)[a]	7.9% (CI 6.2- 9.9%)	0.74 (CI 0.45-1.20)
Ethnicity				
Native Dutch (ref)	22.0% (CI 20.8-23.4%)	1.00	11.3% (CI 10.4-12.3%)	1.00
Other	23.5% (CI 20.0-27.4%)	0.78 (CI 0.47-1.30)	14.3% (CI 11.5-17.6%)	1.43 (CI 0.86-2.39)
Family structure				
Traditional (ref)	9.9% (CI 8.1-12.1%)	1.00	9.9% (CI 8.9-11.0%)	1.00
Non-traditional	18.1% (CI 20.0-27.4%)	1.43 (CI 1.05-1.96)[c]	16.3% (CI 14.5-18.3%)	1.42 (CI 1.00-2.02)[c]
Parental rules				
Zero-tolerance (ref)	16.7% (CI 14.5-19.1%)	1.00	11.5% (CI 9.7-13.6%)	1.00
Partial permission	18.5% (CI 15.3-22.2%)	1.08 (CI 0.73-1.57)	13.6% (CI 10.8-16.9%)	1.03 (CI 0.68-1.56)
Parental approval	27.1% (CI 23.4-31.2%)	1.38 (CI 0.91-2.08)	12.2% (CI 9.6-15.3%)	0.89 (CI 0.54-1.45)
Intoxication				
Smoking status				
Non-smoking (ref)			7.1% (CI 6.3- 8.0%)	1.00
Smoking			26.6% (CI 24.0-29.4%)	4.21 (CI 2.92-6.06)[a]
Illicit drug use				
Negative (ref)	18.4% (CI 17.2-19.6%)	1.00		
Positive	51.5% (CI 47.2-55.9%)	4.26 (CI 3.00-6.20)[a]		
BAC		0.74 (CI 0.55-0.98)[c]		0.59 (CI 0.43-0.82)[b]
Year (2007-2017)		0.88 (CI 0.80-0.97)[b]		1.04 (CI 0.93-1.16)

[a]p<0.001, [b]0.001 < p < 0.01, [c]0.01 < p < 0.05

DESCRIPTIVE STATISTICS PER TYPE OF DRUGS

The results of the descriptive statistics for the different types of illicit drug use are presented in Table 3. The results indicate that among Dutch adolescents admitted for acute alcohol intoxication, the prevalence of illicit drug use was slightly higher among

male adolescents (X2 (1, n=5012) = 15.8, p<.001). However, this difference appears to be related to the increased prevalence of cannabis consumption among male adolescents compared to female adolescents (X2 (1, n=5012) = 29.2, p<.001). Furthermore, a positive urine drug screening for cannabis or (meth)amphetamines was associated with a lower BAC at admissions (ANOVA (6, n=4566) = 11.5, p<.001, post hoc analyses p<.001). The combined use of alcohol and GHB seems to be associated with a lower BAC at admission too, however, the difference is not significant (p=0.36), most likely due to a too small sample size for sub analyses. A positive urine drug screening for cocaine-metabolites seems to be associated with a higher BAC at admission, but the sample size is too small to test this. In the analyses of the association between the subgroups of illicit drug use and BAC, it is important that age at admission might act as a confounder. However, the sample sizes are too small to correct for age using a multivariable linear regression analysis.

Table 3 Descriptive statistics for illicit drug use, NSCK 2007-2017

	None	Cannabis	Cocaine	(Meth) amphetamine	GHB	Polysub-stance
n		342	13	38	104	55
Sex						
% of males	86.4%	8.7%	0.3%	0.8%	1.7%	1.3%
% of females	90.0%	4.8%	0.2%	0.7%	2.4%	0.9%
Age in years	15.4	15.4	16.0	16.0	15.3	15.8
BAC in g/L	1.95	1.77	2.02	1.48	1.81	1.74
EMV reduced hours	3.0	3.3	2.6	1.8	3.2	3.1

4. DISCUSSION

This study has shown that approximately one fifth (22.2%) of the adolescents admitted for acute alcohol intoxication were active smokers, while approximately one eighth (11.8%) of the adolescents had a positive drug screening. According to a World Health Organization collaborative cross-national survey examining the health behaviour of school-aged children, the prevalence of smoking (that is, whether they had smoked in the month prior to the survey) among 15-year-olds declined from 27.4% in 2009 to 14.0% in 2017 [34]. The prevalence rate of 6.8% of positive urine screenings for cannabis appears to be in line with the prevalence of cannabis use among 15-year-olds in the general Dutch adolescent population (ranging from 8.2% in 2013 to 12.6% in 2005 [34]). The results thus indicate that smoking and illicit drug use are common among adolescents admitted for acute alcohol intoxication.

Although the prevalence of illicit drug use did not appear to be higher in adolescents admitted for acute alcohol intoxication than it is for the general adolescent population,

the results of this study demonstrate why it is of vital importance to assess adolescents' smoking status and illicit drug use. Firstly, the assessment of illicit drug use is important in instances of acute intoxication, insofar as this study has demonstrated that the simultaneous consumption of alcohol and various illicit drugs (i.e. cannabis, GHB, (meth)amphetamines) is associated with a lower BAC at admission. This result suggests that in comparison to alcohol alone, simultaneous use of these substances results in admission for reduced consciousness at a lower BAC. Furthermore, assessing smoking and illicit drugs is important for the follow-up of adolescents admitted for acute alcohol intoxication. Specifically, our study shows that among adolescents admitted for acute alcohol intoxication, smoking increased the odds of having a positive drug screening and, moreover, that having a positive drug screening increased the odds of smoking. Smoking was also associated with higher quantities of regular alcohol use during the weekend. These results show that during adolescence, the use of various substances, such as alcohol, tobacco and illicit drugs are intertwined.

Literature review provides insights in multiple concepts that address polysubstance use in adolescents. Recent neuroscience models of adolescent brain development attribute the morbidity of this period to structural and functional imbalances between more fully developed limbic regions that subserve reward and emotion as opposed to the frontal cortex that enables cognitive control [37-40]. The "imbalance model" describes a peak in sensation seeking and impulsive behaviour during adolescence, which produces more risk taking behaviour than in children or adults [37-40]. In contrast to the "imbalance model", "Life-span wisdom models" consider the role that experience plays in healthy adolescent development [40,42]. The "life-span wisdom models" describe a peak in sensation seeking during adolescence motivates greater exploration in ambiguous environments, but risk taking declines monotonically from childhood to adulthood when risks are known, per greater reliance on gist and increasing executive function. Socioemotional influences can promote risk taking, but social experience and positive social influences can promote healthy risk avoidance [40,41]. Other models have been used to address specific types of adolescent risk-taking behaviour: the involvement with psychoactive substances. The "gateway model" focusses on the sequence of drug initiation and considers drug itself as the cause of drug use development. The model states that there is a progressive and hierarchical sequence of stages of drug use that begins with tobacco or alcohol, two classes of drugs that are legal, and proceeds to cannabis, and from cannabis to other illicit drugs, such as cocaine or (meth)amphetamines [42-44]. Whereas the "gateway model" does not specify mechanistic connections between "stages", and does not

extend to the risks for addictions, the concept of "common liability to addictions" incorporates sequencing of drug use initiation as well as extends to related addictions and their severity [42]. Liability denotes a latent (unobservable) quantitative trait that, when measured, "would give us a graded scale of the degree of affectedness or of normality" [45]. The quantity of models reflect researchers eagerness to find options for treatment and prevention of polysubstance abuse in adolescents and therefore, a lot of research has been conducted to risk factors of alcohol use, smoking and illicit drug use.

Our study identified educational level, family structure and alcohol-specific rule-setting as predictors for smoking in adolescents with acute alcohol intoxication. Educational attainment, as indicated by both years of education and level of education, has had a consistent inverse relationship with drug use and drug use problems [46, 47]. Alcohol and drug-related problems have been identified as important predictors of negative school-related outcomes, such as low grade point average and high levels of hours missed from school [48]. Family factors, such as family structure and alcohol-specific rule-setting have been identified as important modifiable factors in adolescent substance abuse [49-51]. Health risk factors for adolescent substance abuse can be classified in various categories: genetic, environmental and personal determinants [52]. Identification of risk-factors of polysubstance abuse among adolescents is essential, as identification of risk-factors form the basis in the development of prevention strategies against negative outcomes of polysubstance abuse.

A recent study among young adults with experience in the simultaneous use of alcohol and cannabis showed that cross-fading motives (i.e. to enhance the effects of either alcohol or cannabis, or to get drunk and high at the same time) are common. In this study, the existence of greater cross-fading motives was associated with greater alcohol use and increased perceived intoxication [53]. In a study examining the perceived acute effects of alcohol use, cannabis use, and simultaneous alcohol and cannabis use, most effects (i.e. clumsiness, confusion, dizzyness and difficulty concentrating) were rated strongest when that person was engaging in simultaneous use, compared to typical alcohol and cannabis use alone [54]. The lower BAC among adolescents with acute alcohol intoxication and positive urine screening for cannabis in comparison to alcohol alone can perhaps also be explained by a pharmacokinetic study, which showed that the simultaneous use of alcohol and cannabis produces significantly higher blood concentrations of the main psychoactive constituent of cannabis, delta-9-tetrahydrocannabinol (THC) [55].

Our study demonstrated that a positive drug screening for (meth)amphetamine was associated with a relatively low BAC at admittance. In order to interpret these study results, it is important to realise that most urine toxicology screenings used in the Netherlands fail to distinguish between 3,4-mythylenedioxymethamphetamine (MDMA), methamphetamines and amphetamines. A pharmacokinetic study showed that co-ingestion of MDMA and alcohol resulted in a 13% increase in the MDMA plasma concentration and a 9 to 15% decrease in the ethanol plasma concentration [56]. The combined use of MDMA and alcohol has also been associated with a dissociation between subjective and objective sedation [56,57]. The effects associated with the co-ingestion of ethanol and MDMA may depend on several factors, including the interval between dosing, ethanol dosage and MDMA dosage [58]. The pharmacokinetics of MDMA, combined with the dissociation between subjective and objective sedation, might contribute to the relatively lower BAC of adolescents with acute alcohol intoxication who simultaneously use (meth)amphetamine. In a small-scale study examining the acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol, there was no difference found in the breath alcohol levels between the placebo + amphetamine group and the methamphetamine + alcohol group. Co-administration of methamphetamine and alcohol produced greater feelings of euphoria and good drug effects than single doses of either drug alone. The drug combination decreased alcohol-specific feelings of intoxication, such as feeling drunk and sedated [59]. The study also noted that the reduction of alcohol-specific feelings increased the risk of higher BAC and alcohol intoxication [59].

Previous studies have shown that the co-ingestion of ethanol increases the adverse effects experienced by patients intoxicated from GHB, in turn, leading to greater depression of consciousness, need for treatment and admission to intensive care units [13,14]. In comparison to co-ingestion of GHB alone, alcohol co-use was associated with increased risk of showing agitation and vomiting [13,15]. The combination of cocaine and alcohol can lead to the production of cocaethylene, which is more lethal than cocaine itself [10,11]. Alcohol has been shown to increase the plasma concentration of cocaine [60]. Consumption of both cocaine and alcohol has also been found to increase the heart rate and systolic blood pressure [60]. Cerebral hypoperfusion was shown to be more common among individuals using both alcohol and cocaine, compared to those who used cocaine and alcohol in isolation [61].

Assessing the illicit drug use of adolescents admitted for acute alcohol intoxication is also necessary for preventing substance use later in life, as research has shown a strong continuity between substance use in adolescence and young adulthood [62].

5. CONCLUSION

Assessing smoking and illicit drug use among adolescents admitted for acute alcohol intoxication is important, insofar as illicit drug use increases the odds of smoking and smoking increases the odds of illicit drug use. This study has demonstrated that smoking is associated with higher quantities of regular alcohol use during weekends. Therefore, in the treatment of adolescents admitted for acute alcohol intoxication, smoking and illicit drug use should serve as a warning for health care professionals, while appropriate attention should also be paid to smoking and illicit drug use in outpatient follow-up and when designing preventive measures. The predictors identified by this research for smoking among adolescents with acute alcohol intoxication were lower educational levels, non-traditional family structures and the absence of alcohol-specific parental rule-setting. The latter was also a predictor for simultaneous usage of alcohol and illicit drugs.

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CHAPTER 7

Electrocardiogram

QTc-prolongation in adolescents with acute alcohol intoxication

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ABSTRACT

In adults, alcohol intoxication is associated with prolongation of the QT interval corrected for heart rate (QTc). The QTc is influenced by age and sex. Although alcohol intoxication is increasingly common in adolescents, there are no data on the prevalence of QTc prolongation in adolescents with alcohol intoxication. This study aimed to determine the prevalence of QTc prolongation in adolescents with alcohol intoxication and identify at-risk adolescents. In this observational study including adolescents aged 10–18 years, heart rate and QT interval were automatically assessed from an electrocardiogram (ECG) at alcohol intoxication using a validated algorithm. The QTc was calculated using both the Bazett formula (QTcB) and Fridericia formula (QTcF). If present, an ECG recorded within 1 year of the date of admission to the emergency department was obtained as a reference ECG. A total of 317 adolescents were included; 13.3% had a QTcB and 7.9% a QTcF longer than the sex- and age-specific 95th-percentile. None of the adolescents had a QTcB or QTcF > 500 ms, but 11.8% of the adolescents with a reference ECG had a QTcB prolongation of > 60 ms, while no adolescents had a QTcF prolongation of > 60 ms. QTc prolongation was mainly attributable to an increase in heart rate rather than QT prolongation, which underlies the differences between QTcB and QTcF. Male sex and hypokalaemia increased the likelihood of QTc prolongation.

Conclusions QTc prolongation was seen in approximately 10% of the adolescents presenting with alcohol intoxication, and although no ventricular arrhythmias were observed in this cohort, QTc prolongation increases the potential for malignant QT-related arrhythmias. Clinicians must be aware of the possibility of QTc prolongation during alcohol intoxication and make an effort to obtain an ECG at presentation, measure the QT interval, and give an adequate assessment of the findings. We advocate admitting adolescents with alcohol intoxication and QTc prolongation. During hospital admission, we recommend limiting exposure to QTc-prolonging medication, increasing potassium levels to a high-normal range (4.5–5.0 mmol/L) and obtaining a reference ECG at discharge.

Keywords*: Adolescent, alcohol, electocardiogram, QTc-prolongation*

List of abbreviations*:* Analysis of covariance(ANCOVA), analysis of variance(ANOVA), beats per minute(bpm), blood alcohol concentration(BAC), Dutch Pediatric Surveillance Unit(NSCK), electrocardiogram(ECG), heart rate(HR), interquartile range(IQR), lower limit of normal(LLN), miliseconds(msec), not applicable(NA), QT-interval corrected for heart rate(QTc), QT-interval corrected for heart rate using Bazett's correction method(QTcB), QT-interval corrected for heart rate using Fridericia's correction method(QTcF), sample size(n), standard deviation(SD), systolic blood pressure(SBP), Torsade de Pointes(TdP), upper limit of normal(ULN)

What is known:

- One out of five deaths in adolescents is alcohol-related. Alcohol intoxication has been related to cardiac arrhythmias and sudden cardiac death.
- In adults, alcohol intoxication is associated with QTc prolongation

What is new:

- Approximately 10% of the adolescents with alcohol intoxication had a QTc longer than the age- and sexspecific cut-off.
- In contrast to adults, in adolescents with alcohol intoxication, QTc prolongation is attributable to an increase in heart rate, rather than a prolongation of the QT interval.
- Especially males and adolescents with hypokalaemia are at risk of QTc prolongation.

1. INTRODUCTION

Alcohol is the most commonly used psychoactive substance among adolescents [1, 2] and can lead to major alcohol-attributed health risks and even death [3]. In recent decades, alcohol intoxication has become an increasing problem in adolescents with rising admissions to the emergency department and rates of hospitalization [4-8]. One out of five deaths in adolescents is even related to alcohol, with approximately 5% being due to cardiovascular causes [3]. Alcohol intoxication is associated with cardiac arrhythmias and sudden cardiac death [9-17].

Cardiovascular symptoms, such as tachycardia and hypotension, caused by both volume depletion (due to inhibition of antidiuretic hormone and vomiting) and vasodilatation have been reported in adolescents with alcohol intoxication [18, 19]. As alcohol intoxication can induce biochemical changes, such as hypoglycaemia and electrolyte disturbances (such as hypokalaemia, hypernatremia, and hyperchloremia) [19-21], there is a potential risk of cardiac arrhythmias. Guidelines advocate performing an ECG when there is evidence of illicit drug use [22] but do not have specific recommendations for alcohol intoxication. However, in clinical practice in adults, an ECG is obtained in most cases [23]. From that, we know that alcohol intoxication is associated with ECG changes, most frequently prolongation of the QT interval corrected for heart rate (QTc) [23-25]. QTc prolongation predisposes the patient to a life-threatening ventricular arrhythmia, known as Torsade de Pointes (TdP) [26] that can precipitate syncope, sudden cardiac arrest, or sudden cardiac death [26]. There are currently, however, no data on the prevalence of QTc prolongation in adolescents with alcohol intoxication.

The QTc is influenced by age and sex, probably under the influence of sex hormones [27]. Puberty is an important transition period during which changes in the QTc occur, with no sex differences in the QTc before the onset of puberty, but thereafter, a longer QTc is present in females compared to males. In patients with long QT syndrome (LQTS), puberty plays an important role in the sex-related risk for cardiac events [27, 28]. We therefore postulate that individuals in the puberty transition period, i.e., adolescents, are more sensitive to modulators that affect the QTc, such as alcohol intoxication. We therefore aimed to determine the prevalence of QTc prolongation and ventricular arrhythmias in adolescents presenting with alcohol intoxication. Additionally, we wanted to identify adolescents at risk for QTc prolongation.

2. MATERIALS AND METHODS

STUDY DESIGN AND SETTING

In this single-centre, retrospective, observational study, we enrolled adolescents aged 10–18 years with a blood alcohol concentration (BAC) > 0.0 g/L who were admitted to the emergency department of the Reinier de Graaf Hospital in Delft, the Netherlands, between January 2009 and December 2019. Adolescents with a history of heart disease were excluded.

COLLECTION OF ECGS AND ADDITIONAL DATA

The first recorded 12-lead ECG during alcohol intoxication was obtained (ECGintox) from all of the included adolescents. ECGs that were not available digitally or were recorded in the presence of conduction disorders or pre-excitation were excluded from the analysis. To compare the ECGintox to baseline conditions, an ECG recorded within 1 year before or after the date of admission to the emergency department was obtained (ECGreference). All ECGs were digitalized and blinded to patient characteristics.

Additional adolescent characteristics were collected, including age, sex, vital functions, urine toxicology screening results (illicit drug use), electrolyte and serum glucose levels, pH, BAC, and medication usage. QT-prolonging medication was defined as described in CredibleMeds [29].

ECG MEASUREMENTS

The RR interval and QT interval were automatically assessed using a previously validated algorithm [30]. All annotations were checked manually and edited when necessary. Heart rate (HR) was calculated from the RR interval, and the QTc was calculated using

both the Bazett (QTcB) [31] and Fridericia (QTcF) formulas [32]. Bazett's formula is the most widely used in clinical practice and for research purposes and therefore enables comparisons to previous studies. However, since Bazett's formula possibly overcorrects the QT interval at higher heart rates [33] and tachycardia occurs in 10% of children with alcohol intoxication [18], we also calculated the QTc with Fridericia's formula.

DATA ANALYSES

All data were analyzed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp, Armonk, NY). The ECG measurements and baseline characteristics are presented as numbers (percentage, %) for categorical variables and as the mean (standard deviation, SD, normal distribution) or median (interquartile range, IQR, skewed distribution) for continuous variables. Age- and sex-specific cut-off values for the QTc were based on the 95th percentile: QTcB > 430 ms or QTcF > 420 for males and QTcB > 450 ms or QTcF > 430 ms for females [34]. In addition, the risk for TdP was estimated based on the prevalence of a QTc > 500 ms [35] or a QTc increase > 60 ms between ECGintox and ECGreference [36]. A p value < 0.05 was considered to be statistically significant.

To identify the adolescents at risk for QTc prolongation, we performed a two-phase analysis. First, we performed a Pearson's correlation test for continuous variables and a point-biserial correlation test for dichotomous variables to identify univariate correlations between the QTc and potential predictors for QTc prolongation. This analysis was also performed for HR and the QT interval to gain insight into the effect on the QTc, by either the effect on the HR or the effect on the QT interval. Second, we performed multivariable logistic regression analyses based on statistically significant correlation coefficients and clinical knowledge of confounding factors for QTc prolongation. P values were adjusted using the Holm–Bonferroni method due to multiple testing [37].

3. RESULTS

POPULATION CHARACTERISTICS

From a total of 420 adolescents who were eligible for the study, 103 (24.5%) were excluded (Figure 1) due to underlying heart disease (n = 6, 5.8%) or on the basis of ECG characteristics (n = 97, 23.1%). The remaining 317 adolescents were included in the analysis. Adolescents excluded based on ECG characteristics were hospitalized less frequently than adolescents in whom an ECGintox was available (Supplementary Table S1). None of the adolescents excluded based on ECG characteristics presented with TdP.

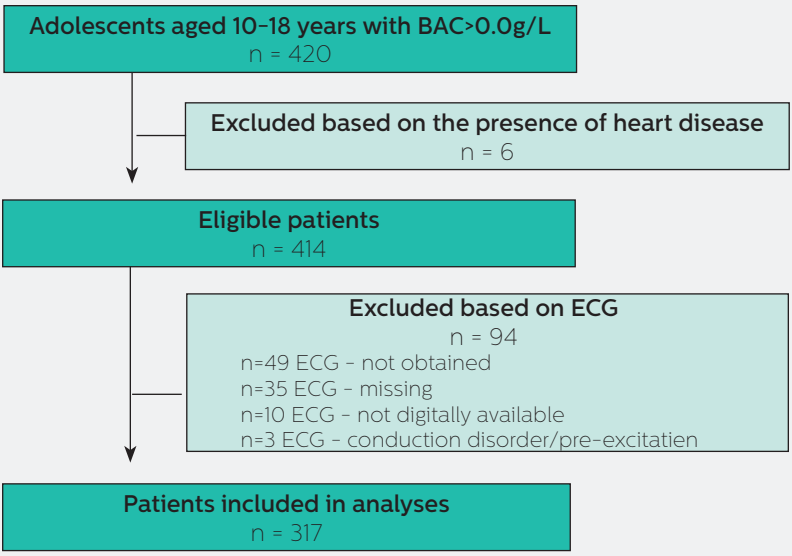

Figure 1 Flowchart of study population

The baseline characteristics of the included adolescents are shown in Table 1. The median age was 16 years (IQR 1.0 years), with no patients aged < 12 years and a slight female predominance (57.1%). Most adolescents did not use medication (76.7%); however, 32 (10.1%) used medications associated with QT prolongation, mainly chronic (psychopharmacological) medications, such as methylphenidate. The mean BAC was 1.9 g/L (SD 0.6 g/L), and 31 (9.8%) adolescents had a positive urine toxicology screening. None of the adolescents presented with TdP. A reference ECG was available for 34 (10.7%) adolescents.

The laboratory findings of the adolescents with alcohol intoxication are shown in Supplementary Table S2. The most common electrolyte disturbances were hyperchloremia (39.1%), hypokalaemia (23.9%), hypocalcaemia (18.5%), and hypernatremia (7.6%).

MEASUREMENTS AT ACUTE ALCOHOL INTOXICATION

ECG characteristics stratified by sex are shown in Table 2, including data from 181 females and 136 males. The mean HR was significantly higher in females than in males (93 bpm versus 84 bpm, $p < 0.001$), while there was no statistically significant difference in the QT interval (344 ms versus 346 ms, $p = 0.52$). As a consequence, the QTc was significantly longer in females than in males (QTcB 422 ms versus 404 ms, $p < 0.001$; QTcF 393 ms versus 384 ms, $p = 0.008$). This finding remained present when the data were stratified by age (Supplementary Table S3). The proportion of adolescents with a QTc above the cut-off value did not differ significantly

Table 1 Baseline characteristics	
Characteristics	**n = 317**
Demographic characteristics	
Girls	181 (57.1%)
Age *in years*	16.0 (IQR 1.0)
Intoxication characteristics	
Medication usage	
None	243 (76.7%)
Medication not associated with QT-interval prolongation	42 (13.2%)
Medication associated with QT-interval prolongation	32 (10.1%)
BAC *in g/L*	1.9 (SD 0.6)
Illicit drug use	31 (9.8%)
Vital functions and monitoring	
Body temperature *in °C*	15.4% (CI 12.1–19.5%)
Glasgow Coma Scale *in EMV points*	14 (IQR 2)
Heart rate *in bpm*	88 (IQR 26)
Systolic blood pressure *in mmHg*	114 (SD 14)
TdP or other ventricular arrhythmias	0 (0.0%)
Follow-up	
Reference ECG	34 (10.7%)
Hospital admission	288 (90.9%)

Note: BAC = Blood Alcohol Concentration, bpm = beats per minute, ECG = Electrocardiogram, EMV = Eye response Verbal response Motor response, IQR = Interquartile Range, n = sample size, SD = Standard Deviation, TdP = Torsade de Pointes

between females and males (QTcB 11.0% versus 16.9%, p = 0.13; QTcF 6.1% versus 10.3%, p = 0.17). Adolescents using QT-prolonging medication did not show a significant difference in the proportion of participants with QTc prolongation compared to adolescents who did not use QT-prolonging medication (QTcB 13.7% versus 12.5%, p = 0.83; QTcF 8.1% versus 6.3%, p = 0.72). None of the adolescents had a QTc > 500 ms.

ECG MEASUREMENTS COMPARED TO BASELINE CONDITIONS

From the 34 adolescents with a reference ECG, the ECGreference was most often recorded at discharge (76.4%) or within 6 months after emergency department presentation (20.6%). Adolescents with a reference ECG more frequently had a QTc longer than age- and sex-specific cut-off values compared to those who did not have a reference ECG (Supplementary S4). Furthermore, although not statistically significant (p = 0.06), adolescents with a reference ECG used QT-prolonging medication more often than those who did not have a reference ECG (20.6% versus 8.8%). However, five out of seven used the medication chronically and during both ECG recordings. One adolescent was on a clarithromycin course on the day of emergency department presentation, and one received one dose of metoclopramide at the emergency department due to profuse vomiting.

Table 2 ECG charachteristics of adolescents with an acute alcohol intoxication stratified by sex		
	Mean (SD)	**Min-Max**
Heart rate *in bpm*		
Girls	93 (SD 18)	48-159
Boys	84 (SD 18)	49-127
QT-interval *in msec*		
Girls	344 (SD 35)	251-469
Boys	346 (SD 35)	275-422
QTcB *in msec*		
Girls	422 (SD 22)	367-476
Boys	404 (SD 30)	321-491
QTcF *in msec*		
Girls	394 (SD 21)	340-452
Boys	383 (SD 26)	326-451

Note: This table shows the ECG characteristics of 181 females and 136 males. bpm = beats per minute, msec = milliseconds, QTcB = QT-interval corrected for heart rate by Bazett's formula, QTcF = QT-interval corrected for heart rate by Fridericia's formula, SD = Standard Deviation

In Figure 2, the differences between ECGintox and ECGreference are shown. There was a significantly higher HR at the time of alcohol intoxication compared to the time of ECGreference acquisition (88 bpm versus 76 bpm, $p < 0.001$) and a shorter QT interval (351 ms versus 362 ms, $p = 0.022$). Interestingly, there was a longer QTcB (421 ms versus 405 ms, $p = 0.002$) for ECGintox compared to ECGreference, while no significant difference was seen in QTcF (396 ms versus 390 ms, $p = 0.18$). There were no significant sex differences for either QTcB or QTcF.

Table 3 shows the extent to which the QTc differs between ECGintox and ECGreference. Compared to baseline conditions, 70.6% of the adolescents had a QTcB prolongation of up to 30 ms during alcohol intoxication, whereas this was only 44.1% for QTcF. Remarkably, females seemed to have more variability in QTcB between ECGintox and ECGreference than males, which was not evident for QTcF.

Table 3 Differences in QTc (ΔQTc) between ECGintox and ECGreference stratified by sex						
	Reference category	**ΔQTc -30-60msec**	**ΔQTc -0-30msec**	**ΔQTc +0-30msec**	**ΔQTc +30-60msec**	**ΔQTc >+60msec**
QTcB	Girls (n=19)	2 (10.5%)	3 (15.8%)	8 (42.1%)	4 (21.1%)	2 (10.5%)
	Boys (n=15)	0 (0.0%)	5 (33.3%)	7 (47.7%)	1 (6.7%)	2 (13.3%)
	Total (n=34)	**2 (5.9%)**	**8 (23.5%)**	**15 (44.1%)**	**5 (14.7%)**	**4 (11.8%)**
QTCF	Girls (n=19)	2 (10.5%)	9 (47.7%)	7 (36.8%)	1 (5.3%)	0 (0.0%)
	Boys (n=15)	1 (6.7%)	7 (46.7%)	7 (46.7%)	0 (0.0%)	0 (0.0%)
	Total (n=34)	**3 (8.8%)**	**16 (47.1%)**	**14 (41.2%)**	**1 (2.9%)**	**0 (0.0%)**

Note: msec = miliseconds, n = sample size, QTcB = QT-interval corrected for heart rate by Bazet-t's formula, QTcF = QT-interval corrected for heart rate by Fridericia's formula

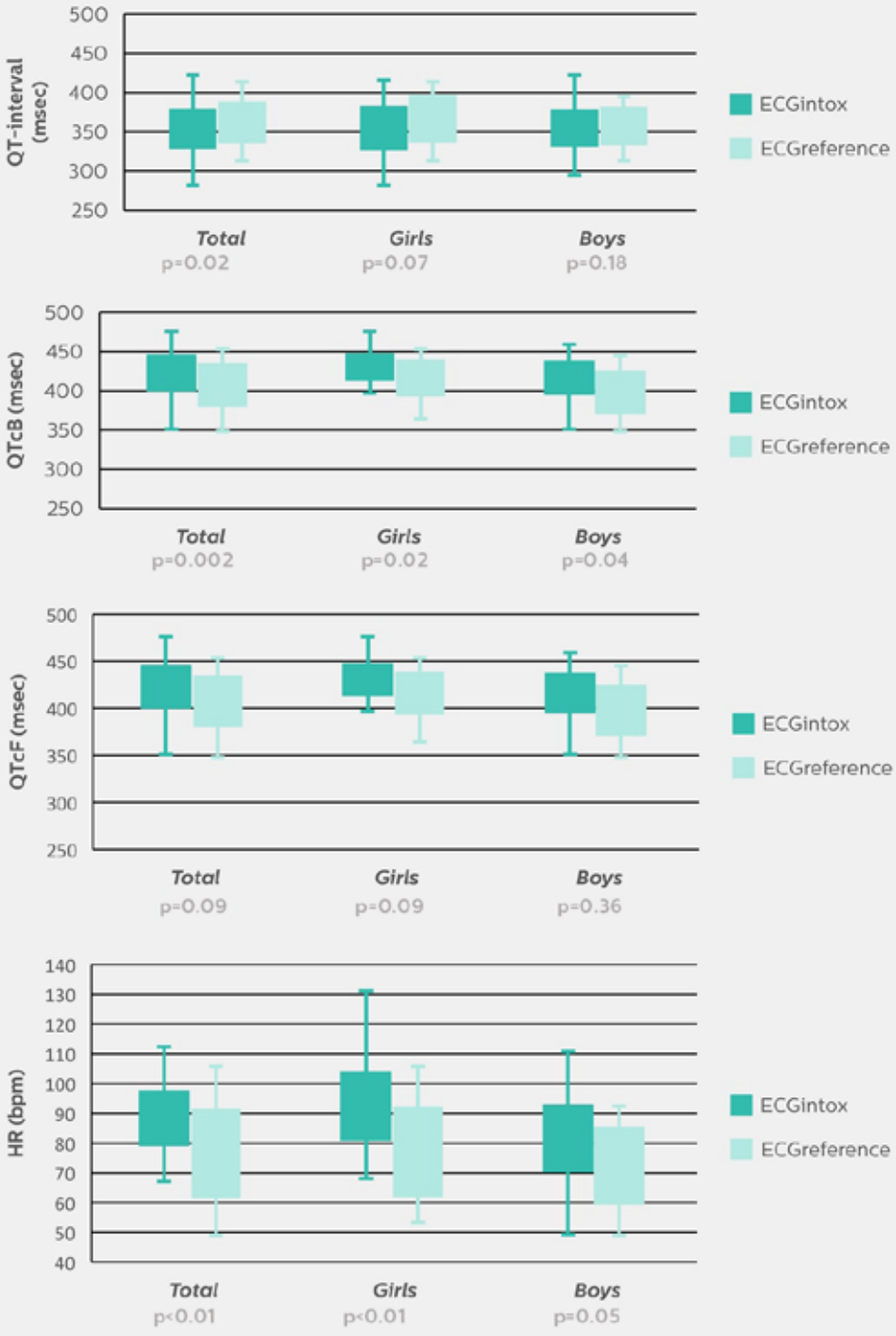

Figure 2 Boxplot of QT-interval, QTc and Heart Rate between ECGintox and ECG reference in 34 adolescents

Four adolescents (11.8%) had a QTcB prolongation >60 ms, while this was not seen for QTcF. Of these four adolescents (Table 4), three had a larger HR increase between ECGintox and ECGreference than the mean HR increase (40 bpm versus 12 bpm). In all four adolescents, there was an additional factor for QTc prolongation, namely, hypokalaemia (n = 1), hypocalcaemia (n = 2), hypernatremia (n = 1), acidosis (n = 2), metoclopramide (n = 1), and (meth)amphetamine intoxication [38].

Table 4 Characteristics of the four patients presented with a ΔQTc (QTcintox-QTcreference) >+60msec

Characteristics	Patient 1 ΔQTcB +73	Patient 2 ΔQTcB +68	Patient 3 ΔQTcB +65	Patient 4 ΔQTcB +65
Demographic characteristics				
Sex	Girl	**Boy**	**Boy**	Girl
Age *in years*	16	15	**14**	15
Intoxication characteristics				
QTc-prolonging medication	-	Metoclopramide	-	-
BAC *in g/L*	2.7	2.0	1.4	1.9
Urine drug screening	-	**Cannabis**	-	**(Meth)amphetamine**
Vital functions				
Body temperature *in °C*	37.5	**35.5**	37.2	**36.0**
GCS *in EMV points*	13	**8**	14	15
SBP *in mmHg*	110	**93**	**140**	100
Laboratory results				
Sodium *in mmol/L*	140	**150**	143	142
Potassium *in mmol/L*	**3.0**	4.2	3.8	4.0
Calcium *in mmol/L*	**2.19**	**2.18**	2.25	2.34
Chloride *in mmol/L*	101	**112**	104	**108**
Glucose *in mmol/L*	7.6	6.1	6.0	8.4
Bloodgas pH	-	**7.33**	7.38	**7.29**
ECGintox				
Heart rate *in bmp*	99	**111**	92	70
QT-interval *in msec*	371	338	333	398
QTcB *in msec*	**476**	**459**	413	429
QTcF *in msec*	**438**	415	385	419
ECGreference				
Heart rate *in bmp*	60	68	51	53
QT-interval *in msec*	403	368	379	386
QTcB *in msec*	403	391	348	364
QTcF *in msec*	403	383	358	371

Note: BAC = Blood Alcohol Concentration, bpm = beats per minute, ECG = Electrocardiogram, msec = milliseconds, QTcB = QT-interval corrected for heart rate by Bazett's formula, QTcF = QT-interval corrected for heart rate by Fridericia's formula. Bold font indicates a value above or below the reference interval.

PREDICTORS OF QTC PROLONGATION

Correlation coefficients for the QTc, HR, and QT interval are presented in Supplementary Table S5. In Tables 5 and 6, predictors for QTc prolongation as well as for HR and the QT interval are shown. Males with alcohol intoxication had a 2.74 (95% confidence interval [CI] 1.21–6.23) times higher risk for QTcB prolongation than females, and a 5.31 (95% CI 1.38–20.49, $p = 0.02$) times higher risk for QTcF prolongation. Increasing age was associated with a reduction in the risk for QTcB prolongation (OR 0.59, 95% CI 0.42–0.83, $p < 0.001$); however, this was not seen for QTcF prolongation. Each mmol/L reduction in serum potassium was associated with a 6.41 (95% CI 2.02–20.41, $p < 0.001$) times higher risk for QTcB prolongation and a 32.89 (95% CI 4.71–228.67, $p < 0.001$) high risk for QTcF prolongation. Remarkably, there was no independent effect of BAC or QTc-prolonging medication use.

4. DISCUSSION

MAIN RESULTS

The present study is the first to determine the prevalence of QTc prolongation and TdP in adolescents with alcohol intoxication and to identify patients at risk for QTc prolongation. We found a prevalence of QTc prolongation of approximately 10%. None of the adolescents had a QTc > 500 ms or ventricular arrhythmias. Compared to baseline conditions, most adolescents with alcohol intoxication had a QTc prolongation of up to 30 ms, and only 11.8% had a QTc prolongation of > 60 ms. Risk factors for QTc prolongation were male sex and a lower serum potassium level. A young age, i.e., 12–14 years, was associated with QTcB prolongation but not QTcF prolongation.

ALCOHOL INTOXICATION AND ITS EFFECT ON HR AND QTC PROLONGATION

Experimental studies in healthy adult volunteers administered predetermined doses of alcohol (either ingested or intravenously infused) show a dose–response relationship between the amount of alcohol administered and QTc prolongation [39, 40]. In adults, alcohol levels of 0.4–1.4 g/L are associated with a 10–30 ms prolongation of the QTc, which is mainly attributable to an increase in the QT interval, as HR does not significantly increase after alcohol administration [39, 40]. This phenomenon is also seen in adults presenting to an emergency department for alcohol intoxication [18, 23]. In addition to the findings in adults, we found that most adolescents with alcohol intoxication also had a QTc prolongation of 0–30 ms. However, this was mainly caused by a difference in HR between baseline conditions and the time of alcohol intoxication rather than to an increase in the QT interval.

Table 5 Logistic-regression-model of predictors of QTcB-prolongation based on age- and sex-specific cut-off values

Predictor	Proportion	Odds Ratio	p-value
Demographic characteristcs			
Sex *Girls* *Boys*	 9.0% 16.3%	 REF 2.70 (1.14-6.39)	 REF p=0.02
Age *12-14* *15-17*	 17.5% 10.8%	0.56 (0.39-0.79)	p=0.001
Intoxication characteristics			
Medication *Not associated with QT-prolongation* *Associated with QT-prolongation*	 12.1% 12.5%	 REF 1.39 (0.40-4.86)	 REF p=0.55
Blood alcohol concentration *<2.0g/L* *>2.0g/L*	 13.1% 11.2%	0.52 (0.21-1.27)	p=0.15
Vital functions			
Body temperature *Hypothermia <35.0* *>35.0*	 14.8% 11.6%	0.65 (0.38-1.11)	p=0.11
Glasgow Coma Score *Mild EMV 13-15* *Moderate EMV 9-12* *Severe EMV <9*	 10.3% 20.4% 16.7%	0.92 (0.80-1.07)	p=0.28
Systolic blood pressure *Hypotension (RRsys <100mmHg)* *Normotenstion* *Hypertension (RRsys >130mmHg)*	 14.0% 12.1% 11.1%	1.00 (0.97-1.03)	p=0.89
Laboratory results			
Serum sodium *<ULN* *Within reference interval* *>ULN*	 - 12.2% 12.5%	0.97 (0.82-1.16)	p=0.75
Serum potassium *<ULN* *Within reference interval* *>ULN*	 19.2% 10.5% -	0.13 (0.04-0.44)	p<0.001
Serum calcium *<ULN* *Within reference interval* *>ULN*	 11.9% 14.5% -	0.10 (0.00-5.08)	p=0.25

Note: Continious variables were entered in the logistic-regression as such. Categories are also shown in the table for the proportion of adolescents with a QTcB above the age- and sex-specific cut-off value. A dash indicates that the sample size of the category was <5 and considered too small to determine the proportion of adolescents with a QTcB above the cut-off.

Table 6 Logistic-regression-model of predictors of QTcF-prolongation based on age- and sex-specific cut-off values

Predictor	Proportion	Odds Ratio	p-value
Demographic characteristcs			
Sex *Girls* *Boys*	 4.0% 9.6%	 REF 5.32 (1.38-20.49)	 REF p=0.02
Age *12-14* *15-17*	 1.6% 7.6%	1.39 (0.77-2.48)	p=0.28
Intoxication characteristics			
Medication *Not associated with QT-prolongation* *Associated with QT-prolongation*	 6.4% 6.3%	 REF 0.76 (0.12-4.75)	 REF p=0.77
Blood alcohol concentration *<2.0g/L* *>2.0g/L*	 4.8% 8.3%	0.49 (0.15-1.64)	p=0.25
Vital functions			
Body temperature *Hypothermia <35.0* *>35.0*	 11.1% 5.8%	1.02 (0.45-2.31)	p=0.95
Glasgow Coma Score *Mild EMV 13-15* *Moderate EMV 9-12* *Severe EMV <9*	 4.2% 10.2% 16.7%	0.84 (0.69-1.02)	p=0.07
Systolic blood pressure *Hypotension (RRsys <100mmHg)* *Normotenstion* *Hypertension (RRsys >130mmHg)*	 9.3% 6.3% 0.0%	0.95 (0.92-0.99)	p=0.02
Laboratory results			
Serum sodium *<ULN* *Within reference interval* *>ULN*	 - 6.3% 8.3%	0.84 (0.65-1.08)	p=0.17
Serum potassium *<ULN* *Within reference interval* *>ULN*	 16.4% 3.5% 0	0.03 (0.00-0.21)	p<0.001
Serum calcium *<ULN* *Within reference interval* *>ULN*	 8.9% 6.2% -	0.43 (0.00-10.22)	p=0.76

Note: Continious variables were entered in the logistic-regression as such. Categories are also shown in the table for the proportion of adolescents with a QTcF above the age- and sex-specific cut-off value. A dash indicates that the sample size of the category was <5 and considered too small to determine the proportion of adolescents with a QTcF above the cut-off.

The more prominent role of HR in adolescents compared to adults can be explained by several mechanisms. First, adolescents have a stronger HR response to environmental changes (e.g., during postural changes, fever, psychosocial stress, and physical exercise [41–45]) than adults due to greater baroreflex sensitivity, which causes a greater autonomic response to either parasympathetic withdrawal [46, 47] or sympathetic stimulation[48].

Second, adolescents reach higher stages of intoxication at a lower BAC [1, 18, 20] than adults. Hence, although BAC is the most objective measure to quantify the level of alcohol intoxication, the extent of alcohol intoxication is influenced by factors such as age, individual body weight, tolerance to alcohol, the percentage of alcohol in the beverage, and the period of alcohol ingestion [18]. In a previous study regarding QTc prolongation in adults with alcohol intoxication, there was a mean BAC of 1.7 g/L, corresponding to the excitement stage of alcohol intoxication characterized by emotional instability and decreased inhibition [24]. In our study, the mean BAC was somewhat similar to that in a study in adults (1.9 g/L). However, as adolescents reach higher stages of alcohol intoxication than adults at a lower BAC, one could postulate that the adolescents in our study were at a more advanced stage of intoxication, the confusion stage. Although there are no available data on HR by intoxication stage, the exaggerated emotions of the confusion stage can be associated with a more substantial HR increase than the excitement stage, as emotions can increase HR compared to baseline [49].

The prominent role of HR in adolescents with alcohol intoxication may underlie the different effects seen in QTc based on the chosen correction formula. Most QT interval correction formulas lead to similar QTc values in the presence of baseline conditions and an HR of approximately 60 bpm [33]. The Bazett formula, however, generally shows a more prominent QTc prolongation than the Fridericia formula when the HR is above 60 bpm [33]. As in our study, the mean HR during alcohol intoxication was 88 bpm (IQR 26 bpm), and this phenomenon could explain the differences found between QTcB and QTcF, with a more pronounced QTcB prolongation compared to QTcF prolongation at the time of alcohol intoxication and when compared to a reference ECG. In addition, QTcB was not correlated with body temperature or SBP (parameters associated with HR), which was seen for QTcF. As HR decreases with age [50], the younger age group showed an increased risk for QTcB prolongation but not QTcF prolongation.

RISK FACTORS FOR QTC PROLONGATION IN ADOLESCENTS WITH ALCOHOL INTOXICATION

QTc is influenced by age and sex, probably under the influence of sex hormones [27]. Before the onset of puberty, no sex differences in QTc are seen, but thereafter, the QTc

shortens in males but not in females [27, 51-53], resulting in a postpubertal QTc that is longer in females than in males. QTc shortening in males after puberty is thought to be caused by testosterone [27, 54]. As our study included individuals with ages corresponding to the pubertal period, i.e., ages 12–18 years, the included males were in a transient period of rising serum testosterone levels [55], and therefore, the QTc-shortening effect of testosterone may not have been fully present, increasing their risk for QTc prolongation in the presence of modulating factors such as alcohol intoxication. The effect of female sex hormones, i.e., oestrogen and progestogen, on the QTc is less clear [27, 54]. In adolescents, female sex hormones are influenced by the menstrual cycle. In healthy adult females, no changes in QTc are seen during the phases of the menstrual cycle, but the HR fluctuates during the menstrual phases [56, 57]. As this also applies to female adolescents, it could be postulated that in the presence of modulating factors such as alcohol intoxication, the HR rather than the QTc will be affected. This could explain why females are more sensitive to HR increase during alcohol intoxication compared to males [58], whereas normally females and males around the age of 16 have a similar HR [50].

Hypokalaemia was not surprisingly associated with QTc prolongation in our study. Low extracellular potassium levels reduce the voltage-gated rapid delayed rectifier outward K^+-current, which is critical to phase 3 repolarization of cardiomyocytes and therefore results in prolongation of the QT interval [59]. Hypokalaemia is a common finding in adolescents with alcohol intoxication [13, 14] and results from several mechanisms. First, with acute stress, i.e., hospital admittance and ambulance rides, there is a catecholamine-induced intracellular potassium shift [60]. Second, although less frequently observed than acidosis, alkalosis in patients with alcohol intoxication does occur and might also result in an intracellular potassium shift [59]. Third, vomiting and volume depletion may result in extrarenal or renal potassium loss [60-62].

LIMITATIONS

As our study had a retrospective design, only 88% of the adolescents had ECGs, and 10.7% had a reference ECG. This reflects, however, the daily clinical practice, as there are currently no guidelines regarding recommendations for ECG screening and follow-up. The proportion of those with ECGs made at emergency department presentation due to alcohol intoxication in our study is similar to what is seen in adults [23]. Our follow-up is similar to a previous study in children and adolescents presenting with an overdose/intoxication [63], where it was postulated that follow-up was limited due to (I) a low estimated probability of LQTS, as QT prolongation was attributed to other risk factors

(such as hypokalaemia or acidosis), (II) a lapse in communication during the transfer of care, and (III) inadequate recognition of abnormal findings [63, 64].

As the majority of the adolescents did not have a reference ECG available, it is difficult to determine if the prolonged QTc was attributable to intoxication or if it was the patients' normal QTc. As the absolute prevalence of QTc prolongation was somewhat higher in the adolescents with reference ECGs, this prolongation could have been the motivation for follow-up. Therefore, the result that 12% of the adolescents had a QTc prolongation >60 ms is most likely an overestimation. However, as age- and sex-specific QTc cut-off values were based on the 95th-percentile of a cohort including LQTS genotype-negative family members [34], it is unlikely that 10% of the adolescents with QTc prolongation during alcohol intoxication had this QTc as their normal QTc.

Although not statistically significant, there was an absolute higher use of QT-prolonging medication in the adolescents with a reference ECG, so the use of QT-prolonging medication could have been the motivation to record an ECGreference. The use of QT-prolonging medication results in a reduced repolarization reserve [65], which may result in overestimation of the difference between the QTc at the time of alcohol intoxication and baseline conditions. However, this overestimation would not have affected the main results to a great extent as the number of adolescents with QT-prolonging medication was limited, and we mainly observed a difference in HR between the time of the alcohol intoxication and baseline, rather than an increase in the QT interval.

RECOMMENDATIONS

Clinicians involved in the acute care of adolescents with alcohol intoxication should be aware of the possibility of QTc prolongation during this period and should therefore always obtain an ECG at presentation and accurately assess the QT interval [66, 67]. Although no ventricular arrhythmias were observed in this cohort, QTc prolongation can predispose patients to malignant QT-related arrhythmias. We advocate admitting adolescents with a QTc longer than the age- and sex-specific cut-off values and if there was an increase of at least 60 ms compared with baseline values, especially in young males and in the presence of hypokalaemia. For continuous cardiac monitoring, general precautions apply, including monitoring for a QTc >500 ms or a QTc prolongation >60 ms compared to a baseline ECG. In all these patients, additional awareness should be given to limiting exposure to QTc-prolonging medication and considering increasing potassium levels to a high-normal range (4.5–5.0 mmol/L). A reference ECG should be made at discharge.

5. CONCLUSION

QTc prolongation was seen in approximately 10% of the adolescents presenting with alcohol intoxication, and although no ventricular arrhythmias were observed in this cohort, these patients may be predisposed to malignant QT-related arrhythmias. In particular, young males and adolescents with hypokalaemia are at risk for QTc prolongation. Clinicians must be aware of the possibility of QTc prolongation during alcohol intoxication and make an effort to obtain an ECG at presentation, measure the QT interval, and give an adequate assessment of the findings. We advocate admitting adolescents with alcohol intoxication and QTc prolongation. During hospital admission, we recommend limiting exposure to QTc-prolonging medication, increasing potassium levels to a high-normal range (4.5–5.0 mmol/L) and obtaining a reference ECG at discharge.

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Supplementary Table S1 Adolescents with ECGintox versus adolescents with missing ECG			
Characteristics	**Missing ECGintox n=97**	**ECGintox available n=317**	**p**
Demographic characteristics			
Girls	56.7%	57.1%	0.95[a]
Age *in years*	15.0 (IQR 2.0)	16.0 (IQR 1.0)	0.15[c]
Intoxication characteristics			
Medication usage			0.25[a]
None	80.4%	76.7%	
Meds not associated with QT-prolongation	7.2%	13.2%	
Meds associated with QT-iprolongation	12.4%	10.1%	
BAC *in g/L*	2.0 (SD 0.6)	1.9 (SD 0.6)	0.54[c]
Illicit drug use	12.4%	10.1%	0.52[a]
Vital functions and monitoring			
Body temperature *in °C*	35.9 (SD 0.8)	36.0 (SD 0.8)	0.36[c]
Glasgow Coma Scale *in EMV points*	13.0 (SD 2.6)	13.3 (SD 2.5)	0.43[c]
Systolic blood pressure *in mmHg*	115 (SD 14)	114 (SD 15)	0.42[c]
Follow-up			
Hospital admission	82.5%	90.9%	0.02[a]
Laboratory results			
Hypernatremia	8.9%	7.6%	0.69[a]
Hypokalemia	22.5%	23.9%	0.78[a]
Hypocalcemia	19.3%	18.5%	0.87[a]
Hyperchloremia	41.9%	39.1%	0.65[a]
Glucose	6.3 (SD 1.1)	6.6 (SD 1.4)	0.10[a]
Acidosis	37.1%	39.1%	0.78[a]

Note: adolescents were excluded because (I) no ECG could be obtained due to aggression or psychomotor agitation), (I) the ECG was missing, (III) the ECG not digitally available, or (IV) because there were conduction disorders or pre-excitation that influences QT-interval measurements. BAC = Blood Alcohol Concentration, bpm = beats per minute, ECG = Electrocardiogram, EMV = Eye response Movement response Verbal response, IQR = interquartile Range. a = Chi-square test, b = Mann-Whitney U-test, c ANCOVA, mean adjusted for age- and sex

Supplementary Table S2 2 Laboratory findings of adolescents presenting with alcohol intoxication						
	Reference range	**n**	**Mean (SD)**	**Min - Max**	**% <LLN**	**% >LLN**
Glucose	3.5-11.1 mmol/L	314	6.6 (SD 1.3)	3.8-16.1	0 (0.0%)	2 (0.6%)
Sodium	134-145 mmol/L	316	142 (SD 2)	137-150	0 (0.0%)	24 (7.6%)
Potassium	3.5-5.0 mmol/L	310	3.8 (SD 0.4)	2.8-5.6	74 (23.9%)	4 (1.3%)
Calcium	2.20-2.65 mmol/L	303	2.29 (SD 0.11)	2.03-2.63	56 (18.5%)	0 (0.0%)
Chloride	97-107 mmol/L	304	106 (SD 4)	95-116	1 (0.3%)	119 (39.1%)
pH	7.35-7.45	274	7.37 (SD 0.06)	7.23-7.64	107 (39.1%)	23 (8.4%)

Note: BAC = Blood Alcohol Concentration, LLN = Lower Limit of Normal, Max = maximum, Min = minimum, n = sample size, ULN = Upper Limit of Normal, SD = Standard Deviation

Supplementary Table S3 Age- and sex- adjusted means of QT, QTc and HR				
Predictor	**QT**	**QTcB**	**QTcF**	**HR**
Demographic characteristcs				
Sex (a) *Girls* *Boys*	p=0.57 344 346	p<0.001 421 404	p<0.001 394 383	p<0.001 93 84
Age (b) *12-14* *15-17*	p=0.11 335 347	p=0.37 410 414	0=0.93 389 389	p=0.40 92 88
Intoxication characteristics				
Medication (c) *Not associated with QT-prolongation* *Associated with QT-prolongation*	p=0.95 343 343	p=0.03 401 411	p=0.56 387 393	p=0.24 84 88
Blood alcohol concentration (c) *<2.0g/L* *>2.0g/L*	p=0.34 345 341	p=0.68 407 405	p=0.76 390 389	p=0.69 86 87
Urine toxicology screening (c) *Positive* *Negative*	p=0.06 334 346	p=0.72 413 414	p=018 384 390	p=0.08 94 88
Vital functions				
Glasgow Coma Score (c) *Mild EMV 13-15* *Moderate EMV 9-12* *Severe EMV <9*	p<0.001 332 339 358	p=0.48 407 403 409	p=0.10 388 390 399	p=0.01 82 84 93
Systolic blood pressure (c) *Hypotension (RRsys <100mmHg)* *Normotenstion* *Hypertension (RRsys >130mmHg)*	p=0.004 353 348 327	p=0.42 409 408 402	p=0.002 395 390 377	p<0.001 82 84

Note: (a) means corrected for age. (b) means corrected for sex. (c) means corrected for age and sex

Supplementary Table S4 Adolescents with missing reference ECG versus those with an available reference ECG

Characteristics	Missing ECGreference n=283	Available ECG reference n=34	p
Demographic characteristics			
Girls	57.2%	55.9%	0.88[a]
Age *in years*	16.0 (IQR 1.0)	16.0 (IQR 3.0)	0.88[c]
Intoxication characteristics			
Medication usage			0.06[a]
None	77.0%	73.5%	
Meds not associated with QT-prolongation	14.1%	5.9%	
Meds associated with QT-iprolongation	8.8%	20.6%	
BAC *in g/L*	1.9 (SD 0.5)	2.0 (SD 0.5)	0.80[c]
Illicit drug use	10.2%	8.8%	0.80[a]
Vital functions and monitoring			
Body temperature *in °C*	36.0 (SD 0.8)	35.8 (SD 0.8)	0.07[c]
Glasgow Coma Scale *in EMV points*	13.3 (SD 2.6)	13.1 (SD 2.5)	0.59[c]
Systolic blood pressure *in mmHg*	114 (SD 15)	110 (SD 15)	0.15[c]
Follow-up			
Hospital admission	90.5%	94.1%	0.49[a]
Laboratory results			
Hypernatremia	7.8%	5.9%	0.69[a]
Hypokalemia	23.6%	26.5%	0.71[a]
Hypocalcemia	18.5%	18.2%	0.96[a]
Hyperchloremia	38.7%	42.4%	0.68[a]
Glucose	6.6 (SD 1.3)	6.6 (SD 1.4)	0.91[a]
Acidosis	36.6%	58.1%	0.02[a]
ECGintox parameters			
HR *in bpm*	89 (SD 18)	88 (SD 18)	0.89[c]
QT-interval *in msec*	344 (SD 35)	351 (SD 35)	0.32[c]
QTcB *in msec*	413 (SD 25)	421 (SD 26)	0.08[c]
QTcB >95th percentile	36 (12.7%)	7 (20.6%)	0.21[a]
QTcF *in msec*	388 (SD 24)	396 (SD 25)	0.10[c]
QTcB >95th percentile	19 (6.7%)	6 (17.6%)	0.02[a]

Note: BAC = Blood Alcohol Concentration, bpm = beats per minute, ECG = Electrocardiogram, IQR = Interquartile Range, n = sample size, QTcB = QT-interval corrected for heart rate by Bazett's formula, QTcF = QT-interval corrected for heart rate by Fridericia's formula, SD = Standard Deviation. a = Chi-square test. b = Mann-Whitney U-test. c = ANCOVA, mean adjusted for age- and sex.

Supplementary Table S5 Bivariate correlations										
Characteristics	**BAC**		**HR**		**QT**		**QTcB**		**QTcF**	
	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p
Demographics										
Female sex	+0.10	0.49	−0.10	0.49	−0.03	1.00	**+0.33**	**<0.001**	**+0.22**	**<0.001**
Age	**+0.21**	**0.003**	−0.06	1.00	−0.01	1.00	−0.13	0.27	−0.10	0.32
Intoxication										
QTc-prolonging med	−0.04	1.00	+0.04	1.00	−0.00	0.98	+0.06	1.00	+0.04	1.00
BAC	NA	NA	−0.12	0.37	+0.06	1.00	−0.06	1.00	−0.01	0.92
Positive tox screen	−0.11	0.42	+0.05	1.00	−0.10	0.56	−0.09	1.00	−0.12	0.32
Vital functions										
Body temperature	**−0.25**	**<0.001**	**+0.18**	**0.02**	**−0.22**	**<0.001**	−0.06	1.00	**−0.16**	**<0.001**
GCS	**−0.18**	**<0.001**	**+0.21**	**0.02**	**−0.22**	**0.001**	+0.02	0.79	−0.11	0.31
HR	−0.12	0.41	NA	NA	**−0.79**	**<0.001**	NA	NA	NA	NA
SBP	−0.12	0.39	**+0.26**	**<0.001**	**−0.33**	**<0.001**	−0.08	1.00	**−0.24**	**<0.001**
Laboratory results										
Sodium	+0.03	0.65	+0.03	1.00	−0.09	0.54	−0.08	1.00	−0.11	0.35
Log10(Potassium)	−0.08	0.94	+0.03	1.00	**−0.17**	**0.03**	**−0.21**	**<0.001**	**−0.25**	**<0.001**
Calcium	**−0.33**	**<0.001**	+0.14	0.16	**−0.17**	**0.03**	−0.04	1.00	−0.12	0.3
Chloride	−0.04	1.00	−0.09	0.86	+0.12	0.28	+0.06	1.00	+0.11	0.39
Log10(Glucose)	**+0.23**	**<0.001**	−0.02	0.75	+0.13	0.22	+0.15	0.11	**+0.18**	**<0.001**
pH	**−0.25**	**<0.001**	+0.11	0.54	−0.10	0.56	+0.04	1.00	−0.02	1.00

Note: BAC = Blood Alcohol Concentration, GCS = Glasgow Coma Scale, HR = Heart Rate in beats per minute, NA = Not Applicable, QTcB = QT-interval corrected for heart rate by Bazett's formula, QTcF = QT-interval corrected for heart rate by Fridericia's formula, SBP = Systolic Blood Pressure. a = Pearson's correlation. b = point-biserial correlation. c = p-values are adjusted with Holm-Bonferroni method, $p<0.05$ is considered to be statistically significant.

SECTION 3

Outpatient follow-up

CHAPTER 8

Outpatient follow-up

The co-occurrence of mental disorders among Dutch adolescents admitted for acute alcohol intoxication

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ABSTRACT

Adolescents with substance use disorders are often diagnosed with co-occurring mental disorders. However, it is unknown if adolescent hospital admission for acute alcohol intoxication is also associated with co-occurring mental disorders. Therefore, the primary aim of this study is to estimate the prevalence of co-occurring mental disorders among Dutch adolescents admitted for acute alcohol intoxication. Secondly, this study aims to explore the cross-sectional relationship between the co-occurrence of mental disorders and patient characteristics, such as sex, age and blood alcohol concentration at admittance. Data were retrospectively collected from 726 adolescents admitted for acute alcohol intoxication. Overall, 245 (34%) of the 726 adolescents treated for acute alcohol intoxication were diagnosed with a co-occurring mental health disorder, such as attention deficit hyperactivity disorder (13%) or autism spectrum disorder (2.1%). Attention deficit hyperactivity disorder in particular seems to be more prevalent in the study population than in the general Dutch adolescent population.

Conclusion: This study demonstrates that among adolescents admitted for acute alcohol intoxication, the prevalence of co-occurring mental disorders is a common and a relevant issue for treatment and prevention strategies.

What is known?

- Alcohol consumption among adolescents has been associated with negative psychosocial effect
- Among adolescents admitted for acute alcohol intoxication, risk factors for psychological dysfunction appear to be inadequately assessed, documented and followed up.

What is new?

- The current study reports on the prevalence of co-occurring mental disorders among a substantial sample of adolescents admitted for acute alcohol intoxication.
- Understanding the prevalence of co-occurring mental disorders is clinically relevant for the outpatient follow-up of adolescents admitted for acute alcohol intoxication.

Keywords*: Adolescent, alcohol, mental disorders, neuropsychological assessment, ADHD*

List of abbreviations*:* anxiety disorder (ANX), autism spectrum disorder (ASD), attention deficit (hyperactivity) disorder (ADD/ADHD), blood alcohol concentration (BAC), depressive disorder (DD), disruptive, impulse control and conduct disorders (DIC), diagnosis and treatment combination codes (DBC-codes), substance use disorder (SUD), trauma- and stressor related disorder (TRAUMA)

1. INTRODUCTION

Detecting the possible co-occurrence of mental disorders among adolescents admitted for acute alcohol intoxication is primarily necessary to treat each individual patient to the best extent possible. The detection of co-occurring mental disorders also aims at the prevention of repeated hospital admissions and the prevention of regular alcohol consumption in later life. Prevention of alcohol use in later life is important because a recent study noted that alcohol use of >100 grams per week at the age of 40 not only is a causal factor in many diseases but also increases all-cause mortality [1].

According to the global status report on alcohol and health 2018 published by the World Health Organization, more than half of the European population aged 15-19 years has used or is currently using alcohol. With regards to patterns of alcohol consumption, heavy episodic drinking among young people aged 15-19 years is particularly prevalent in Europe and high-income countries such as Australia, Canada and the United States [2]. From an international perspective, studying adolescent alcohol use in the Netherlands is an important case study as during the last decade a discrepancy has been observed between the declining trend of regular alcohol use in the Dutch adolescent population [3] and the rising trend of hospital admissions for alcohol intoxication on the other [4].

At admission for acute alcohol intoxication the presence of other mental disorders should be considered. Prior research showed an association between alcohol exposure and mental disorders [5,6]. For adolescents, initiation of alcohol usage has been correlated with mental disorders; symptoms of depression were more prevalent in adolescents who had tried alcohol compared to adolescents who never tried alcohol [7]. Although these studies indisputably associate alcohol misuse among adolescents with negative psychosocial effects, studies about the psychosocial consequences of single episodes of alcohol intoxication are scarce.

This might be explained by research that suggests that risk factors for psychological dysfunction among adolescents admitted for acute alcohol intoxication appears to be inadequately assessed and documented [8]. A recent study among 40 adolescents with acute alcohol intoxication did not find diferences in psychosocial well-being and health-related quality of life to matched controls. However, due to the sample size it remains unclear whether significant relations are absent or untraceable [9].

Understanding the prevalence and patterns of co-occurring mental health disorders among adolescents admitted for acute alcohol intoxication could assist paediatricians

in organizing appropriate outpatient follow-up care with the aim to reduce repetitive admissions. In the current study, medical records of 726 Dutch adolescents were analysed with the prior aim to establish an estimate of the prevalence of co-occurring mental disorders in the population of adolescents admitted for acute alcohol intoxication in contrast to the general Dutch adolescent population.

2. METHOD

STUDY DESIGN AND STUDY POPULATION

This retrospective observational study was conducted in the Reinier de Graaf hospital, Delft, The Netherlands, where in 2007 a prevention-intervention program at the 'Outpatient Department for Adolescents and Alcohol' was implemented for adolescents with acute alcohol intoxication [10]. Participants were selected using the diagnosis and treatment combination code 'intoxication', which is used by all Dutch hospitals to register and declare expenses related to intoxication. All patients aged 10-18 with alcohol intoxication were manually included. Patients not invited for the program were excluded from the analysis.

DATA COLLECTION

All data were extracted from two data sources: the registration form for report to the Dutch Paediatric Surveillance System (NSCK) form for measures related to the acute alcohol intoxication event and electronic medical records for measures related to the follow-up of patients with acute alcohol intoxication. Since 2007, the NSCK has been collecting data of adolescence admitted for acute alcohol intoxication, such as demographic characteristics, intoxication characteristics and substance use patterns. Requirement for inclusion for this study was the written consent of adolescents (and his/her parents if the adolescent was younger than 16 years of age) for reporting to the Dutch Paediatric Surveillance System. As the NSCK registration form does not contain details on outpatient follow-up, additional data were extracted from electronic patient records.

To determine the prevalence of mental disorders among adolescents invited to participate in the prevention-intervention program, first, the process at the 'Outpatient Department of Adolescents and Alcohol' was evaluated. The program consisted of four consecutive stages: invitation to the program (1), consultation with a paediatrician aimed at reflecting on the alcohol intoxication incident (2), a screening consultation with the child psychologist aimed at identifying risk factors for binge drinking and symptoms of underlying neuropsychological disorders (3), neuropsychological assessment if the

screening consult revealed an indication for further research. Flowchart 1 represents the different stages of the program. Adolescents could quit the program at any stage.
Secondly, a standardized abstraction form was used to systematically screen different sections within the electronic health records, namely past medical history, medication, medical records on date of emergency department visit for acute alcohol intoxication, medical records on visits to the 'Outpatient Department for Adolescents and Alcohol' and the outpatient letter by the child psychologist. Each subcategory of co-occurring mental disorders was registered as a binary categorical variable: Attention-deficit (hyperactivity) disorder (ADD/ADHD), Autism spectrum disorder (ASD), Anxiety disorder (ANX), Trauma- and stressor-related disorder (TRAUMA), Disruptive, impulse-control and conduct disorders (DIC), Substance use disorders (SUD), Depressive disorders (DD), other unspecified mental health disorder. Other unspecified mental health disorders were recorded as a string variable and consisted of a heterogeneous group of disorders. In order to prevent traceability to a person, this subgroup will not be specified any further. Data were extracted by two of the researchers independently and any discrepancies in coding were reviewed jointly and discussed to improve reliability.

Co-occurring mental disorders were either diagnosed prior to the hospital admission for acute alcohol intoxication or diagnosed during the follow-up program. Pre-diagnosed co-occurring disorders were derived from medical history. As the diagnostics were performed in specialist mental health care institutions, the process of diagnosis is unknown. Pre-diagnosed disorders were verified by either the general practitioner or the external practitioner of mental health care institution.

The coding of mental health disorders during the program was based on the outpatient letter from the child psychologist to the paediatrician containing the results of the psychological screening and if applicable the a summary statement about the results of neuropsychological assessment. The screening consultation with the child psychologist consisted of a semi-structured interview and the Child Behaviour Checklist (CBCL) (11), a validated instrument for identification of problem behaviour in adolescents. When indicated neuropsychological assessment was performed using a standardized tests for multiple cognitive functions: intelligence (Wechsler Intelligence Scale for Children), short- and long-term verbal memory (15 Words Test and Rey's Visual Design Learning Task), concentration (Amsterdam Neuropsychological Task), cognitive flexibility and inhibition (Stroop Color Test and Wisconsin Card Sorting Test), personality traits (Dutch Personality Questionnaire), coping styles (Utrecht Coping List) and ego-development (Washington University Sentence Completion Test).

ETHICAL APPROVAL AND CONSENT

The study protocol was approved by the Medical Ethical Research Committee Zuid Holland West (ref: 19-080). Partial waiver of informed consent for data extraction from electronic patient records was approved by the medical ethical research committee as the research could not practicably be carried out without the waiver as subjects, especially those age >16 at the moment of admission for acute alcohol intoxication, could be burdened by using the contact information in the medical records, as parents might not have been informed due to the medical confidentiality regulations. However, similar inclusion criteria (adolescents <18 years, BAC >0.0) have been adhered by the NSCK for research to acute alcohol intoxication and therefore consent for this study was deduced from the NSCK registration form. Adolescents (and in case of adolescents <16 years of age parents) that did not provide written consent for NSCK registration were excluded from the study in step 1A, only age and sex were registered and their health records were not screened for coding (Flowchart 1).

For the interpretation of the study results, it is important to realize that in the hospital where this study was performed the department clinical paediatric psychology is independent from the paediatric department. Due to local policies and privacy measures, the patients records and specific test results are registered in a restricted area of the electronic health records not accessible for paediatricians and doctors. Patients of the child psychology department provide informed consent for the report of the results of the screening consult and if applicable neuropsychological assessment to the paediatrician. In case of a missing outpatient letter, the other sections of the medical record were decisive. If the other sections were negative for a co-occurring mental disorders, patients were included in the category 'absence of mental disorders', even though this methodology might cause underrepresentation of the prevalence of co-occurring mental disorders.

STATISTICAL ANALYSES

IBM SPSS Statistics for Windows, version 25.0 (released 2017 by IBM Corp, Armonk, NY), was used to analyse the data. Proportions were expressed as percentages, with 95% confidence intervals (CIs). All continuous data were expressed as the average with standard deviation (SD).

In the determination of the prevalence of mental disorders, adolescents that dropped-out before the first visit to the paediatrician could be considered as missing data, as follow-up might have resulted in a diagnosis. In order to prevent overestimation of the

prevalence of mental health disorders, these study participants were not excluded fromanalysis, but the medical records on date of emergency department presentation were used for coding. The prevalence of mental disorders in the study population was compared to the prevalence of mental disorders in a sample that was representative of the Dutch adolescent population with a mean age of 19.1 years old: the TRacking Adolescents' Individual Lives Survey (TRAILS) sample (12) using binomial z-tests.

Flowchart 1 Frequency of neuropsychological assessment and co-occurring mental health disorders

			BAC (g/L)	Age (years)	Sex (% male)
	1. Invited for preventive program n=726		1.9 (SD 0.5)	15.4 (SD 1.2)	M: 49.2% (CI 45.6-52.9%)
1a n=42	(5.8% of 726)	Total = 65, of which 26 were pre-diagnosed		15.5	M: 38.1%
1b n=23	(3.2% of 726)			15.6	M: 47.8%
	2. Visited peadiatric consult n=661 (91.0% of 726)		1.9 (SD 0.5)	15.4 (SD 1.2)	M: 49.9% (CI 46.2-53.9%)
2a n=62	(9.4% of 661)	Total = 170, of which 38 were pre-diagnosed		15.8	M: 66.1%
2b n=23	(3.4% of 661)			15.4	M: 43.5%
2c n=4	(0.6% of 661)			16.3	M: 75.0%
2d n=81	(12.3% of 661)			15.9	M: 56.8%
	3. Screening consult child psychologist n=491 (74.4% of 661)		2.0 (SD 0.5)	15.2 (SD 1.2)	M: 46.8% (CI 42.5-51.3%)
3b n=54	(11.0%491%)	Total = 407, of which 129 were diagnosed		15.2	M: 35.2%
3c n=58	(11.8% of 491)			15.3	M: 39.7%
3d n=295	(44.7% of 491)			15.3	M: 51.5%
	4. Neuropsychological assessment n=84 (17.1% of 491)		1.9 (SD 1.5)	14.9 (SD 1.2)	M: 43.5% (CI 33.5-54.1%)
4b n=7	(8.3% of 84)	Total = 84, of which 52 were diagnosed		14.4	M: 57.1%
4c n=48	(57.1% of 84)			15.0	M: 45.8%
4d n=29	(34.5% of 84)			14.8	M: 34.5%
		Total diagnosed = 245			

Note:
Total diagnosed = total count of adolescent with alchol intoxication and co-occurring mental health disorder

a=dropped-out. b=coninuation of pre-existing mental health care, c=new referral to mental health care, d=ended program

Abbreviations: BAC=blood alcohol concentration, CI=confidence interval, M=male. SD=standard deviation

Within the study population, adolescents with a co-occurring mental disorder were compared to the control group without co-occurring mental disorder on several outcome parameters: sex, educational level, family structure, ethnicity, age at first alcohol use, age at admission and BAC. The association between categorical variables and presence of co-occurring mental disorders was determined using Pearson's chi-square test. For each continuous variable, normality was assessed using the Kolmogorov-Smirnov test and depending on the results either an independent sample t-test or a Mann-Whitney U test was performed. The association between co-occurring mental disorders and continuous variables were corrected for covariates by a multilinear regression model. The significance level of all these tests was set to p = .05. Descriptive statistics were used to display qualitative differences in patient characteristics between the earlier mentioned subcategories of mental health disorders. Due to expected small group sizes and the risk of multiple testing, no separate statistical analyses have been performed on these subcategories.

3. RESULTS

STUDY POPULATION AND DROP-OUT ANALYSES

During the period 2007-2017, 747 individual adolescents received the diagnosis and treatment combination code 'intoxication' for an alcohol intoxication. Of these 747 adolescents, 726 were invited for the prevention-intervention program at the 'Outpatient Department for Adolescents and Alcohol' and included in the current study population. The exclusion of 21 adolescents was either due to deviation from protocol (n =12) or referral for follow-up to province/country of origin (n =9).

The mean age of the study population was 15.4 years and the study population consisted of slightly more female adolescents (50.1%) than male adolescents (49.9%). Four different reasons for discontinuation were noted: dropping out (A), continuation of care at other health care institutions (B), new referral to mental health care (C) or completion of the program (D). The group that dropped out directly after invitation (1A) consisted of 2 categories: no written consent for NSCK registration (n = 15) and not showing up at/ cancellation of appointment with paediatrician (n=27).

As displayed in Flowchart 1, the total number of adolescents who were already mental health care clients prior to the preventive program (total of category B) was 108 (15%, CI 12%-18%). During the program 109 adolescents (15%, CI 12-18%) were referred to mental health care or addiction care (category C). Overall, among the adolescents invited for the program, 217 (30%, CI 27%-33%) received a form of mental health care prior to the acute alcohol intoxication or were referred to a mental health care institution after the intoxication.

PREVALENCE OF CO-OCCURRING MENTAL DISORDERS

As displayed in the grey box in Flowchart 1, overall, 245 out of 726 (34%, CI 30%-37%) adolescents were diagnosed with a co-occurring mental health disorder. The prevalence of mental disorders in the study does not differ from the prevalence in the TRAILS sample (Table 1).

Table 1 Prevalence of mental disorders amongs adolescents with acute alcohol intoxication

Mental disorder	Prevalence in study population	Prevalence in TRAIL-sample	Binomial z-test
Any disorder	33.7% (CI 30.7-37.3%)	31.0%	2P (Y=245 | n=726, p=0.31) = .06
AD(H)D	12.8% (CI 10.6-15.7%)	3.2%	2P (Y=94 | n=726, p=0.032) = <.001
ASD	2.1% (CI 1.3-2.1%)	-	-
DD	5.8% (CI 4.3-7.8%)	8.8%	2P (Y=15 | n=726, p=0.088) = .002
ANX	0.7% (CI 0.3-1.6%)	18.4%	2P (Y=5 | n=726, p=0.184) = <.001
TRAUMA	2.1% (CI 1.3-2.1%)	-	-
DIC	3.7% (2.5-5.4%)	4.2%	2P (Y=27 | n=726, p=0.042) =.30
SUD	4.0% (2.7-5.8%)	4.9%	2P (Y=29 | n=726, p=0.049) = .15

Note: hyphen indicated that the prevalence has not been assessed in the TRAIL-sample and that therefore no binomial z-test has been performed. Abbreviations: AD(H)D=attention deficit (hyperactivity) disorder, ANX=anxytie disorder, DIC=disruptive, impulse-control and conduct disorder, SUD=substance use disorder, TRAUMA=trauma- and stressor-related disorder.

ADHD was the most frequently co-occurring mental disorder in the study population with a prevalence of 13% (61 with ADHD and 33 diagnosed with multiple co-occurring mental disorders including ADHD). A binomial z-test indicated that the prevalence of ADHD was higher amongst the study population than in the reference population. The prevalence of ASD in the study population was 2.1% out of 727 (6 with ASD and 9 with multiple comorbidities including ASD). The TRAILS study did not assess ASD.

Both the 12-month prevalence of DD and the 12-month prevalence of ANX were lower in the study population than in the reference population. There were no differences between the study population and the TRAILS sample for the prevalence of DIC and for SUD. The prevalence of TRAUMA in the study population was 2.1%, the TRAILS study did not research the prevalence of TRAUMA.

Out of 245 adolescents with co-occurring mental disorders, 46 adolescents were diagnosed with multiple co-occurring mental disorders. Of these 46, most were diagnosed with ADHD and one or more other mental disorders (n = 33).

ACUTE ALCOHOL INTOXICATION CHARACTERISTICS

Table 2 displays the patient characteristics of adolescents with versus adolescent without co-occurring mental health disorder. The proportion of females was significantly higher in adolescents with co-occurring mental disorders (50.8%) than in adolescents without co-occurring mental disorders (48.2%).

Pearson's chi-square test indicated that the presence of co-occurring mental disorders is sex-related ($X^2(1, n=726) = 3.84, p < .05$). The educational level was significantly higher

Table 2 Acute alcohol intoxication characteristics

	Absence of co-occurring mental health disorder	Presence of co-occurring mental health disorder	p-value
(a) Sex Female	48.2% (CI 43.7-52.8%)	55.9% (CI 49.5-62.5%)	**p=0.05**
(a) Educational level Low (VMBO) Middle (HAVO) High (VWO) Other	 36.0% (CI 31.5-40.7%) 31.2% (CI 26.9-35.8%) 22.7% (CI 18.9-27.0%) 10.1% (CI 7.5-13.4%)	 48.6% (CI 41.8-55.5%) 20.6% (CI 15.5-27.7%) 15.4% (CI 11.0-21.1%) 15.4% (CI 11.0-21.1%)	**p<0.001**
(a) Ethnicity Non-native Dutch	15.4% (CI 12.1-19.5%)	13.6% (8.4-19.4%)	p=0.56
(a) Family structure Not living with both parents	25.0% (CI 20.8-29.7%)	47.2% (39.6-54.2%)	**p<0.001**
(b) Age at first alcohol use	14.4 years (SD 1.4)	13.9 years (SD 1.7)	**p<0.001**
(b) Age at admission (intox)	15.4 years (SD 1.2)	15.3 years (SD 1.2)	p=0.21
(b) BAC	1.94 g/L (SD 0.50)	1.85 g/L (SD 0.56)	**p=0.03**
(a) Urinary tox screen Urinary tox screen performed	57.6% (CI 52.8-61.8%)	60.8% (CI 54.4-66.9%)	p=0.40
(a) Results urinary tox screen Positive	7.6% (CI 4.5-11.%)	24.8% (CI 28.3-32.7%)	**p<0.001**
Subtypes Cannabis (Meth)amphetamines Cocaine Different Multiple	 n=16 n=2 n=0 n=2 n=1	 n=18 n=5 n=3 n=5 n=8	

Note: (a)=Chi-square test, (b)=Mann-Whitney U-test

amongst adolescents without a co-occurring mental disorder than in adolescent with a mental disorder ($X^2(3, n=650) = 18.72, p < .05$). Furthermore, adolescents with a co-occurring mental disorder were more frequently raised in a non-traditional family structure (47.3%) than adolescents without a co-occurring mental disorder (25.0%), $X^2(1, n=566) = 27.52, p < .05$. Although the proportion of cases in which a drug screening was

performed did not differ significantly between the those with a co-occurring mental disorder and the reference group, a positive screening was found more frequently in adolescents with co-occurring mental disorder, compared to those without a co-occurring mental disorder.

The descriptive statistics for the subcategories are displayed in Table 3. Adolescents with co-occurring mental disorders were younger at the age of first alcohol use than adolescents without a co-occurring disorder. After correction for the co-variates sex, educational level, ethnicity and family structure by linear regression analysis, the association between the presence of co-occurring mental disorders and age at first alcohol use remained significant ($p < .01$). The association between co-occurring mental disorders and BAC became insignificant after correction for co-occurring mental disorders ($p = .10$).

Table 3 Relationship between co-occurance of mental disorders and acute alcohol intoxication characteristics

Mental disorder	Proportion	Sex % female	Age in years	BAC in g/L
Absence	66.4% (CI 62.7-69.6%)	48.2%[a]	15.4 (SD 1.2)[b]	1.94 (SD 0.50)[c]
Presemce	33.8% (CI 30.4-37.2%)	55.9%[a]	15.3 (SD 1.2)[b]	1.85 (SD 0.56)[c]
AD(H)D		45.9%	15.4 (SD 1.3)	1.98 (SD 0.58)
ASD		33.3%	14.5 (SD 1.5)	2.02 (SD 0.82)
DD		78.6%	14.8 (SD 1.2)	1.80 (SD 0.50)
ANX		100.0%	15.7 (SD 1.5)	1.63 (SD 0.71)
TRAUMA		77.8%	15.1 (SD 1.5)	1.65 (SD 0.46)
DIC		41.7%	14.6 (SD 1.1)	1.62 (SD 0.82)
SUD		42.9%	16.0 (SD 1.0)	2.10 (SD 0.76)
Other		69.2%	15.3 (SD 1.2)	1.78 (SD 0.52)
Multiple		40.4%	15.5 (SD 1.2)	1.81 (SD 0.53)

Note: [a]=Pearson chi-square test $p<0.05$, [b]=Mann-Whitney U-test. not significant, [c]=Mann-Whitney U-test, $p<0.05$. Abbreviations: AD(H)D=attention deficit (hyperactivity) disorder, ANX=anxytie disorder, DIC=disruptive, impulse-control and conduct disorder, SUD=substance use disorder, TRAUMA=trauma- and stressor-related disorder.

4. DISCUSSION

The current study reports the prevalence of co-occurring mental disorders among a substantial sample of adolescents admitted for acute alcohol intoxication. The purpose of the comparison between the highly selective study population (with a mean age of 15.4) and the TRAILS-sample (mean age 19.1 years old) was to set a frame of reference

for clinicians. Although some of the prevalence differences might be partly attributable to this age difference, setting a frame of reference was considered more important than the risk of bias. Preferably, the reference population or a control group would have been similar in mean age and representative of the general Dutch adolescent population.

Selection of a reference group representative of the general Dutch adolescent population with such a specific mean age is challenging and as far as the authors know, Dutch studies studying the prevalence of mental health disorders in adolescents are scarce. Although the age difference between the 2 populations provokes challenges and bias, associations between age and the prevalence of mental health disorders are relatively well explored. For example, a group of matched controls within the hospital setting (for example age-matched adolescents at the outpatient department or emergency department) would results in other confounding factors which might be harder to interpret than age. Furthermore, the TRAILS-sample displays standardized cumulative prevalence graphs by age, which help to explain differences between the study population and reference population attributable to age. Although the comparison might not be relevant from an epidemiological perspective, the comparison is relevant from a clinical paediatric perspective as it might help clinicians involved in the acute care for adolescents with acute alcohol intoxication to value the prevalence of co-occurring mental disorders in the study population and assist them in organizing appropriate follow-up. The relevance of the age differences will be assessed later in this discussion for various mental health disorders.

Overall, 33.8% of the adolescents admitted for acute alcohol intoxication had at least one co-occurring mental disorder, and 29.9% of the adolescents invited to participate in the program had an indication for mental health care or care by youth social services. This is in line with several prior studies that suggest that the prevalence of mental health disorders [13,14] and social problems is elevated among young adults admitted for alcohol intoxication [15,16].

Acute alcohol intoxication and the presence of concurrent mental disorders were sex-specific and occurred more frequently in girls than in boys. This is in line with prior research. Women with SUD have a significantly higher prevalence of comorbid psychiatric disorders than men [17]. Another explanation might be that girls are considered to be more vulnerable to the neurotoxic effects of binge drinking during adolescence (18). The presence of co-occurring mental disorders was significantly associated with a younger age at first alcohol use, which is worrisome since age at first alcohol use has frequently been

associated with increased alcohol consumption later in life [19, 20]. As the prevalence of co-occurring mental disorders among adolescents admitted for acute alcohol intoxication is substantial, prevention of acute alcohol intoxication might be improved by the identification of substance use among adolescents, especially those with a mental health disorder. A recent article provided interview tools that can assist primary care providers efficiently to address problematic substance use by adolescents [21].

The prevalence of ADHD in the study population was significantly higher than the prevalence of ADHD in the TRAILS sample. This result can be partially explained by a higher mean age of adolescents in the TRAILS-sample compared to the study population, as prior epidemiological studies with a large sample size found a negative association between age and prevalence of ADHD [22,23]. The cumulative prevalence graphs in the TRAILS study indicate that ADHD occurred earliest in childhood, with virtually no new onset after age 6 years [12]. The overrepresentation of ADHD in the study population is in line with prior research that indicated that adolescents with ADHD were significantly more likely to develop SUD than adolescents without ADHD [24]. Research has also shown that amongst adults with a SUD, 23% also meet the criteria for ADHD, and even impulsivity facets without the diagnosis of ADHD were related to a higher prevalence of alcohol disorders [25]. The results of our study support a recent modified Delphi study in which a multidisciplinary group of 55 experts from 17 countries agree on the statement that routine screening for ADHD is recommended in substance abuse treatment [26].

The prevalence of ASD in the study population was 2.1%, while a recent meta-analysis reported a global prevalence of ASD of 0.7 per 100 [27].This might suggest an overrepresentation of adolescents with ASD in the study population, which is in contrast to a prior study that shows that elevated autistic trait scores were not significantly associated with adolescent alcohol use and misuse [28].Therefore, an overrepresentation of ASD in the study may indicate that in the case of engagement, adolescents with ASD seem to be more vulnerable to binge drinking resulting in acute alcohol intoxication.

Prior research shows that depressive symptoms are associated with harmful use of alcohol [6,29]. However, the prevalence of DD was significantly lower in the study population than in the TRAILS population. This might be the result of a lower mean age of the study population in comparison to the TRAILS sample. The TRAILS study shows that mood disorders were not prevalent until early adolescence, after which their incidence rose steadily. Dutch national statistics indicate that the self-reported

half-year prevalence for depression is higher amongst older adolescents. In 2017, the self-reported 12-month prevalence of DD of 12- to 16-year-old adolescents was 3.1%, while the self-reported 12-month prevalence of adolescents older than 16 years of age is 10.2% [30].

The prevalence of co-occurring ANX disorders in the study population was low in comparison to the TRAILS sample in which the most common ANX disorder was specific phobia. Specific phobias might be missed in the screening of the psychologist in the follow-up for acute alcohol intoxication patients. Research among adults diagnosed with both alcohol dependence and a social phobia, drinking alcohol eventually became unable to alleviate social phobia symptoms or worsened symptoms [31]. A Finnish study among adolescents revealed that co-morbid general anxiety increased the persistence of frequent alcohol use while co-morbid symptoms of social phobia decreased its persistence [32].

The prevalence of TRAUMA in the study population was 2.1%. Prior research among pre-adolescent children 10-13 years old indicated that PTSD symptoms may be associated with early onset of alcohol use [33]. Several studies indicate that university students with trauma and, in particular, post-traumatic stress disorders are at elevated risk for a problematic drinking pattern [34-36].

The prevalence of DIC amongst adolescents invited for the prevention-intervention program did not differ significantly from the 12-month prevalence in the TRAILS sample. A recent prospective follow-up study indicated that conduct disorder was associated with elevated adjusted hazards for initiation of all substances, with comparatively greater hazard ratios of initiating illicit drug use than alcohol use, at the age of 15 [37].

The prevalence of co-occurring SUD in the study population was 4.0% and did not differ significantly from the prevalence of SUD in the TRAILS population. Therefore, it appears that a co-occurring SUD is not directly associated with an increased risk of hospital admission for acute alcohol intoxication. The standardized cumulative prevalence graphs in the TRAILS study show that drug and alcohol dependence had the latest age of onset, with incidences beginning at the age 14 years and steadily increasing after that [12]. Therefore, a non-significant comparison between the study population with a mean age of 15 years and the TRAILS-sample with a mean age of 19 years might suggest that adolescents admitted for acute alcohol intoxication are at risk of an early SUD, which is in line with prior research has shown that adolescents younger than 15 years of age who

consume alcohol have a 4-6 times higher risk of developing alcohol dependence than adolescents who do not drink alcohol [38-39].

The subcategory other unspecified co-occurring mental disorders exists of a heterogeneous group from various Diagnostic and Statistical Manual of Mental Disorders (DSM) categories, for example schizophrenia spectrum and other psychotic disorders, dissociative disorders, somatic symptom and related disorders, feeding and eating disorders or another unspecified mental health disorder. As each separate group consisted of only a few individuals per diagnosis (<5), specification of the category OTHER would lead to traceable and identifiable patient information. The relatively low frequency of schizophrenia spectrum and other psychotic disorders (<5) is an interesting results as according to the DSM-5, between 7 and 25% of first-episode psychosis subjects have a substance-induced psychosis [40]. In a recent study, even a novel and separate clinical entity named as substance-related exogenous psychosis has been outlined [41]. However, the low prevalence of co-occurring psychotic disorders in the study population can be explained by both the study design and the organisation of mental health care in the Netherlands. This specific study was focused on alcohol intoxication and although approximately 10% of the adolescents combined alcohol and illicit drug use, the numbers of illicit drug use were limited. Furthermore, if patients with a first-episode of substance-induced psychosis have stable vital functions, patients will be assessed by the local crisis intervention team of specialised mental health care institutions. This might explain why adolescents with a first-episode of substance-induced psychosis do not present in the hospital setting and therefore are underrepresented in the study population.

5. CONCLUSION

This study indicated that the presence of mental disorders is common among adolescents admitted for acute alcohol intoxication. The descriptive statistics suggested that some of the subcategories seemed to be sex-specific or age-related. However, further research and an even larger study population are necessary to explore these potential links further. Attention deficit hyperactivity disorder in particular seems to be more prevalent in the study population than in the general Dutch adolescent population. This overrepresentation requires further research in the medical and psychological domains. Co-occurrence of mental disorders is present among 34% of adolescents admitted for acute alcohol intoxication. Therefore, during admittance to the hospital, the social circumstances and signs of mental disorders should be considered. Follow-up of adolescents admitted for acute alcohol intoxication is necessary to prevent repeated admissions, to signalise mental disorders and to determine whether the patient requires

referral to specialised mental health care. Neuropsychological assessment during follow-up of adolescents admitted for acute alcohol intoxication is indicated if screening provides signals for mental disorders. In our opinion, this assessment should take place in well-equipped centres with dedicated and professional specialised staff.

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CHAPTER 9

Preventive measures

Effects of preventive measures against alcohol intoxications among young people in the Netherlands and future plans for Belgium

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ABSTRACT

Alcohol use among young people can lead to irreversible health damage. In 2014, the minimum age for obtaining low-alcohol drinks was raised to eighteen years in the Netherlands. The number of adolescents admitted to hospital with an alcohol intoxication was analyzed in the period 2007-2017. The number increased annually from 2007 to 2011, after which it became reasonably stable with approximately 700-900 admissions per year. The mean age increased from 14.9 to 15.4 years and the number of ten- to fourteen-year-olds decreased. Parents of young people admitted with an alcohol intoxication became stricter. There was an increase in blood ethanol level and duration of loss of consciousness. It remains necessary to invest in preventive measures to protect adolescents against the risks of alcohol in both the Netherlands and Belgium. The effects of the raised minimum age for consuming alcohol in the Netherlands can be used to encourage the discussion among the minimum age in Belgium.

SAMENVATTING

Alcoholgebruik bij jongeren kan leiden tot onomkeerbare gezondheidsschade. In Nederland geldt er sinds 2014 een minimumleeftijdsgrens voor alcohol. Deze ligt op achttien jaar. Het afgelopen decennium heeft men de ziekenhuisopnames van jongeren met een alcoholintoxicatie geregistreerd en geanalyseerd. In de periode 2007-2011 nam dit aantal jaarlijks toe, waarna het redelijk stabiel bleef tussen 700-900 opnames per jaar. Tussen 2007 en 2017 steeg de gemiddelde leeftijd van 14,9 tot 15,4 jaar, terwijl het aantal tien- tot veertienjarigen daalde. Ouders zijn strenger geworden naar minderjarige kinderen toe. Er is echter een toename merkbaar in de ethanolspiegel en de duur van het bewustzijnsverlies. Het blijft noodzakelijk om verder te investeren in preventieve maatregelen om jongeren te beschermen tegen de gevaren van alcohol, zowel in Nederland als in België. De effecten van het verhogen van de leeftijdsgrens in Nederland kunnen brandstof zijn voor de discussie hieromtrent in België.

INLEIDING

Alcoholgebruik bij jongeren blijft een groot maatschappelijk probleem in zowel België als Nederland. In Nederland werden in 2017 in totaal 671 jongeren met een alcoholintoxicatie opgenomen in een ziekenhuis. In België analyseerde men het aantal bloedafnames voor ethanolspiegels bij jongeren tussen twaalf en zeventien jaar: in 2018 waren er ruim 2.200 gevallen. Gezien de verschillende onderzoeks-methodes kan men de cijfers niet met elkaar vergelijken, maar het gaat duidelijk om een groot aantal dat ondanks de nodige sensibilisatie niet daalt [1]. Alcoholgebruik is de belangrijkste risicofactor, die bijdraagt aan "disability-adjusted life years" bij jongeren van tien tot vierentwintig jaar [2]. De kortetermijngevolgen van een alcoholintoxicatie bij jongeren bestaan uit een verminderd bewustzijn, hypothermie, elektrolytstoornissen, metabole acidose, convulsies, [verkeers] ongevallen en verwondingen [3,4]. Alcoholgebruik bij jongeren kan schade geven aan de ontwikkeling van de hersenen, met mogelijk geheugenproblemen tot gevolg [5]. Op lange termijn kan het leiden tot levercirrose, pancreatitis, hart- en vaatziekten en verschillende vormen van kanker. Wereldwijd overlijden bovendien jaarlijks 3.3 miljoen mensen eraan [6-8]. Wanneer men reeds op jonge leeftijd begint met alcohol, geeft dit op latere leeftijd meer kans op verslaving [9]. Maatschappelijk gezien leidt alcoholmisbruik tot overlast en hoge kosten (bijvoorbeeld door ziekenhuiskosten en verkeersongevallen) [10]. Om deze redenen is het belangrijk om overmatig alcoholgebruik te reduceren middels preventie. Recent publiceerde het Nederlands Tijdschrift voor Geneeskunde de resultaten van een tienjarig onderzoek naar alcoholintoxicaties bij jongeren in Nederland [11]. Men verrichtte onderzoek naar de kenmerken van deze jongeren, de getroffen beleidsmaatregelen in Nederland en de effecten van deze inspanningen. De resultaten zijn bruikbaar voor de discussie in België.

PREVENTIE IN NEDERLAND

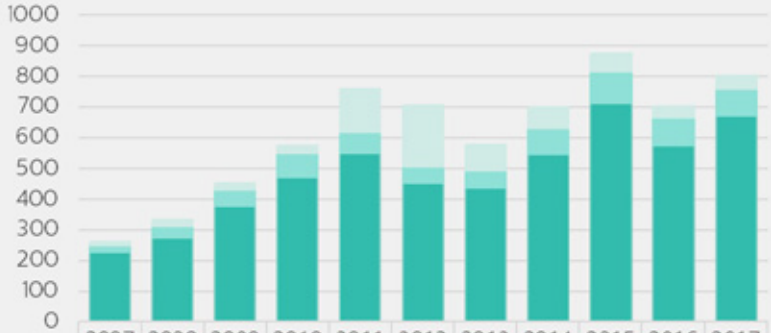
Gezien alle risico's van alcoholgebruik is het alleen al vanuit gezondheidsperspectief beter dat minderjarige kinderen geen alcohol drinken. Daarom is er sinds 1 januari 2014 in Nederland een nieuwe wet, die verbiedt dat jongeren onder de achttien jaar alcohol kunnen kopen of drinken. De leeftijdsgrens stond voordien op zestien jaar voor zwak-alcoholhoudende dranken (< 15%) en op achttien jaar voor sterke drank. Dit was ongeveer vergelijkbaar met de huidige regelgeving in België, waar zestienjarigen bier en (schuim)wijn mogen kopen en vanaf achttien jaar andere drank. Met de nieuwe wet startte men gelijktijdig een landelijke campagne op, genaamd "NIX18". Het doel was om de sociale omgeving te veranderen naar een leefwereld waarin het normaal is dat jongeren onder de achttien jaar niet roken of drinken. Verder kregen ouders en jongeren op sportclubs en scholen voorlichting over de gevaren van alcohol. Alcoholmisbruik

kan een teken zijn van een psychosociale problematiek of psychische stoornissen. In 2007 werd er een multidisciplinair screenings- en nazorgtraject opgezet voor kinderen die men na een opname voor een alcoholintoxicatie verder opvolgde in het Reinier de Graaf Gasthuis in Delft. Enerzijds screent men op tekenen van psychische stoornissen en anderzijds overtuigt men de jongere door middel van individuele voorlichting van de gevaren van alcohol. De speciale alcoholpoli's bevinden zich nu verspreid over het land. Het onderzoek naar de huidige trends werd mogelijk via het landelijke registratiesysteem "Nederlands Signaleringscentrum Kindergeneeskunde" (NSCK). Kinderartsen meldden hierbij anoniem de sociale en de demografische gegevens van de opgenomen jongeren. Ook sloot men een "Nationaal Preventieakkoord", waarbij men op grote schaal met meerdere partijen de alcoholproblematiek aanpakt [12].

RESULTATEN VANUIT DE NEDERLANDSE REGISTRATIE

In de periode 2007-2017 verzamelde men via het NSCK gegevens van Nederlandse jongeren tot en met zeventien jaar, opgenomen in het ziekenhuis met een alcoholintoxicatie. Tijdens hun opname vulden de patiënten een vragenlijst in, die de kinderarts vervolgens opstuurde naar het NSCK. Redenen voor de opname konden een verminderd bewustzijn, een (verkeers)ongeval, agressie of een suïcidepoging zijn. De analyses omvatten alleen jongeren met een verminderd bewustzijn. In totaal werden er in deze periode 7.364 jongeren opgenomen.

Figure 1 Ziekenhuisopnames per jaar van Nederlandse jongeren <18 jaar als gevolg van overmatig alcoholgebruik



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Niet geregistreerd	15	20	20	27	143	199	83	71	58	36	48
Andere reden*	22	37	51	76	71	54	60	84	103	91	85
Alcoholintoxicatie	226	274	379	471	547	451	434	545	713	574	671

* Bijvoorbeeld een verkeersongeval, agressie of suicidepoging

De auteurs voerden een trendanalyse uit van de beschikbare gegevens over de periode 2007-2017. Er was sprake van een statistisch significante stijging in het aantal meldingen van ziekenhuisopnames van jongeren als gevolg van overmatig alcoholgebruik in deze periode. Het aantal nam tot en met 2011 jaarlijks toe en bleef daarna redelijk stabiel met ongeveer 700 tot 900 opnames per jaar (fig. 1).

KENMERKEN VAN OPGENOMEN JONGEREN

De gemiddelde leeftijd steeg statistisch significant van 14,9 tot 15,4 jaar in de periode 2007-2017 (tabel 1) (fig. 2).

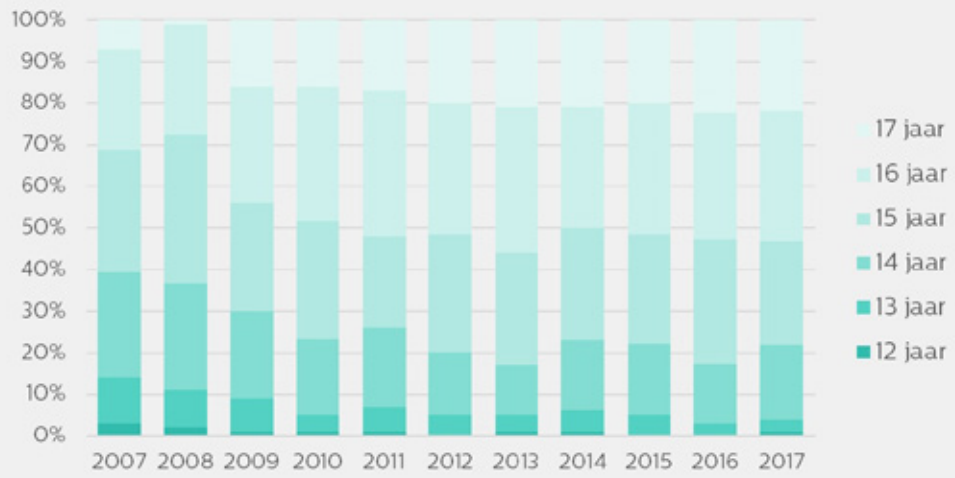
Tabel 1 Kenmerken van jongeren (<18 jaar) opgenomen met een alcoholintoxicatie, NSCK 2007-2017

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Trend
Opnames	226	272	279	464	548	474	454	558	726	574	671	p<.001
Geslacht % Jongens	52%	52%	49%	57%	54%	53%	51%	51%	47%	52%	50%	p=.14
Leeftijd *jaar*	14.9	14.9	15.2	15.4	15.3	15.5	15.5	15.4	15.5	15.4	15.4	p<.001
Jongens	14.9	15.2	15.5	15.6	15.4	15.6	15.7	15.5	15.7	15.6	15.5	p<.001
Meisjes	14.9	14.7	14.9	15.0	15.3	15.3	15.5	15.3	15.3	15.2	15.2	p<.001
Ethanolspiegel	1.82	1.86	1.85	1.84	1.85	1.94	1.92	1.97	1.98	2.01	2.01	p<.001
Jongens g/L	1.87	1.91	1.98	1.92	1.88	2.03	1.98	1.97	2.00	2.05	2.06	p<.001
Meisjes g/L	1.78	1.82	1.75	1.72	1.82	1.83	1.85	1.96	1.97	1.97	1.94	p<.001
Gedaald EMV *uren*	2.24	2.89	3.06	3.14	2.94	2.83	2.97	3.14	3.15	3.12	3.38	p=.22
Opnameduur *dagen*	1.07	0.98	0.95	0.95	0.70	0.98	1.00	1.02	0.78	0.79	1.00	p<.001

Daarnaast daalde het aantal opgenomen tien- tot veertienjarigen van 37% naar 23%. De gemiddelde ethanolspiegel nam statistisch significant toe van 1,82‰ tot 2,01‰. Ook de duur van de bewustzijn-sdaling steeg significant van 2,2 tot 3,4 uur. Het aantal jongens en meisjes bleef ongeveer gelijk verdeeld. De jongens waren wel gemiddeld ouder dan de meisjes (15,5 versus 15,2 jaar). Wat tevens opviel in de groep jongens, was een significant hogere ethanolspiegel dan bij de meisjes (1,98‰ versus 1,88‰). Het grootste gedeelte van de opgenomen jongeren had een Nederlandse achtergrond (88%). De geïntoxiceerde jongeren situeerden zich op verschillende school-niveaus: 40% voorbereidend middelbaar beroepsonderwijs (VMBO), 24% hoger algemeen voortgezet onderwijs (HAVO) en 19% voorbereidend wetenschappelijk onderwijs (VWO). In 2011 gaf 24% van de ouders geen toestemming voor alcoholgebruik onder de achttien jaar, wat in 2017 was gestegen naar 53%. Vanaf 2011 hield men de toestemming van de ouders bij in de vragenlijsten. Wanneer men de periode vóór en na de leeftijdsverhoging in 2014 vergelijkt, zijn er ook significante verschillen: een leeftijdstoename van 15,3 naar 15,4 jaar, een ethanol-spiegelstijging van

1,87‰ naar 1,99‰, een toename in de duur van het bewustzijnsverlies van 2,9 uur naar 3,2 uur en een toename in het aantal ouders die geen toestemming gaven van 29% naar 54%.

Figuur 2: Leeftijdsverdeling van Nederlandse jongeren opgenomen met alcoholintoxicatie



BESPREKING

Het aantal jongeren opgenomen met een alcoholintoxicatie in Nederland steeg tot 2011 en bleef daarna redelijk stabiel tussen 700 à 900 jongeren per jaar. Met de tegenwoordig bekende gevolgen van alcoholmisbruik blijft het een aanzienlijk maatschappelijk probleem. Het is niet mogelijk om te objectiveren hoeveel alcoholintoxicaties hadden plaatsgevonden indien de minimumleeftijd voor het drinken van alcohol niet was verhoogd in 2014. Wel is duidelijk dat het aantal niet doorgestegen en gestabiliseerd is. Daarnaast is de gemiddelde leeftijd bij de opname in de afgelopen jaren toegenomen. Men ziet relatief meer vijftien- tot zeventienjarigen en minder tien- tot veertienjarigen. Daarentegen zijn de ethanolspiegel en de duur van de bewustzijnsdaling toegenomen. Volgens het Peilstationsonderzoek Scholieren van het Trimbos-instituut is het aantal drinkende middelbare scholieren van twaalf tot achttien jaar gedaald in de periode 2011-2015 (13). Daarnaast bleek dat het aantal bingedrinkers in deze periode stabiel is gebleven. Dit betekent dat jongeren die drinken vaker te veel drinken, met een alcoholintoxicatie tot gevolg. Uit hetzelfde onderzoek blijkt dat jongens vaker bingedrinkers zijn dan meisjes (74% versus 67%). Deze bevindingen sluiten aan bij de ethanolspiegelstijging, met een hogere spiegel bij jongens, hetgeen blijkt uit de resultaten.

Wanneer men jongens en meisjes verder vergelijkt, dan ziet men dat meisjes gemiddeld een lagere leeftijd hebben bij de opname. Een mogelijke verklaring is dat meisjes vroeger in de puberteit komen en daardoor eerder experimenteren met alcohol [14,15].

Tegenwoordig geeft men voorlichting over de schadelijke effecten van alcoholgebruik onder jongeren. Uit de resultaten blijkt dat de ouders van de patiënten de afgelopen jaren strenger zijn geworden. Het percentage ouders dat toestemming gaf voor het alcoholgebruik van hun minderjarige kind, nam af. Deze resultaten sluiten aan bij de landelijke steekproef vanuit de "Health Behaviour in School-Aged Children"-studie naar de gezondheid en het welzijn van jongeren in Nederland [16]. Verder onderzoek is nodig om deze positieve trend te bevestigen.

TOEKOMSTPLANNEN

De eerste belangrijke stap in de bescherming van minderjarigen tegen alcohol is naar de mening van de auteurs het verhogen van de minimum-leeftijdsgrens voor álle alcoholhoudende dranken naar achttien jaar in België. Dit is conform de "best buys" van de Wereldgezondheidsorganisatie [17]. Daarnaast moet men de komende jaren in zowel Nederland als België verder investeren in de preventie van alcoholmisbruik op verschillende gebieden [18]. In Nederland bestaat het "Nationaal Preventie-akkoord", waarin meerdere partners, zoals de overheid, zorgaanbieders, zorgverzekeraars, scholen, sportbonden en de industrie, samenwerken aan het verminderen van de alcoholproblematiek [12]. De fysieke en de sociale omgeving moeten veranderen middels het beperken van de fysieke beschikbaarheid van alcohol in bijvoorbeeld sportclubs. Daarnaast moeten campagnes en minder alcoholreclames ervoor zorgen dat alcohol geen normaal consumentenproduct voor adolescenten wordt. Het doel is regelgeving en hand-having van wetten zoals de leeftijdsgrens, bijvoorbeeld door het opleiden van horecamede-werkers en straffen voor de horecasector. Een andere belangrijke maatregel is het vergroten van de "awareness" onder de bevolking via voorlichting, met gedragsverandering tot gevolg. Verder zijn een vroege signalering en ondersteuning van mensen met een alcoholpro-blematiek van belang. Tot slot heeft het verzamelen van gegevens rond alcohol-intoxicaties geleid tot significante conclusies. Het is daarom belangrijk om te investeren in een adequaat registratiesysteem in zowel België als Nederland om de effecten te monitoren. Het IJslandse preventiemodel, ontwikkeld uit de successen in IJsland, kan als voorbeeld dienen [19].

BESLUIT

De inspanningen rond alcoholgebruik onder jongeren in Nederland laten positieve effecten zien. De gemiddelde leeftijd waarop jongeren worden opgenomen met een

alcoholintoxicatie, is gestegen. Verder is het aantal tien- tot veertienjarigen met een alcoholintoxicatie gedaald en de ouders zijn strenger geworden. Daarentegen is er een toename van de gemiddelde ethanolspiegel en van de duur van het bewustzijnsverlies. Het aantal alcoholintoxicaties is gestabiliseerd, maar niet gedaald. De visie op alcohol zou onder de hele bevolking moeten veranderen van een "normaal" consumentenproduct naar een product met schadelijke effecten, mede aangezien overmatig alcoholgebruik ook bij volwassenen aanzienlijke gezondheidsschade kan veroorzaken. Preventieve maatregelen kunnen, naast het verhogen van de leeftijdsgrens in België, bestaan uit alcohol-reclame en het beperken van de beschikbaarheid van alcohol.

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DISCUSSION

Main findings per section, general discussion and general conclusion

GENERAL DISCUSSION AND MAIN FINDINGS

ADOLESCENT ALCHOHOL USE: A REMAINING PUBLIC HEALTH CONCERN

Adolescent alcohol use remains a persistent public health concern. In 2019, 47% of the Dutch secondary school students aged between 12 and 16 reported alcohol consumption at least once ever, and 26% reported alcohol use in the last month [1, Figure 1].

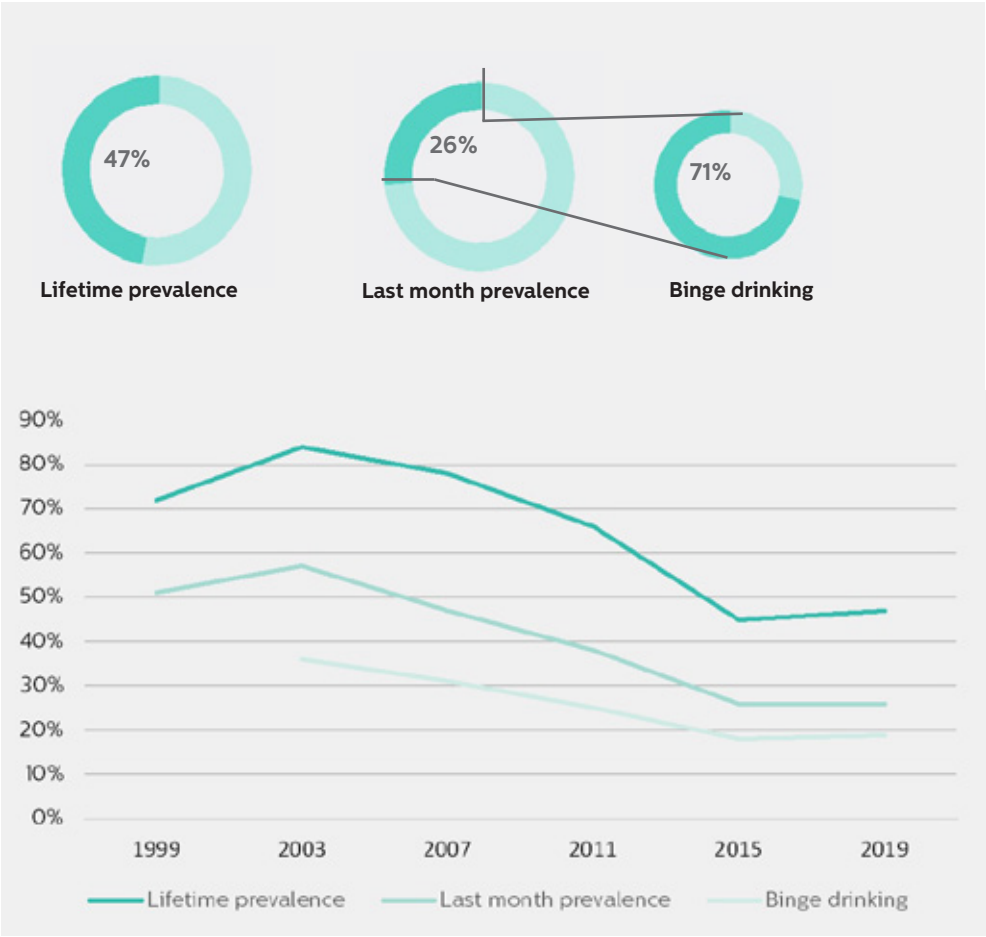

Figure 1 Statistics alcohol use Dutch secondary school students aged 12 to 16, 2019. Adapted from Peilstationsonderzoek, National Institute of Mental Health and Addiction, Utrect, the Netherlands [1]

In comparison to adults, adolescents drink less frequently but consume higher quantities per occasion [2]. Of the Dutch secondary school students that reported alcohol consumption in the last month, 71% reported binge drinking, which is defined as the consumption of >4 standard units of alcohol per occasion [1, Figure 1]. Whereas adolescent alcohol use among Dutch adolescents gradually declined from 2003 to 2015, the prevalence of lifetime

alcohol use, past month alcohol use, and binge drinking stabilized between 2015 and 2019 [1, Figure 1]. Chapter 9 of this thesis demonstrates that alcohol-related hospital admissions of adolescents <18 years of age showed an increasing trend, a trend which can also be seen in other countries [3–7]. Combining a stabilizing prevalence of adolescent alcohol use with an increasing trend of adolescent alcohol-related hospital admissions demonstrates that adolescent alcohol use remains a persistent public health concern.

Socio-cultural norms influence adolescent alcohol use, and therefore, the prevalence of lifetime alcohol use and binge drinking among 15 to 16-year-old adolescents varies across European countries. The proportion of adolescents that reported an emergency department presentation or hospital admissions ranges from 2 to 3 percent in most European countries [8]. It is estimated that of all adolescent emergency department presentations, 10 to 15% is alcohol-related [9–12]. The impact of alcohol consumption on adolescent emergency department presentations and hospital admissions was the driving motivation to study the three main aspects of adolescent acute alcohol intoxication management in the Netherlands: prevention, acute treatment, and outpatient follow-up.

SECTION 1: PREVENTION

A socio-ecological framework is frequently used in research to understand adolescent alcohol use in which individual, relationship, community, and societal domains influence the likelihood of alcohol use and subsequently alcohol-related hospital admission [13–16]. One of the most integrative socio-ecological frameworks on health behaviour is the theory of triadic influence [17,18]. The triadic influence theory explains behavior as the result of three streams of causes of behaviour (intrapersonal, interpersonal, sociocultural-environmental) that flow through several levels of causation (ultimate, distal, proximal). Factors in each of the three streams interact with factors in each of the other streams. All three streams converge on decisions/intentions as the final predictor of behaviour. Integrative socio-ecological frameworks have been used at a population level to study alcohol consumption parameters, such as the initiation of alcohol use, the frequency of alcohol use, and involvement in binge drinking [17,18]. Despite the multi-faced nature of adolescent alcohol use, studies of risk factors of alcohol-related emergency department presentations and hospital admissions only emerged in the last two decades and therefore still mainly rely on single predictors. In this thesis, four single predictors of various influence domains have been studied in a population of Dutch adolescents admitted for acute alcohol intoxication: age at first alcohol use (individual domain), birth order (relationship domain), alcohol-specific parental rule-setting (relationship domain), and time of intoxication and admission (community or societal domain).

Age at first alcohol use is a predictor for the quantity of alcohol consumption in adulthood [19-27]. A prospective study among Dutch adolescents admitted for acute alcohol intoxication was conducted to determine whether the age at first alcohol use is also associated with the age at admission. The study was based on data collected by the Dutch Paediatric Surveillance Unit. This study shows a linear relationship between the age at first alcohol use and the age at hospital admission for acute alcohol intoxication. In this specific study population, female sex, low or middle educational level, and living in a family structure without both biological parents were associated with age at first alcohol use <14 years. Therefore, postponing the age at first alcohol use remains an essential aim for preventive strategies.

Birth order and family composition are associated with various types of risk-taking behaviour, such as smoking, substance abuse, sexual risk-taking, and delinquent behaviour[28-32]. Younger siblings of children displaying risk-taking adolescent behaviour are at increased of displaying that behaviour themselves. It is unknown if birth order is also associated with adolescent acute alcohol intoxication. A case-control study was set up to examine whether the distribution of birth order (lastborn, middle, and firstborn) and sibling status (siblings yes/no) is different for adolescents with acute alcohol intoxication compared to the general Dutch adolescent population. The study shows that compared to the general Dutch adolescent population, adolescents with acute alcohol intoxication more frequently have siblings and are the youngest of the family.

Time of day variation in admission time for acute alcohol intoxication is country-specific [33-39]. In the Netherlands, more than 9 out of 10 adolescents with acute alcohol intoxication have been admitted in the evening or at night. The rising trend of hospital admissions due to acute alcohol intoxication is mainly attributable to nighttime admissions. Although it is just a minor proportion of the study population, special care should be provided for adolescents admitted in the afternoon. Adolescents admitted in the afternoon are more frequently lower educated, younger upon admission, having a zero-tolerance rule-setting (and thus showing rule-breaking behaviour), and more frequently drink on streets. Insights in the patterns of hospital admission are relevant for the development of prevention strategies.

Research shows that political measures in many countries transferred from harm-minimisation to zero-tolerance policies [40-42]. A recent systematic review and meta-analysis shows that alcohol-specific parental-rule setting is related to the risk of

alcohol-use [43]. It is unknown if alcohol-specific parental rule-setting is also associated with acute alcohol intoxication measures of adolescents admitted for acute alcohol intoxication, such as the age at first alcohol use or drinking location. The results of our study show that the proportion of adolescents raised in a zero-tolerance parental rule-setting significantly increased between 2011 and 2017. A zero-tolerance alcohol-specific parental rule setting was associated with lower quantities of regular alcohol use and lower frequencies of smoking. Therefore, assessing the subject of alcohol-specific parental-rule settings seems to be particularly important during late adolescence, as this subgroup is more frequently raised with parental approval.

SECTION 2: ACUTE TREATMENT AND DIAGNOSTICS

It is difficult to predict which intoxicated youth develops an alcoholic coma [44]. Furthermore, the measured blood alcohol concentration does not correlate well with the clinical physical signs of intoxication [45]. The level of consciousness is the leading sign in the clinical evaluation of children with acute alcohol intoxication and correlates better with the blood alcohol intoxication than altered speech or balance [46].

The most common reason for alcohol-related emergency department presentations is reduced consciousness[47], caused by depression of the central nervous system, which can result in coma and respiratory depression[48]. Accompanying circulatory symptoms due to alcohol intoxication have also been reported, including tachycardia(10%) and hypotension(2%) caused by both volume depletion(due to inhibition of antidiuretic hormone and vomiting) and vasodilatation[47,48]. Vomiting due to alcohol intoxication can induce biochemical changes, such as hypoglycemia and electrolyte disturbances(hypokalemia, hypernatremia, and hyperchloremia)[48-50], giving a predisposition for cardiac arrhythmias.

The overall goal in the acute treatment and management of an intoxicated youth is to rapidly assess their respiratory, cardiovascular, metabolic, and neurological status in order to provide lifesaving supportive and corrective care, if needed. This may include respiratory support, intravenous fluid resuscitation and electrolyte correction as well as identifying and ruling out traumatic injury [51]. Because alcohol is absorbed rapidly, gastric lavage is not indicated [52]. There is no evidence that intravenous fluids will expedite sobriety in patients with acute alcohol intoxication [53,54]. This section of the thesis will focus on the relevance of two acute diagnostic tools that can be used during emergency department presentation: urine toxicology screening and electrocardiogram.

The performance of a urine toxicology screening for drug use is important, as the combined use of alcohol and illicit drugs (such as cannabis, XTC, cocaine and GHB) has been found to be associated with various short-term deleterious health consequences [55-58]. This study demonstrates that among adolescents admitted for acute alcohol intoxication in the Netherlands, 22.8% also smokes tobacco and 11.8 % used illicit drugs. The study showed that the most important risk factor for a positive urine toxicology screening is smoking. This finding indicates that alcohol, smoking tobacco and illicit drug use are intertwined. Therefore, the urine toxicology screening is relevant for both the acute treatment and the outpatient prevention intervention program.

In this thesis, the value of an electrocardiogram (ECG) as diagnostic tool in the acute treatment of adolescents with acute alcohol intoxication was explored. In adults, alcohol intoxication is associated with QTc-prolongation [59,60]. QTc is influenced by age and sex [61], and although alcohol use is increasingly common in adolescents [61-67], there is no data on the prevalence of QTc-prolongation in adolescents with alcohol intoxication. An observational study including adolescents aged 10-18 years admitted with an acute alcohol intoxication was performed. Heart rate and QT-interval were automatically assessed using a validated algorithm. QTc was calculated using the Bazett formula(QTcB) and the Fridericia formula(QTcF). If present, a reference ECG was obtained. Approximately 10% of the adolescents with an acute alcohol intoxication have QTc-prolongation; however, this rarely results in ventricular arrhythmias. Male sex and hypokalemia are risk-factors for QTc-prolongation. Clinicians must be aware of the QTc-prolongation during acute alcohol intoxication and make an effort to measure the QT-interval and give an adequate assessment of the findings. In contrast to adult, in adolescents QTc-prolongation was attributable to an increased heart rate, rather than an increased QT-interval. Therefore, it is recommended to repeat the ECG at a moment of normalized heart rate in case of QTc-prolongation.

SECTION 3: OUTPATIENT FOLLOW-UP

Emergency department presentation for acute alcohol intoxication can be considered as a 'window of opportunity' for interventions aimed at counteracting alcohol intoxication in the future [68]. Follow-up assessments of adolescents admitted for acute alcohol intoxication show that emergency department presentation is effective in the reduction of general alcohol consumption directly after the event [65-69]. Numerous studies [68-77], literature reviews [78-84] and a few meta-analyses [85-87] focusing on young people (age 12-21 years) have reported additional positive effects of brief interventions on a range of alcohol consumption measures. The term brief intervention encompasses a range

of therapeutic processes, ranges from advice to extended counseling, and is typically delivered in short sessions on one or more occasions. Brief interventions are attractive, given the fact that they are efficient, cost-conscious, teachable to a wide range of service providers, and clinically applicable for a sizeable percentage of substance users with a mild-to-moderate problem [88]. Moreover, brief interventions are particularly fitting for adolescents: the content can readily be organized around a developmental perspective; many substance-using teenagers do not need intensive long-term treatment; and the client-centered, non-confrontational interviewer approach common to brief interventions be likely appealing to youth [89]. Positive effects persisted for up to 1 year after intervention and did not vary across participant demographics, intervention length, or intervention format [85]. Certain intervention modalities, such as motivational interviewing, were associated with larger effects [86]. Interventions are most promising if delivered in an individual format and over multiple sessions [86].

Just like suggested by prior literature, the outpatient follow-up program in the Reinier de Graaf Hospital, Delft, the Netherlands is standardized and delivered in an individual format over multiple sessions: invitation for follow-up at discharge, consultation with the pediatrician, screening consultation with child psychologist and if indicated, neuropsychological assessment. The standardization of the follow-up program provides opportunities study for example participation rates of the follow-up program and its results. In the Reinier de Graaf Hospital in Delft, more than 90% of the adolescents admitted for acute alcohol intoxication visit the pediatrician for a prevention consult during the outpatient follow-up program. In this section the results of this outpatient follow-up program are studied. Overall, 245 (34%) of the 726 adolescents invited for the prevention-intervention program in Delft were diagnosed with a co-occurring mental health disorder, such as attention-deficit hyperactivity disorder (13%) or autism spectrum disorder (2.1%). Attention-deficit hyperactivity disorder in particular seems to be more prevalent in the study population than in the general Dutch adolescent population. In the follow-up of patients with acute alcohol intoxication, assessment of possible co-occurring mental health disorders is important, as those may form predisposing, enabling or reinforcing risk factors.

GENERAL CONCLUSION

This thesis demonstrates that some significant achievements have been reached during the last two decades in adolescent acute alcohol intoxication prevention in the Netherlands. The mean age of adolescents admitted for acute alcohol intoxication in the Netherlands decreased from 14.9 in 2007 to 15.4 in 2017. Furthermore, the increasing trend in absolute

number of hospital admissions observed between 2007 and 2017 seems to flatten. The absolute number of hospital admissions peaked in 2015 and fluctuated between eight and nine hundred alcohol-related hospital admissions yearly since then. This thesis studies three main aspects of adolescent acute alcohol intoxication: prevention, acute treatment and outpatient follow-up.

The most effective prevention programs work both on reducing risk and enhancing protective factors. Despite the scientific efforts in the last two decades, unravelling the contribution factors of adolescent acute alcohol intoxication still remains a challenge. The challenge arises due to the multifactorial origin of acute alcohol intoxication. Individual, relationship, community and societal factors all play a role in adolescent acute alcohol intoxication. To make research to alcohol intoxication even more complex, risk factors are influenced by socio-cultural norms, which differ between regions and change over time. Yet, studying predictors designed on studying single relations or correlations are clearly important and helps us to better understand the behaviour of adolescent alcohol consumption. Identified risk factors for adolescent alcohol intoxication in this these are: the presence of siblings, being the youngest child of the family, age at first alcohol use ≤14 year, and being admitted in the afternoon.

Research to the second aspect of acute alcohol intoxication management, acute treatment and diagnostics, can be complicated. Studies to the pathophysiological effects of acute alcohol intoxication, such as QTc-prolongation, rely on observational studies for the best clinical evidence. However, the standardization of the acute treatment protocol provided opportunities to study the results of certain empirically used diagnostic tools. The electrocardiogram is proven to be necessary to detect QTc-prolongation, even though ventricular arrhythmias were not observed in the study population. The urine toxicology screening is effective for the acute treatment, but also helps to determine the likelihood of future smoking, alcohol use and drug use.

The last aspect of acute alcohol intoxication management, outpatient follow-up, has also been standardized. The standardization of the follow-up has been developed based on the best evidence so far, but also provided additional research opportunities to examine its results. This thesis contributes to its research field by determining the prevalence of co-occurring mental health disorders placing adolescents at risk of recidivism for acute alcohol intoxication. As adolescent alcohol use is influenced by socio-cultural norms, which differ between places and change over time, continuous research is necessary for the identification of risk factors. An example of changes over time that possibly have its

effect on adolescent acute alcohol intoxication emergency department presentations is the emergence of COVID-19 pandemic and the associated lockdowns. Other aspects that offer opportunities for further research are socio-cultural differences between countries. Continuation of research on adolescents with acute alcohol intoxication remains necessary to increase awareness of the consequences of adolescent alcohol intoxication on an individual level, contribute to changing socio-cultural norms on a community level, and communicate the importance of prevention in public policy on a societal level.

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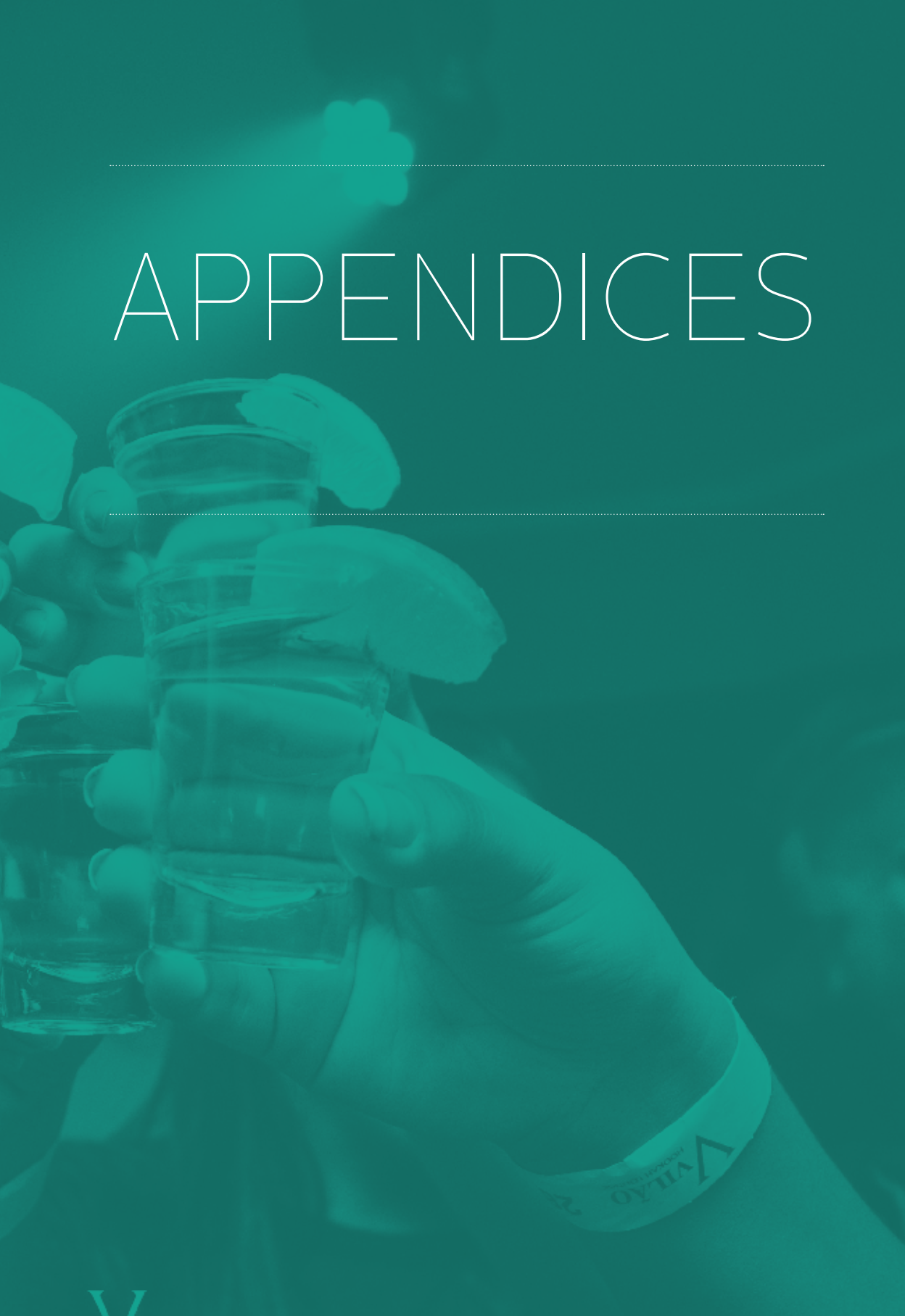
APPENDICES



APPENDIX 1

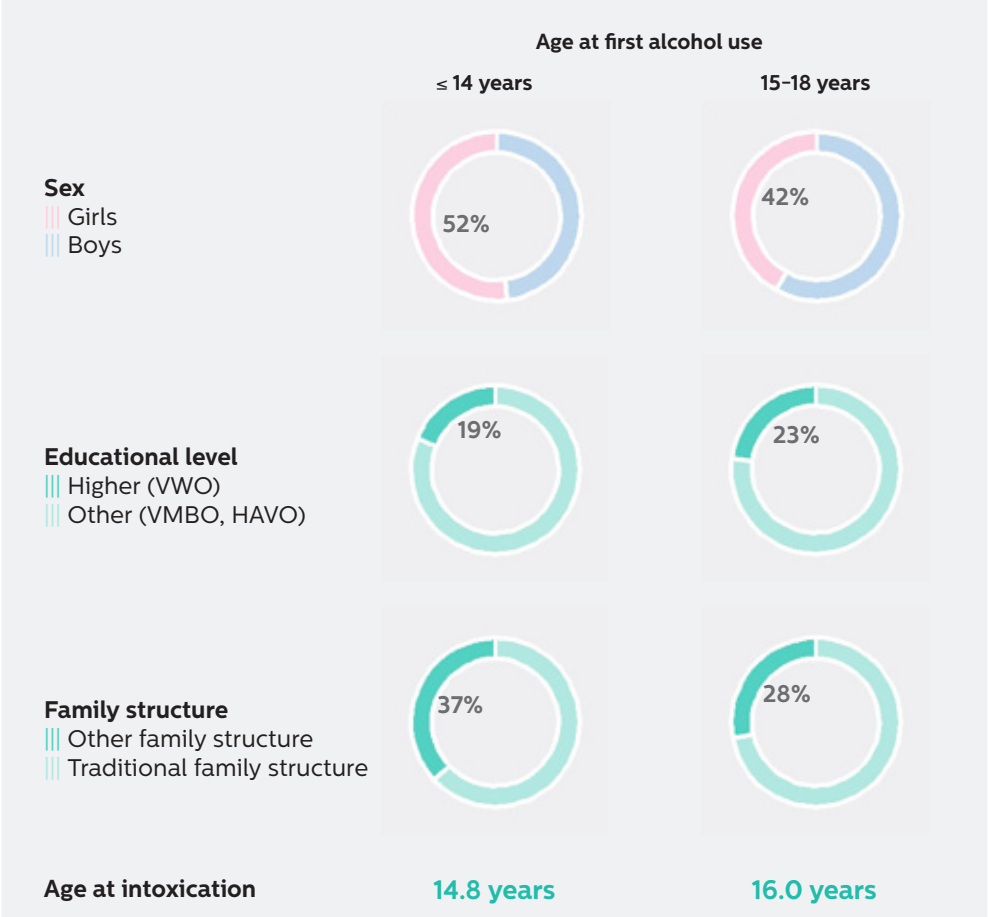
English summary

SUMMARY

The care of adolescents with acute alcohol intoxication forms an important part of the care for adolescents and contributes to the transition of adolescents to healthy adults. The management of acute alcohol intoxication in adolescents exists of several aspects: prevention, acute treatment, and outpatient follow-up.

Part 1 consists of 4 chapters about the prevention of acute alcohol intoxication. Risk factors and determinants for acute alcohol intoxication will be studied in these chapters.

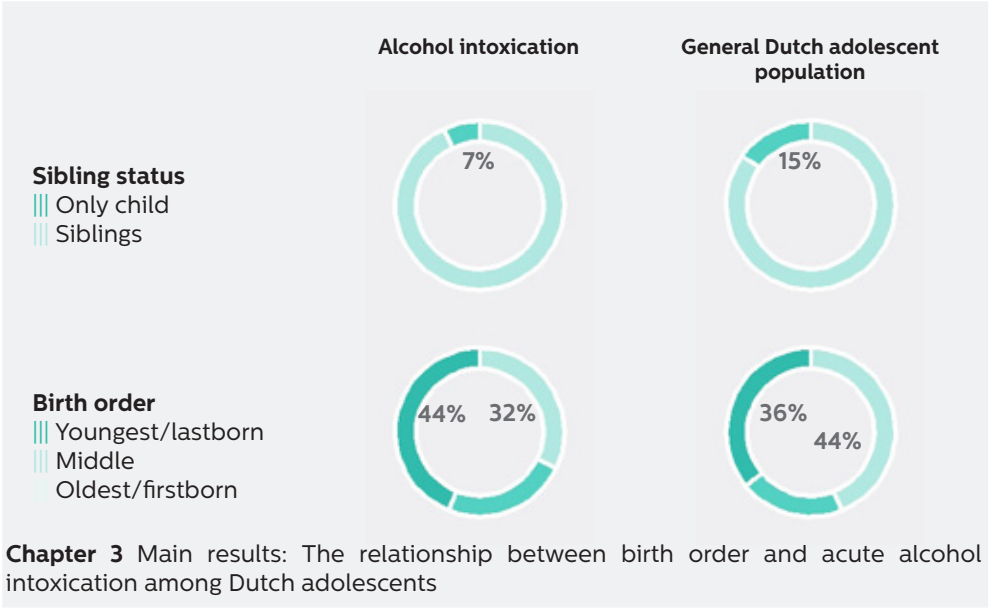
Chapter 2 explores the association between age at first alcohol use and various outcome measures in adolescents with acute alcohol intoxication



Chapter 2 Main results: Age at first Alcohol Use as a Possible Risk Factor for Adolescent Acute Alcohol Intoxication Hospital Admission in the Netherlands

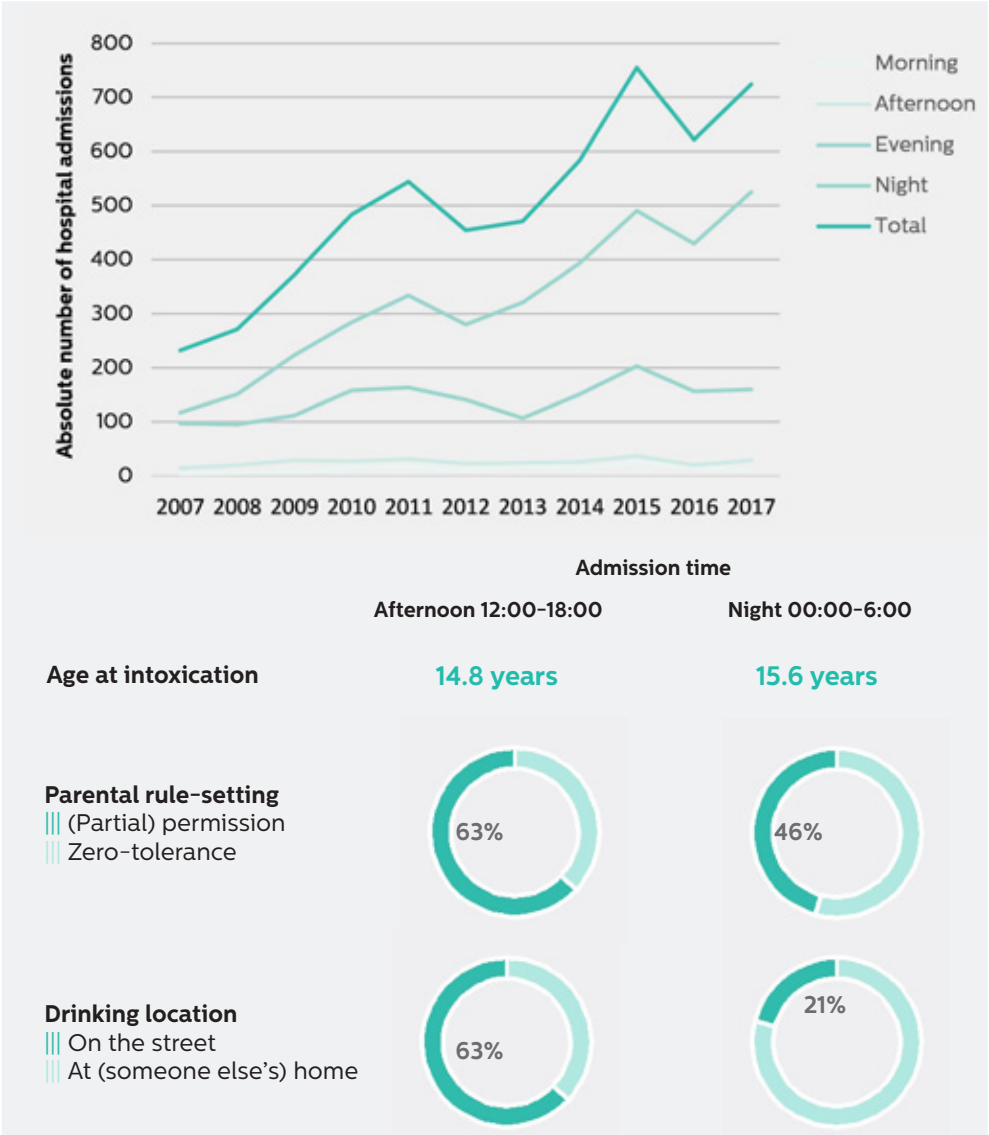
Age at first alcohol use is a predictor for the quantity of alcohol consumption in adulthood. A prospective study among Dutch adolescents admitted for acute alcohol intoxication was conducted to determine whether the age at first alcohol use is also associated with the age at admission. The study was based on data collected by the Dutch Paediatric Surveillance Unit. This study shows a linear relationship between the age at first alcohol use and the age at hospital admission for acute alcohol intoxication. In this specific study population, female sex, low or middle educational level, and living in a family structure without both biological parents were associated with age at first alcohol use <14 years. Therefore, postponing the age at first alcohol use remains an essential aim for preventive strategies.

Chapter 3 eexplores the association between birth order and acute alcohol intoxication. Birth order and family composition are associated with various types of risk-taking behavior, such as smoking, substance abuse, sexual risk-taking, and delinquent behaviour.



Chapter 3 Main results: The relationship between birth order and acute alcohol intoxication among Dutch adolescents

Younger siblings of children displaying risk-taking adolescent behaviour are at increased of displaying that behaviour themselves. It is unknown if birth order is also associated with adolescent acute alcohol intoxication. A case-control study was set up to examine whether the distribution of birth order (lastborn, middle, and firstborn) and sibling status (siblings yes/no) is different for adolescents with acute alcohol intoxication compared to the general Dutch adolescent population. The study shows that compared to the general Dutch adolescent population, adolescents with acute alcohol intoxication more frequently have siblings and are the youngest of the family.

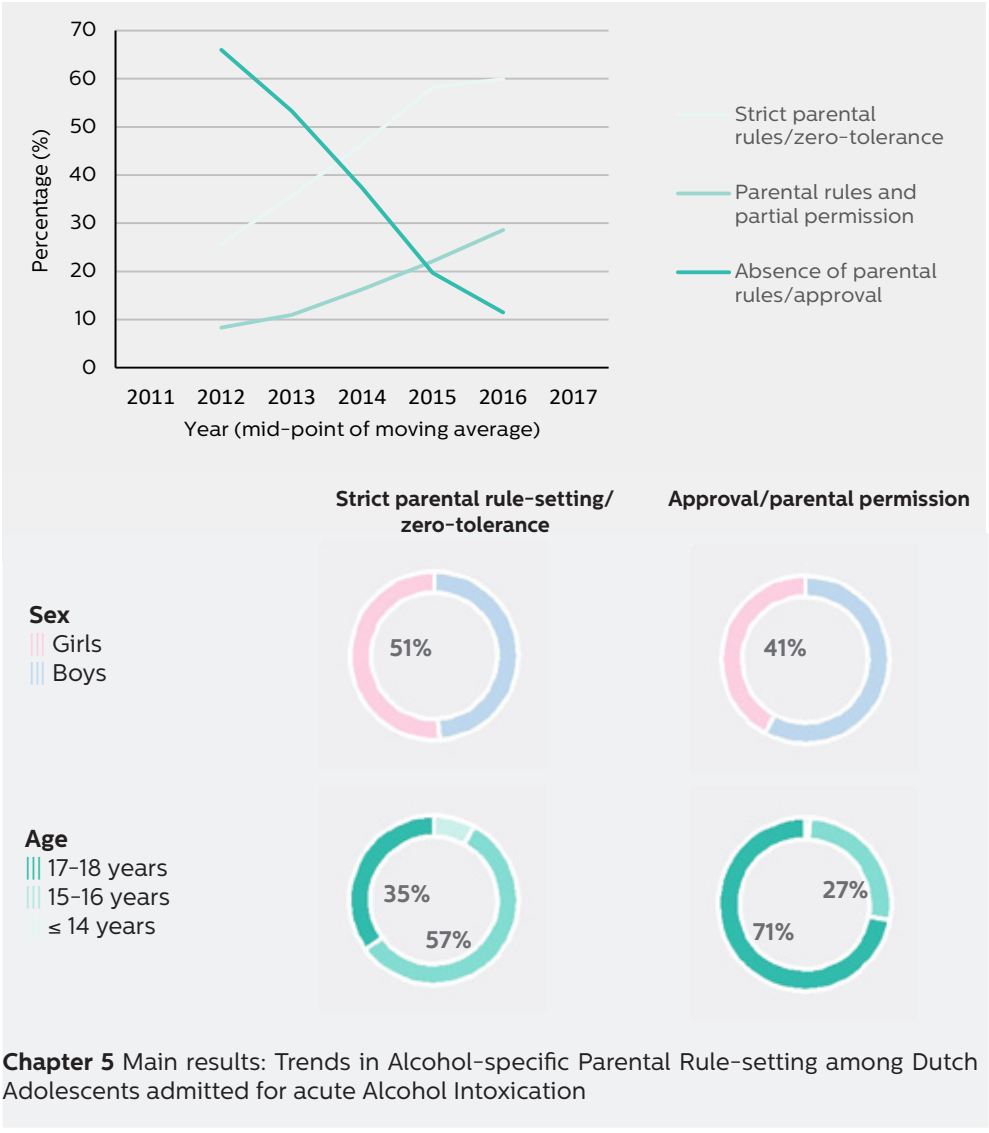


Chapter 4 Main results: Time of day as indicator of adolescent alcohol intoxication emergency department presentations

Chapter 4 explores the time of day variation in adolescent hospital admissions for acute alcohol intoxication. Time of day variation in admission time for acute alcohol intoxication is country-specific. In the Netherlands, more than 9 out of 10 adolescents with acute alcohol intoxication have been admitted in the evening or at night. The rising trend of hospital admissions due to acute alcohol intoxication is mainly attributable to nighttime admissions. Although it is just a minor proportion of the study population, special care

should be provided for adolescents admitted in the afternoon. Adolescents admitted in the afternoon are more frequently lower educated, younger upon admission, having a zero-tolerance rule-setting (and thus showing rule-breaking behaviour), and more frequently drink on streets. Insights in the patterns of hospital admission are relevant for the development of prevention strategies.

Chapter 5 explores alcohol-specific parental rule-setting in adolescents with acute alcohol intoxication. Research shows that political measures in many countries transferred from harm-minimisation to zero-tolerance policies.

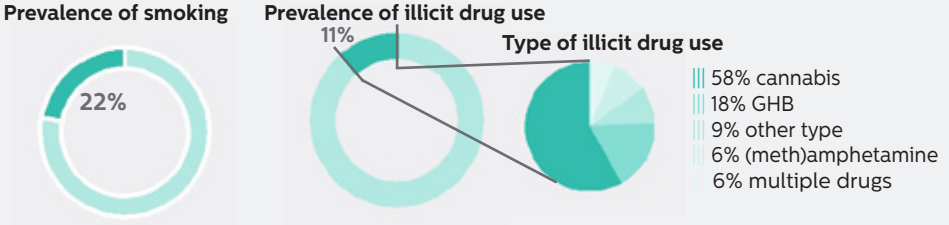


Chapter 5 Main results: Trends in Alcohol-specific Parental Rule-setting among Dutch Adolescents admitted for acute Alcohol Intoxication

It is unknown if alcohol-specific parental rule-setting is also associated with acute alcohol intoxication measures of adolescents admitted for acute alcohol intoxication, such as the age at first alcohol use or drinking location. The results of our study show that the proportion of adolescents raised in a zero-tolerance parental rule-setting significantly increased between 2011 and 2017. A zero-tolerance alcohol-specific parental rule setting was associated with lower quantities of regular alcohol use and lower frequencies of smoking. Therefore, assessing the subject of alcohol-specific parental-rule settings seems to be particularly important during late adolescence, as this subgroup is more frequently raised with parental approval.

Part 2 consists of two chapters that focus on the results of an acute diagnostic measure used in the initial treatment of adolescents with acute alcohol intoxication.

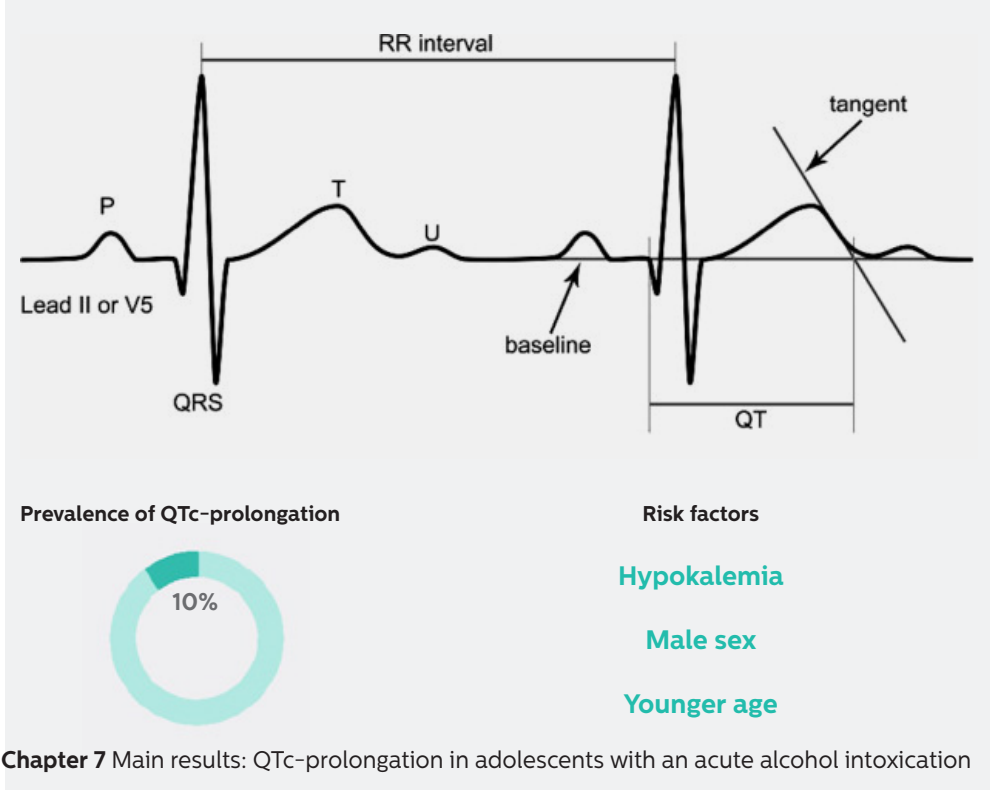
Chapter 6 explores the role of urine toxicology screening. The performance of a urine toxicology screening for drug use is important, as the combined use of alcohol and illicit drugs (such as cannabis, XTC, cocaine, and GHB) has been found to be associated with various short-term deleterious health consequences. This study demonstrates that among adolescents admitted for acute alcohol intoxication in the Netherlands, 22.8% also smokes tobacco, and 11.8 % used illicit drugs. The study showed that smoking is the most important risk factor for a positive urine toxicology screening. This finding indicates that alcohol, smoking tobacco, and illicit drug use are intertwined. Therefore, urine toxicology screening is relevant for acute treatment and outpatient prevention intervention programs.



Chapter 6 Main results: The role of tobacco smoking and illicit drug use in adolescent acute alcohol intoxication

Chapter 7 explores the value of an electrocardiogram (ECG) as a diagnostic tool in the acute treatment of adolescents with acute alcohol intoxication. In adults, alcohol intoxication is associated with QTc-prolongation. QTc is influenced by age and sex, and although alcohol use is increasingly common in adolescents, there is no data on the

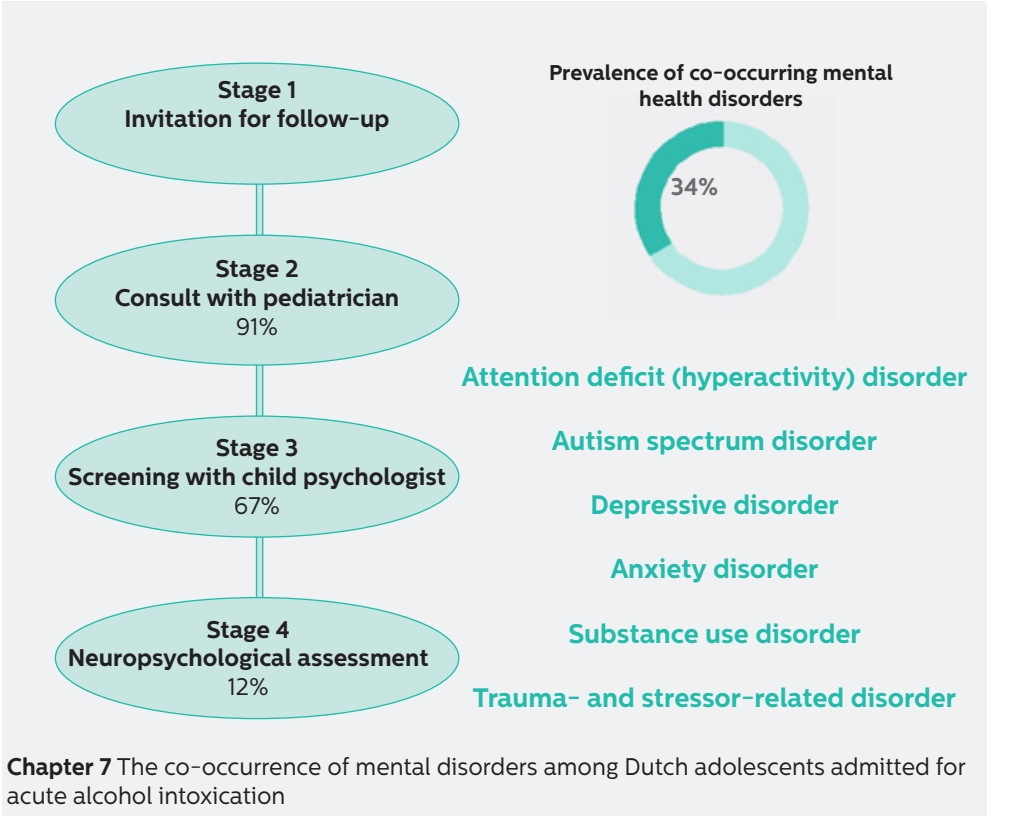
prevalence of QTc-prolongation in adolescents with alcohol intoxication. An observational study included adolescents aged 10-18 years who were admitted with an acute alcohol intoxication was performed. Heart rate and QT-interval were automatically assessed using a validated algorithm. QTc was calculated using the Bazett formula(QTcB) and the Fridericia formula(QTcF). If present, a reference ECG was obtained. Approximately 10% of the adolescents with acute alcohol intoxication have QTc-prolongation; however, this rarely results in ventricular arrhythmias. Male sex and hypokalemia are risk factors for QTc-prolongation. Clinicians must be aware of the QTc-prolongation during acute alcohol intoxication and make an effort to measure the QT-interval and assess the findings adequately. In contrast to adults, in adolescents, QTc-prolongation was attributable to an increased heart rate, rather than an increased QT-interval. Therefore, it is recommended to repeat the ECG at a moment of normalized heart rate in the case of QTc-prolongation.



Chapter 7 Main results: QTc-prolongation in adolescents with an acute alcohol intoxication

Part 3 consists of two chapters and focus on the outpatient follow-up of adolescents with acute alcohol intoxication.

Chapter 7 examines the outpatient follow-up and the co-occurrence of mental health disorders among adolescents admitted with acute alcohol intoxication. More than 90% of the adolescents admitted for acute alcohol intoxication visit the pediatrician for a prevention consult during the outpatient follow-up program. Overall, 245 (34%) of the 726 adolescents treated for acute alcohol intoxication were diagnosed with a co-occurring mental health disorder, such as attention-deficit hyperactivity disorder (13%) or autism spectrum disorder (2.1%). Attention-deficit hyperactivity disorder, in particular seems to be more prevalent in the study population than in the general Dutch adolescent population. Adolescents with a co-occurring mental health disorder were younger than those without co-occurring mental health disorder. In the follow-up of patients with acute alcohol intoxication, assessment of possible co-occurring mental health disorders is important, as those may form predisposing, enabling, or reinforcing risk factors.



Chapter 7 The co-occurrence of mental disorders among Dutch adolescents admitted for acute alcohol intoxication

Chapter 8 reflects on prior studies performed on trends of adolescent alcohol use. Research shows that the absolute number of hospital admissions shows an increasing trend. However, since the raise of the minimum legal age to 18 years old for all alcoholic

beverages, the mean age of adolescents admitted for acute alcohol intoxication showed an increasing trend from 14.9 in 2007 to 15.4 in 2017. The proportion of adolescents younger than 14 years of age upon admission shows a decreasing trend too. However, it stays important to focus on preventive measures. The trends in the Netherlands may provoke the debate in Belgium to raise the minimum legal age to 18 too.

APPENDIX 2

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

De zorg voor jongeren met een acute alcoholintoxicatie is een belangrijk onderdeel in de zorg voor adolescenten en draagt bij aan het opgroeien tot een gezonde volwassene. De zorg voor adolescenten bestaat uit verschillende aspecten, waaronder preventie, acute diagnostiek en behandeling, en poliklinische follow-up.

Deel 1 bestaat uit vier verschillende hoofstukken waarin gekeken wordt naar de preventie van acute alcoholintoxicatie onder jongeren. In dit hoofdstuk zullen risicofactoren en determinanten van een acute alcoholintoxicatie onderzocht worden.

In ***hoofdstuk 2*** wordt de associatie tussen de leeftijd van het eerste alcoholgebruik en diverse uitkomstmaten van jongeren met een alcoholvergiftiging onderzocht. Uit voorgaand onderzoek blijkt dat hoe jonger een persoon begint met alcoholgebruik, hoe groter de hoeveelheden van alcoholgebruik later in het leven en hoe groter het risico op een stoornis in het gebruik van alcohol. De resultaten van deze prospectieve studie op basis van de data van het Nederlands Signaleringscentrum voor Kindergeneeskunde laten zien dat er een lineair verband bestaat tussen de leeftijd van het eerste glas en de leeftijd van opname voor een acute alcoholintoxicatie. Risicofactoren voor het beginnen met alcoholgebruik die worden geïdentificeerd zijn het vrouwelijk geslacht, een laag tot gemiddeld opleidingsniveau (VMBO/HAVO) en een gebroken gezinsstructuur. Deze studie laat zien dat het uitstellen van het eerste alcoholgebruik loont en daarom ook een belangrijke pijler is in de preventie van alcoholintoxicatie onder jongeren.

In ***hoofdstuk 3*** is er gekeken naar de associatie tussen de positie van het kind in het gezin en uitkomstmaten van een acute alcoholintoxicatie, zoals leeftijd bij opname en bloedalcoholconcentratie (BAC). Voorgaand onderzoek suggereert dat er mogelijk een verband is tussen de samenstelling van het gezin en risicovol gedrag tijdens adolescentie. Zo blijkt dat het jongste kind een verhoogd risico heeft op onveilig seksueel gedrag, betrokkenheid bij criminele activiteiten, roken en drugsgebruik. In deze case-control studie zal gekeken worden of de studiepopulatie van jongeren met een alcoholintoxicatie relatief frequenter de jongste uit het gezin in vergelijking tot de algemene Nederlandse populatie (Centraal Bureau voor Statistiek). Het onderzoek toont aan dat jongeren met een alcoholintoxicatie minder frequent enig kind zijn in vergelijking tot de referentie populatie en dit suggereert dat eerstgeborene zijn een beschermende factor is voor opname door alcoholintoxicatie.

H***oofdstuk 4*** gaat over het tijdstip waarop jongeren met een alcoholintoxicatie zich presenteren op de spoedeisende hulp. Uit voorgaand onderzoek blijkt dat het tijdstip van

presentatie op de spoedeisende hulp wisselt tussen verschillende landen. In Nederland is dit nog niet eerder onderzocht. Deze studie laat zien dat de absolute toename van het aantal opnames voor acute alcoholintoxicatie grotendeels het gevolg is van een toename aan alcoholintoxicaties in de nacht. Ruim 9 van de 10 adolescenten met een alcoholvergiftiging wordt opgenomen in de avond of nacht. De groep die opgenomen wordt in de middag is weliswaar een kleine groep, maar wel een groep die extra aandacht behoeft. Adolescenten opgenomen in de middag zijn vaak jonger, zitten vaker op een lager opleidingsniveau, hebben vaker strenge regels ten aanzien van alcoholgebruik (en overtreden deze regels dus) en drinken vaker op straat. Inzicht in het patroon van opname is van belang voor verder onderzoek naar preventieve maatregelen van alcoholintoxicaties bij adolescenten.

In ***hoofdstuk 5*** wordt er gekeken naar de associatie tussen alcohol-specifieke regels van ouders en uitkomstmaten, zoals leeftijd bij opname en BAC. Daarnaast wordt er een trendanalyse uitgevoerd die laat zien hoe alcohol-specifieke ouderlijke regels zich door de jaren heen hebben ontwikkeld. Onderzoek laat zien dat het politieke beleid in veel landen is overgegaan van schade beperkende maatregelen (harm-minimisation) naar zero tolerantie. Uit een recente systematic review en meta-analyse blijkt dat de aanwezigheid van alcohol-specifieke regels het risico op alcoholgebruik in adolescentie te reduceren. Deze studie laat zien dat er de afgelopen jaar een significante stijging is van het percentage adolescenten dat thuis niet mag drinken en een significante afname is van het percentage adolescenten dat thuis toestemming heeft voor alcoholgebruik. De toename van het percentage jongeren met gedeeltelijke toestemming, bijvoorbeeld op bijzondere gelegenheden, is echter zorgelijk. Strenge alcohol-specifieke ouderlijke regels waren geassocieerd met een latere leeftijd van eerste alcoholgebruik, een gemiddeld lager aantal eenheden alcohol geconsumeerd in het weekend en een lagere frequentie van roken. Het lijkt daarom van belang om specifiek in groepen waarin het percentage jongeren met strenge alcohol-specifieke ouderlijke regels laag is te informeren over deze bevindingen: late adolescentie (ouders van 15-16 jarige en ouders van 17-jarige adolescenten) en jongeren met een autochtone Nederlandse afkomst.

Deel 2 bestaat uit twee studies die betrekkingen hebben op de acute diagnostiek en behandeling van jongeren met een alcoholvergiftiging.

In ***hoofdstuk 6*** wordt de rol van roken en drugsgebruik door jongeren met een alcoholvergiftiging onderzocht. Onderzoek toont aan dat roken, alcohol- en drugsgebruik gedurende de adolescentie vaak samengaan. Echter leidt het combinatiegebruik van alcohol met andere soorten drugs, zoals bijvoorbeeld cannabis, XTC, cocaine of GHB juist tot grotere gezondheidsrisico's. Van de jongeren met een alcoholvergiftiging, rookt 22.8% ook en heeft

11.8% drugs gebruikt. Net als in de algemene Nederlandse bevolking, laat het percentage jongeren dat rookt ook onder jongeren met een alcoholintoxicatie een dalende trend zijn. De belangrijke risicofactor voor drugsgebruik bij jongeren met een alcoholvergiftiging is roken. De resultaten van de urinetoxicologie screening zijn daarom zowel relevant voor de acute behandeling, als voor het preventieve traject na de opname.

In ***hoofdstuk 7*** wordt gekeken naar de waarde van het ECG als diagnostisch middel tijdens de acute opvang van jongeren met een alcoholvergiftiging. In een volwassen populatie is alcoholvergiftiging geassocieerd met QTc-verlenging. Hoewel QTc beinvloed wordt door leeftijd en geslacht en alcoholvergiftiging veel voorkomt tijdens de adolescentie, is de prevalentie van QTc-verlenging bij adolescenten met een alcoholvergiftiging onbekend. Om die reden werd er een observationele studie uitgevoerd onder adolescenten tussen de 10 en 18 jaar met een alcoholvergiftiging. Hartfrequentie en QT-interval werden automatisch bepaald middels een gevalideerd algoritme. QTc werd berekend middels de formule van Bazett (QTcB) en Fridericia (QTcF). In totaal werden er 317 patienten geincludeerd, waarvan 13.3% een QTcB en 7.9% een QTcF langer dan de geslachts- en leeftijdsspecifieke referentiewaarden hadden. Geen van de adolescenten had een QTc >500msec en 4 patienten hadden een verlenging >60msec QTcB. Er werden geen ventriculaire ritmestoornissen geobserveerd. Risicofactoren voor een verhoogde likelihood van QTc-verlenging waren onder andere het mannelijk geslacht en hypokalemie.

Deel 3 bestaat uit twee studies die betrekking heeft op de poliklinische follow-up van jongeren met een acute alcoholvergiftiging.

In ***hoofdstuk 8*** wordt gekeken naar de poliklinische follow-up van jongeren met een alcoholvergiftiging en wordt de prevalentie van psychische stoornissen bij jongeren met een alcoholintoxicatie onderzocht. De meeste jongeren die met een alcoholvergiftiging worden opgenomen in het Reinier de Graaf ziekenhuis, komen naar poliklinische follow-up. Ruim 90% bezoekt de kinderarts en 67% van de kinderen gaat naar het screeningsconsult bij de kinderpsycholoog. Adolescenten met een alcoholvergiftiging zijn in 12.8% van de gevallen of in het verleden, of tijdens het follow-up programma, gediagnosticeerd met ADHD. In vergelijking met adolescenten zonder psychische stoornis, zijn adolescenten met psychische stoornis vaker meisjes, zijn ze jonger bij opname en hebben ze vaker ook drugs gebruikt. In de follow-up is het belangrijk om onderzoek te doen naar psychische stoornissen, omdat deze mogelijk een luxerende of onderhoudende factor zijn in middelengebruik bij jongeren.

In ***hoofdstuk 9*** wordt ingegaan op trends die tussen 2007 en 2017 zijn gezien in de opnames van jongeren met een alcoholintoxicatie. In Nederland geldt er sinds 2014 een minimumleeftijdsgrens van 18 voor alcohol. In de periode 2007-2011 nam het aantal jongeren met een alcoholintoxicatie jaarlijks toe, waarna het aantal redelijk stabiel bleef tussen de 700 en 900 opnames per jaar. In deze periode steeg de gemiddelde leeftijd van jongeren met een alcoholvergiftiging van 14.9 naar 15.4 jaar en het percentage jongeren <14 jaar nam af. Het blijft echter noodzakelijk om te investeren in de preventieve maatregelen. De effecten van het verhogen van de leeftijdsgrens in Nederland kunnen brandstof zijn voor de discussie hieromtrent in België.

APPENDIX 3

List of abbreviations

Table 1 List of abbreviations per section (1/4)

Abbreviation		Definitions
General introduction/statistics		
ANCOVA	Analysis of covariance	Analysis of covariance (ANCOVA) is a general linear model which blends ANOVA and regression. The one-way ANCOVA (analysis of covariance) can be thought of as an extension of the one-way ANOVA to incorporate a covariate
ANOVA	Analysis of variance	The one-way analysis of variance (ANOVA) is used to determine whether there are any statistically significant differences between the means of two or more independent (unrelated) groups (although you tend to only see it used when there are a minimum of three, rather than two groups)
BAC	Blood alcohol concentration	Blood alcohol content (BAC), also called blood alcohol concentration, is a measurement of alcohol intoxication used for legal or medical purposes. A BAC of 0.10 (0.10%) means that there is 0.10 g of alcohol for every 100 ml of blood, which is the same as 1.0 grams per liter blood = 1g/L.
CBS	Centraal Bureau voor Statistiek (Dutch Central Bureau of Statistics)	Statistics Netherlands, also known as the Dutch Central Bureau of Statistics (Centraal Bureau van Statistiek) or CBS, is an autonomous agency with the mandate to collect and process data, which it publishes in statistical reports
CI	Confidence Interval	In statistics, a confidence interval (CI) is a type of estimate computed from the statistics of the observed data. This gives a range of values for an unknown parameter (for example, a population mean). The interval has an associated confidence level that gives the probability with which an estimated interval will contain the true value of the parameter.
DBC-code	Diagnosis and treatment combination code (Diagnose en Behandeling Combinatie Code)	Funding- and classification- system used by all Dutch hospitals to declare expenses of diagnostic procedures and treatment
IQR	Interquartile range	In descriptive statistics, the interquartile range (IQR), also called the midspread, middle 50%, or H-spread, is a measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles.
LLN	Lower Limit of Normal	The lower limit of normal is defined as the result of the mean predicted value (based on the patient's sex, age, and height) minus 1.64 times the standard error of the estimate from the population study on which the reference equation is based
N/n	Sample size	If there is only one sample, the letter "N" is used to designate the sample size. If samples are taken from each of "a" populations, then the small letter "n" is used to designate size of the sample from each population

Table 1 List of abbreviations per section (2/4)		
Abbreviation		**Definition**
NA	Not Applicable	N/A or sometimes n/a is a common abbreviation in tables and lists for the phrase not applicable, not available or no answer. It is used to indicate when information in a certain table cell is not provided.
NSCK	Nederlands Signalerings Centrum voor Kindergeneeskunde (Dutch Pediatric Surveillance Unit)	The Dutch Paediatric Surveillance System was initiated by the Dutch Paediatric Society and is housed. The purpose of the surveillance system is (a) to gain insight on a population level into the prevalence of rare and new diseases in youths (0–18 year), and (b) to promote scientific research
SD	Standard Deviation	In statistics, the standard deviation is a measure of the amount of variation or dispersion of a set of values. A low standard deviation indicates that the values tend to be close to the mean, while a high standard deviation indicates that the values are spread out over a wider range
ULN	Upper Limit of Normal	The upper limit of normal is defined as the result of the mean predicted value (based on the patient's sex, age, and height) plus 1.64 times the standard error of the estimate from the population study on which the reference equation is based

Section 1: identification of risk factors		
HAVO	Hoger Algemeen Voortgezet Onderwijs (Senior general secondary education)	The Dutch secondary school system consists of 3 main levels: pre-vocational education (VMBO), senior general secondary education (HAVO) and pre-university education (VWO). HAVO is the preparatory education for higher professional education
HBO	Hoger Algemeen Beroeps Onderwijs (Higher professional education)	The HBO institutions, or higher professional education, together offer 200 programmes in a wide range of disciplines. They provide theoretical and practical training for occupations for which a higher vocational qualification is either required or useful.
MBO	Middelbaar Beroeps Onderwijs (Secondary Vocational Education)	Secondary vocational education (MBO) prepares students for a wide range of occupations, from franchise manager to mechanic or nursing assistant.
VMBO	Voortgezet Middelbaar Beroeps Onderwijs (pre-vocational education)	The Dutch secondary school system consists of 3 main levels: pre-vocational education (VMBO), senior general secondary education (HAVO) and pre-university education (VWO). HAVO is the preparatory education for secondary vocational education
VWO	Voortgezet Wetenschappelijk Onderwijs (pre-university education)	The Dutch secondary school system consists of 3 main levels: pre-vocational education (VMBO), senior general secondary education (HAVO) and pre-university education (VWO). VWO is the preparatory education for university

Section 2: Acute diagnostics: urine tox		
GHB	gamma-Hydroxybutyric acid	Gamma-Hydroxybutyric acid, is a naturally occurring neurotransmitter and a psychoactive drug. It is a precursor to GABA, glutamate, and is a central nervous system depressant
MDMA	3,4-Methylenedioxymethamphetamine (MDMA)	3,4-Methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, E, or molly, is a psychoactive drug primarily used for recreational purposes. The desired effects include altered sensations, increased energy, empathy, as well as pleasure

Section 2: Acute diagnostics (ECG)		
bpm	beats per minute	Unit of heart rate
ECG	Electrocardiogram	It is a graph of voltage versus time of the electrical activity of the heart using electrodes placed on the skin. These electrodes detect the small electrical changes that are a consequence of cardiac muscle depolarization followed by repolarization during each cardiac cycle (heartbeat)
HR	Heart Rate	Heart rate is the speed of the heartbeat measured by the number of contractions (beats) of the heart per minute (bpm).
msec	milisecond	One thousandth of a second, unit for time
QTc	QT-interval corrected for heart rate	The QT interval changes in response to the heart rate - as heart rate increase the QT interval shortens. These changes make it harder to compare QT intervals measured at different heart rates. To account for this, and thereby improve the reliability of QT measurement, the QT interval can be corrected for heart rate using a variety of mathematical formulae
QTcB	QTc-Bazett	QTc using the Bazett formula
QTcF	QTc-Fridericia	QTc using the Fridericia formula
SBP	Systolic Blood Pressure	The highest pressure within the bloodstream, occurring during each heartbeat, because of the systole. Unit: mmHg.
TdP	Torsade de Pointes	Torsades de pointes, translated as "twisting of peaks", is a polymorphic ventricular tachycardia that can lead to sudden cardiac death.

Section 3: outpatient follow-up		
ANX	Anxiety disorder	Anxiety disorders include disorders that share features of excessive fear and anxiety and related behavioral disturbances. These disorders include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, and anxiety disorder due to another medical condition.

AD(H)D	Attention Deficit (Hyperacitivity) Disorder	AD(H)D is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development
DD	Depressive disorder	Depressive disorders include disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. The common feature of all of these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to functio
DIC	Disruptive, Impulse-control and Conduct disorder	Disruptive, impulse-control, and conduct disorders include conditions involving problems in the self-control of emotions and behaviors. While other disorders in DSM-5 may also involve problems in emotional and/or behavioral regulation, the disorders in this chapter are unique in that these problems are manifested in behaviors that violate the rights of others (e.g., aggression, destruction of property) and/or that bring the individual into significant conflict with societal norms or authority figures
DSM	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is the 2013 update to the Diagnostic and Statistical Manual of Mental Disorders, the taxonomic and diagnostic tool published by the American Psychiatric Association (APA)
SUD	Substance Use Disorder	The substance-related disorders encompass 10 separate classes of drugs, of which alcohol; caffeine; cannabis; hallucinogens (opioids; sedatives, hypnotics, and anxiolytics; stimulants (amphetamine-type substances, cocaine, and other stimulants); tobacco; and other (or unknown) substances. All drugs that are taken in excess have in common direct activation of the brain reward system, which is involved in the reinforcement of behaviors and the production of memories. They produce such an intense activation of the reward system that normal activities may be neglected
TRAUMA	Trauma- and stressor-related disorders	Trauma- and stressor-related disorders include disorders in which exposure to a traumatic or stressful event is listed explicitly as a diagnostic criterion. These include reactive attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder (PTSD), acute stress disorder, and adjustment disorders

APPENDIX 4

About the author

ABOUT THE AUTHOR

Loes de Veld was born in Delft, The Netherlands, on the 28th of August 1994. She graduated from secondary school in 2012 at the Grotius College in Delft (Gymnasium degree). In the same year she started her medical training at the Leiden University Medical Center (LUMC) in Leiden. In 2014, she followed a minor Global Health in Cuba, where the health care system focusses on family-centered care and prevention. Her Bachelor Thesis was already conducted on a topic in the pediatric field: "Dexamethasone versus prednisone for acute asthma exacerbations". During the clinical rotations, she did her pediatric rotation at the Bronovo Hospital, Haaglanden Medisch Centrum, Den Haag. She finished medical school with a clinical elective at the Pediatric Intensive Care Unit of the LUMC.

In 2018, she completed her Master thesis on the relationship between birth order and acute alcohol intoxication among Dutch adolescents, which resulted in her first publication (supervisor Drs. I.M. Wolberink and Prof. Dr. van der Lely). She continued with research to adolescents with acute alcohol intoxication and officially started the PhD programme at the Erasmus School for Health Policy and Management in 2018. The PhD programma was combined with clinical activities as a pediatric resident at the pediatric department, neonatology department and pediatric outpatient department.

CURRICULUM VITAE

EDUCATION

2018 - 2021 | PhD-student Erasmus University | Erasmus School of Health Policy and Management, the Netherlands

2016-2019 | Master of Medicine | University of Leiden, the Netherlands

- 02-2018 Research Internship "Adolescents and Alcohol" at Pediatric Department Reinier de Graaf Hospital
- 07-2018 Clinical elective internship 1: Pediatric Department Haaglanden Medisch Centrum, Bronovo, The Hague, the Netherlands
- 01-2019 Clinical elective internship 2: Pediatric Intensive Care Unit, Leiden University Medical Center, Leiden, the Netherlands
- 02-2019 Clinical elective internship 3: Primary Health Care Service for Children and Youth, Ypenburg/Leidschenveen, the Netherlands

2012-2015 | Bachelor of Medicine | University of Leiden, the Netherlands

- 2014: Minor Global Health and primary care/prevention in Havana, Cuba

2006-2012 | Secondary education | Grotius College Delft, the Netherlands

- Pre-university education: mathematics, physics, biology, chemistry, geography, economics
- International Baccalaureate (IB): English Standard Level

PROFESSIONAL EXPERIENCE

2019-2021 | Junior Doctor Pediatric Department| Reinier de Graaf Hospital, Delft, the Netherlands

- Clinical experience at the pediatric department, neonatology department, outpatient department

2019-2021 | Junior Doctor Foundation for Adolescents and Alcohol

-

2015-2016| Phlebotomist | OCRE Medical Services, The Hague, the Netherlands

APPENDIX 5

PhD portofolio

PhD PORTOFOLIO

Erasmus MC Department: Erasmus School of Health Policy & Management, Health Services & Management

PhD Period: June 2019 -February 2022

Promotors: Prof. dr. C.G.J.M. Hilders & Prof. dr. N. van der Lely

Co-promotor: Dr. J.J. van Hoof

Table 1 PhD portofolio

	Year	Workload (ECTS)
Course/Training		
"De kunst van communiceren"	2020	1,0
Oral Presentations		
7th Internation EuroScicon Conference on Psychiatry, Psychology and Mental Health	2018	1,0
Virtual Congress and Mastercourse European Academy of Pediatrics 2021	2021	1,0
Prevention presentation on secondary schools, local governmental organisations, sport clubs, student organizations (20x)	2019-2021	5,0
Participation (inter)national conferences		
7th International EuroScicon Conference on Psychiatry, Psychology and Mental Health	2018	0,9
Virtual Congress and Mastercourse European Academy of Pediatrcs 2021	2021	1,2
Teaching		
Supervision of research project by master student (2x)	2019-2021	5,8
Supervision of research projects by secondary school students	2019-2021	4,3
Additional publications		
Reinier Research (3x)	2019-2021	1,2
Committees		
Project "Verantwoord Alcoholgebruik door Delftse Studenten"	2019-2021	4,3
Werkzaamheden Stichting Jeugd en Alcohol	2019-2021	4,3

LIST OF PUBLICATIONS

De Veld L, Van Hoof JJ, Ouwehand S & Van der Lely N (2019) Age at first alcohol use as a possible risk factor for adolescent acute alcohol intoxication hospital admission in the Netherlands. Alcohol Clin Exp Res 44(1):219-224. doi:10.1111/acer.14226

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Ouwehand S, **De Veld L**, Callens M, Van Hal G, De Dooyd, Van der Lely N (2020) Effects of preventive measures against alcohol intoxications among young people in The Netherlands and future plans for Belgium. BTVG 76(20):1027-1032. doi:10.47671/TVG.76.20.4002

Manuscripts in preparation

De Veld L, Van Hoof J, Ouwehand S, Van der Lely N (xxxx) Trends in Alcohol-specific Parental Rule-setting among Dutch Adolescents admitted for acute Alcohol Intoxication. Status: manuscript in preparation

List of presentations on international conferences

De Veld L, Wolberink IM, Van Hoof JJ, Van der Lely N (2018) The association between position in the family and acute alcohol intoxication. International Conference on Psychiatry, Psychology and Mental Health 2018, Prague, Czech Republic 2018

Van der Lely N, **De Veld L**, Van Hoof JJ (2019) Characteristics of a decade of alcohol intoxications in adolescents in Pediatric departments in Dutch hospitals. European Academy of Paediatrics Congress and Mastercourse 2019, Porto, Portugal

De Veld L, Wolberink IM, Van Hoof JJ, Van der Lely (2021) The Role of Alcohol-Specific Parental Rules in Admission for Acute Alcohol Intoxication of Dutch Adolescents. Virtual European Academy of Paediatrics Congress and Mastercourse 2021

APPENDIX 6

Dankwoord

DANKWOORD

Eigenlijk zou de omslag van dit proefschrift moeten zijn volgeschreven met namen van mensen die bij hebben gedragen aan dit proefschrift. Mijn dank is groot aan allen die mee hebben gewerkt aan de totstandkoming van hetgeen voor u ligt!

In de eerste plaats al die jongeren met een alcoholintoxicatie en hun ouders. Hoewel ik me realiseer dat een presentatie op de spoedeisende hulp of zelfs een opname een impactvolle gebeurtenis is, waren jullie bijna altijd bereid om deel te nemen aan mijn onderzoek. De data die door jullie tot stand is gekomen, maken het mogelijk om in de toekomst de zorg voor jongeren met een alcoholintoxicatie nog beter te maken.

Prof. Dr. N. van der Lely, beste Nico, dank voor het vertrouwen wat ik heb gekregen om te starten met dit promotietraject. In dezelfde periode dat ik van PhD-kandidaat ben gegroeid naar doctor, heb jij ontwikkeld van doctor tot professor met als hoogtepunt de inauguratie van de 'Reinier de Graaf Leerstoel Jongeren en Alcohol' in Antwerpen. Veel dank voor je inzet, je altijd snelle feedback, vooral ook om 03:00 's nachts. Jouw energie en motivatie hebben zo aanstekelijk gewerkt, dat ik dit hele promotieonderzoek ook als een speer heb kunnen doen!

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Dr. J.J van Hoof, beste Joris, dank voor je bijdrage aan bijna al mijn artikelen. Ik heb veel van je geleerd, met name over statistiek en wetenschappelijke notaties. Je precisie en zorgvuldigheid in het lezen van mijn stukken zullen mij altijd bij blijven. Hoewel de meeste communicatie op afstand plaatst vond, heb ik onze lunches met jou en Nico altijd enorm kunnen waarderen.

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waren een enorme motivator voor mijn onderzoek. Mijn dank is dan ook groot voor jouw deelname in de leescommissie en voor de uiteindelijke beoordeling van dit proefschrift. Veel succes met jullie onderzoek in Belgie, ik zal jullie resultaten blijven vervolgen.

Prof. dr. ir. C.T.B. Ahaus en prof. dr. J.M. Cramm, veel dank voor jullie positie in de leescommissie en jullie inzet om mijn proefschrift te beoordelen. Mijn proefschrift geeft blijk van de breedte van de zorg voor jongeren met een alcohol intoxicatie en daarom ben ik ook dankbaar voor de beoordeling vanuit zowel kindergeneeskundig, als maatschappelijk perspectief.

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