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SLEEP BRUXISM – GENETIC FACTORS AND PSYCHOACTIVE SUBSTANCES

Studies in Finnish twins

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ABSTRACT

Background: Genetic and environmental factors have a varying influence on oral health-related problems. Although studies have been conducted, the contribution of genetic factors to sleep-related bruxism remains obscure. Bruxism causes several physical problems, including abnormal tooth wear, pain in the temporomandibular joint or jaw muscles, and headaches, as well as social problems. The detailed aetiology of bruxism is unknown. In addition to genetic factors, psychoactive substances are considered to be potential risk factors for bruxism.

Aims: The aim of the present study was to explore the role of genetic and environmental factors in the phenotypic variance of self-reported sleep-related bruxism. A second aim was to investigate the potentially independent roles of three commonly used legal psychoactive substances, tobacco, alcohol, and coffee, in the occurrence of self-reported sleep-related bruxism.

Subjects: The study was based on two large twin cohorts, one of young adults and the other of middle-aged twins. The data of young adult twins were derived from the fourth wave of the longitudinal *FinnTwin16* cohort study consisting of twins born in 1975–1979. The participants (n=3124 subjects, mean age 24 years) completed a questionnaire in 2000–2002 enquiring about the, the occurrence of sleep-related bruxism in young adults and the use of tobacco products. The data of middle-aged adult twins derived from the *Finnish Twin Cohort* study consisting of twins born in 1930–1957. The participants (n=12 502 subjects, mean age 44 years) completed a questionnaire in 1990 enquiring about sleep-related bruxism and the use of psychoactive substances, tobacco products, alcohol, and coffee.

Methods: Quantitative genetic modelling was based on the genetic similarity of monozygotic and dizygotic twins and on the decomposition of phenotypic variance into the following components: additive genetic effects (A), dominant genetic effects (D), and non-shared environmental effects (E). Quantitative genetic modelling was used to evaluate the relative proportion of genetic factors of the phenotypic variance in the liability to bruxism. Multinomial logistic regression was used to explore the association between bruxism and psychoactive substances as independent risk factors.

Results: The models revealed a clear genetic component behind bruxism. The best fitting genetic model for bruxism was the AE-model in which additive genetic effects

accounted for 52% of the total phenotypic variance with no gender differences. The three legal psychoactive substances (tobacco, alcohol, and coffee) were clearly associated with bruxism. In addition, all of them raised the odds for bruxism independently, and there were no significant interactions between them.

Conclusions: Genetic factors contribute to inter-individual differences and account for a substantial proportion of the phenotypic variation of the liability to sleep-related bruxism. Bruxism has no gender difference in its genetic architecture. Psychoactive substances are associated strongly with bruxism, and the relationship is independent of other psychoactive substances, cumulative, and dose-dependent. The twin approach provides evidence of a possible causal link between psychoactive substances and bruxism. Thus, this study consolidates new information about genetic and environmental factors in sleep-related bruxism.

TIIVISTELMÄ

Tausta: Geneettiset tekijät ja ympäristötekijät vaikuttavat suuterveyteen liittyviin ongelmiin. Geneettisten tekijöiden merkitys unenaikaisessa bruksismissa on edelleen epävarma, vaikkakin tutkimuksia aiheesta on tehty. Bruksismi aiheuttaa useita fysiologisia ongelmia, kuten hampaiden kulumista, kipuja leukanivelten alueella ja puremalihaksissa sekä päänsärkyä. Lisäksi se saattaa aiheuttaa myös sosiaalisia ongelmia häiritessään kanssanukkujien yöunta. Bruksismin etiologia on yhä epäselvä. Bruksismialttiutta lisäävinä riskitekijöinä pidetään geneettisten tekijöiden lisäksi psykoaktiivisia aineita.

Tavoitteet: Tutkimuksen tavoitteena on selvittää geneettisten tekijöiden ja ympäristötekijöiden merkitystä itseraportoidun unenaikaisen bruksismin fenotyyppisessä varianssissa. Toisena tavoitteena on selvittää kolmen laillisen psykoaktiivisen aineen, tupakan, alkoholin ja kahvin, merkitystä itseraportoidun unenaikaisen bruksismin itsenäisinä riskitekijöinä.

Aineisto: Tutkimusaineisto koostuu kahdesta suuresta kaksoskohorttitutkimuksesta, joista toinen käsittää nuoria aikuisia ja toinen keski-ikäisiä aikuisia. Nuorten aikuisten aineisto koostuu *FinnTwin16* -pitkittäistutkimuksen neljännestä kyselystä, johon osallistui vuosina 1975–1979 syntyneitä kaksospareja. Kaksoset (n=3124 yksilöä, keski-ikä 24 vuotta) täyttivät vuosina 2000–2002 kyselylomakkeen, jossa oli kysymyksiä sekä unenaikaisesta bruksismista että tupakkatuotteiden käytöstä. Keski-ikäisten aikuisten aineisto koostuu *Finnish Twin Cohort* -tutkimuksesta, johon osallistui vuosina 1930–1957 syntyneitä kaksospareja. Kaksoset (n=12 502 yksilöä, keski-ikä 44 vuotta) täyttivät vuonna 1990 kyselylomakkeen, jossa kyseltiin unenaikaisen bruksismin esiintymistä ja psykoaktiivisten aineiden, tupakan, alkoholin ja kahvin, käyttöä.

Metodit: Kvantitatiivinen geneettinen mallinnus perustuu identtisten ja epäidenttisten kaksosten geneettiseen samankaltaisuuteen. Malli jakaa fenotyyppisen varianssin kolmeen komponenttiin, jotka ovat additiiviset geneettiset tekijät (A), dominantit geneettiset tekijät (D) ja yksilölliset ympäristötekijät (E). Kvantitatiivista geneettistä mallinnusta käytetään tutkittaessa geneettisten tekijöiden ja ympäristötekijöiden suhteellista osuutta yksilön bruksismialttiuden fenotyyppisessä vaihtelussa. Multinomiaalista logistista regressiota käytetään arvioimaan bruksismin ja psykoaktiivisten aineiden välistä yhteyttä ja psykoaktiivisten aineiden merkitystä bruksismin itsenäisinä riskitekijöinä.

Tulokset: Geneettiset tekijät selittivät selkeän osan bruksismialttiudesta. AE-malli osoittautui parhaaksi malliksi ja geneettiset tekijät selittivät mallissa 52% varianssista. Sukupuolten välillä ei esiintynyt eroja. Kaikki kolme tutkittua psykoaktiivista ainetta (tupakka, alkoholi ja kahvi) liittyivät merkitsevästi bruksismiin. Psykoaktiiviset aineet eivät muodostaneet keskenään interaktioita, vaan psykoaktiiviset aineet toimivat itsenäisinä riskitekijöinä.

Johtopäätökset: Geneettiset tekijät vaikuttavat merkittävästi yksilöiden välisiin eroavaisuuksiin unenaikaisessa bruksismialttiudessa ja selittävät siitä merkittävän osan. Geneettisten tekijöiden osuus vaihtelussa on riippumaton sukupuolesta. Psykoaktiivisilla aineilla on tärkeä merkitys bruksismin riskitekijöinä ja niiden yhteys bruksismiin on kumulatiivinen, annosriippuvainen ja toisista psykoaktiivisista aineista riippumaton. Kaksostutkimusasetelma tukee psykoaktiivisten aineiden ja bruksismin välistä mahdollista kausaalisuhdetta. Tutkimus vahvistaa ja tuo esiin uutta informaatiota geneettisten tekijöiden ja ympäristötekijöiden merkityksestä unenaikaisessa bruksismissa.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following four original publications referred to in the text by their Roman numerals:

I. Rintakoski K., Hublin, C., Lobbezoo, F., Kaprio J. (2012). Genetic Factors Account for Half of the Phenotypic Variance in Liability to Sleep-Related Bruxism in Young Adults: A Nationwide Finnish Twin Cohort Study. *Twin Research and Human Genetics*, vol. 15, no. 6, pp. 714-719. doi: 10.1017/thg.2012.54

II. Rintakoski, K., Ahlberg, J., Hublin, C., Lobbezoo, F., Rose, R.J., Murtomaa, H., Kaprio, J. (2010). Tobacco use and reported bruxism in young adults: A nationwide Finnish twin cohort study. *Nicotine & Tobacco Research*, vol. 12, no. 6, pp.679-683. doi:10.1093/ntr/ntq066

III. Rintakoski K., Ahlberg J., Hublin C., Broms U., Madden P.A.F., Könönen M., Koskenvuo M., Lobbezoo F., Kaprio J. (2010). Bruxism Is Associated With Nicotine Dependence: A Nationwide Finnish Twin Cohort Study. *Nicotine & Tobacco Research,* vol. 12, no.12, pp.1254-1260. doi: 10.1093/ntr/ntq190

IV. Rintakoski K, Kaprio J. (2012). Legal psychoactive substances as risk factors for sleep-related bruxism: a nationwide Finnish Twin Cohort Study. *Alcohol and Alcoholism*, vol. 48, no. 4, pp. 487-94. doi: 10.1093/alcalc/agt016

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ABBREVIATIONS

A	Additive genetic effect
C	Common environmental effect
CI	Confidence interval
CPD	Cigarettes per day
D	Dominant genetic effect
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DZ	Dizygotic twin
DZF	Dizygotic female
DZM	Dizygotic male
DZ-OS	Dizygotic opposite sex
E	Unique environmental effect
EMG	Electromyography
FTND	Fagerström Test for Nicotine Dependence
GABA	Neurotransmitter gamma-aminobutyric acid
GWAS	Genome-wide association studies
h^2	Heritability estimate
ICD-10	International Classification of Diseases, 10th version
IRB	Institutional Review Board
MZ	Monozygotic twin
MZF	Monozygotic female
MZM	Monozygotic male
nAChR	Nicotinic acetylcholine receptor
NAG	Nicotine Addiction Genetics Study
NMDA	*N*-methyl-D-aspartic acid
OR	Odds ratio
PSG	Polysomnography

1. INTRODUCTION

Bruxism is defined as teeth grinding and/or clenching during sleep or while awake (American Academy of Sleep Medicine 2005). It is classified as a sleep-related movement disorder linked to micro-arousals of sleep (Macaluso *et al.* 1998, De Laat & Macaluso 2002, Lavigne *et al.* 2003). It causes several problems, including abnormal tooth wear, pain in the temporomandibular joint or jaw muscles, headaches, and even social problems (Kato *et al.* 2001, Lavigne, Manzini & Kato 2005), which makes it a significant concern for many people. The aetiology of bruxism remains partly unknown, although many theories exist. Initially, peripheral theories about the morphological factors causing bruxism governed, but nowadays theories about central regulation of pathophysiological or psychological mechanism dominate (Lavigne *et al.* 2008, Van der Zaag *et al.* 2008). Like most other traits, the liability to bruxism is probably affected by both genetic and environmental factors. Generally, the risk factors of bruxism are considered to be disorders in the dopaminergic system, stress, sleep disturbances, psychoactive substances like smoking, alcohol, and coffee, age, gender, and genetics (Hublin *et al.* 1998, Lavigne & Manzini 2000, Lavigne *et al.* 2001, Ohayon, Li & Guilleminault 2001, Chen *et al.* 2005, Lobbezoo, Van Der Zaag & Naeije 2006, Lavigne *et al.* 2008).

Although the underlying mechanisms of the aetiology of bruxism are unknown, psychoactive substances, among others, are considered to be risk factors for bruxism (Lobbezoo & Naeije 2001, Ohayon, Li & Guilleminault 2001, Lavigne, Manzini & Kato 2005, Lobbezoo, Van Der Zaag & Naeije 2006). Psychoactive substances are substances that affect the central nervous system in a variety of ways and cause several changes to cognitive behaviour (World Health Organization 2004). The role of tobacco, alcohol, and coffee in bruxism has been studied, but the results have been controversial (Hartmann 1979, Hartmann *et al.* 1987, Bastien, Gale & Mohl 1990, Lavigne *et al.* 1997, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Johansson *et al.* 2004, Ahlberg *et al.* 2004, Ahlberg *et al.* 2005, Bellini *et al.* 2011, Kato *et al.* 2012, Abe *et al.* 2012). Yet, because the dominating theory explaining bruxism is the central regulation (Lobbezoo & Naeije 2001), it is justified to hypothesize that psychoactive substances affecting the brain have an impact on bruxism. While the use of medicinal psychoactive substances may confound the relationship between substances and bruxism because the medicated disease itself might affect bruxism, investigating these medicinal psychoactive substances are beyond the scope of this study. The use of illegal psychoactive substances, i.e. drugs, is also excluded because their use is likely to be enormously underreported.

Genetic and environmental factors explain an individual's phenotypic liability to bruxism (Hublin *et al.* 1998, Lavigne, Manzini & Kato 2005). However, evidence of genetic factors affecting bruxism is limited because of the small number of studies done in this area. Nevertheless, at least one study has shown genetic factors to play an important role in bruxism in adults (Hublin *et al.* 1998). Large-scale epidemiological studies are needed to elucidate the role of genetic factors.

The present study focuses on the role of genetic and environmental factors and possible sex-specific genetic effects in the liability to bruxism by using a unique Finnish twin data. In addition to genetic effects, this study investigates three legal non-medicinal psychoactive substances, namely tobacco, alcohol, and coffee, as potential risk factors for bruxism.

2. REVIEW OF THE LITERATURE

This review focuses on sleep-related bruxism and the use of psychoactive substances, namely tobacco, alcohol, and coffee, as well as on bruxism and genetic factors, heritability, and twin studies. The psychoactive substances are viewed in light of their association with bruxism. The focus on the use of tobacco and smokeless tobacco is shifted towards nicotine and nicotine dependence as important parts of tobacco use. Alcohol use is viewed as alcohol consumption, binge drinking, and passing out due to alcohol. Coffee use is viewed as total consumption of coffee and caffeine as a psychoactive substance.

OVERVIEW OF ORAL HEALTH, GENETIC EPIDEMIOLOGY, AND PSYCHOACTIVE SUBSTANCE USE

Oral health is an important part of general health and has been widely studied (Petersen 2003). Variation in oral health is a unique mixture of genetic and environmental factors and gene-environment interactions. Twin studies are an excellent way to examine oral health-related issues. Based on epidemiological family and twin studies, some of the dental health variables have a strong genetic component, while others are more prone to environmental factors. A strong genetic component explains dental caries, tooth size and morphology, and dental arch dimensions (Boraas, Messer & Till 1988, Conry *et al.* 1993, Kabban *et al.* 2001, Shuler 2001, Race, Townsend & Hughes 2006, Townsend *et al.* 2006). However, most studies of the genetic liability to dental diseases are based on rather moderate-sized samples, but the results are still statistically significant. Dental caries, for instance, has been estimated to have a heritability of up to 70% in young twins aged under 8 years, and genetic factors seem to affect inter-individual variation in children's susceptibility to caries (Bretz *et al.* 2005, Bretz *et al.* 2006). However, not all dental health-related diseases and problems are genetically regulated. Especially diseases of the soft tissue, mainly the gums and parodontium (gingivitis and periodontitis), are generally thought to be caused by environmental factors such as lack of proper dental hygiene and content of oral flora (Michalowicz *et al.* 1991, Michalowicz *et al.* 2000a). Moreover, no evidence of the heritability of temporomandibular disorders, TMD has been found (Michalowicz *et al.* 2000b). Still, a minor genetic component does not reveal everything about an individual's liability to contract a disease. However, assessment of oral health is somewhat difficult using questionnaires alone. Interestingly, instead of using multi-item measures, the use of single-item

measures improves the validity in oral health studies (Locker 1996). Nevertheless, self-reported oral health findings may differ from clinical findings, but self-report has been shown to be useful at least in ascertaining the number of teeth and the presence of dentures, fillings, root canal therapy, and fixed and removable prostheses (Könönen, Lipasti & Murtomaa 1986, Palmqvist, Söderfeldt & Arnbjerg 1991, Pitiphat *et al.* 2002). However, self-report is less useful for identifying current dental caries and periodontal disease (Kallio 1996, Östberg, Halling & Lindblad. 2003, Goodman *et al.* 2004).

Overall, dentists see many oral health problems in addition to caries and gingivitis. Among others, these include periodontitis, oral cancers, temporomandibular disorders, and bruxism. It is important for dentists to deepen their understanding of the aetiology of these diseases, and thus, improve their prevention and treatment. Although all of these diseases do not act as general indicators of oral health, they are still relevant and uncomfortable problems for patients as well as cost-consuming for public dental care. Moreover, while each is an important separate research branch, it is common to all of them that specific genetic and environmental factors and gene-environment interactions affect individuals' phenotypic liability to them (Boraas, Messer & Till 1988, Michalowicz *et al.* 1991, Conry *et al.* 1993, Michalowicz *et al.* 2000, Kabban *et al.* 2001, Shuler 2001, Race, Townsend & Hughes 2006, Townsend *et al.* 2006). Genetic epidemiology is a branch of research that can study them all.

Genetic epidemiology investigates the role of the genetic basis of traits together with environmental factors and their potential interactions with genes in families and populations (Khoury, Beaty & Cohen 1993, Duncan 2004b). Because different environments can have different effects on people, genetic epidemiological studies are usually population-dependent and the results may differ widely in different populations. Moreover, some clusters of genes may be highly population-specific such that the importance of genetic factors varies between populations (Duncan 2004b, Li *et al.* 2010). One way to study genetic epidemiology is to use twins. Twins share all or some of their segregating genes and by comparing twin pairs it is possible to estimate the relative proportion of genetic and environmental factors in the studied trait (Boomsma, Busjahn & Peltonen 2002, Duncan 2004a). However, twin design alone does not give information about the exact genes affecting the trait, and therefore, molecular epidemiology improves the study of genetic background. Molecular epidemiology, which examines the role of genetic and environmental factors at the molecular level, can be done by linkage studies or association studies (Duncan 2004b). At the moment, genome-wide association studies (GWAS) are the conventional approach, and they examine the common genetic variants and their relationship to a studied trait (Manolio 2010, Visscher *et al.* 2012). The present study apart from genetic epidemiology is a twin study, and twin studies in general as well as genetic modelling are reviewed later in this literature review.

In addition to genetic factors, environmental factors are important and may have an even more prominent role in some diseases than genetic factors. Generally, environmental factors are any factors influencing individuals, regardless of their unique combinations of genes. Although the relevance of environmental factors varies, their role in individuals' liability to any oral health problem is important. Depending on the studied trait, their share of the outcome varies (Boraas, Messer & Till 1988, Michalowicz *et al.* 1991, Conry *et al.* 1993, Kabban *et al.* 2001, Shuler 2001, Race, Townsend & Hughes 2006, Townsend *et al.* 2006), but they always play some role. Therefore, environmental factors should also be investigated using epidemiological studies. One key environmental factor is psychoactive substances, which are widely used and also cause a variety of harmful health effects and costs to the health care sector (Rehm *et al.* 2007). The present study largely focuses on psychoactive substance use in addition to genetic factors. Below is a review of psychoactive substance and substance dependence.

Substances affecting the central nervous system, including the brain, are called neurochemicals. These can be divided into two groups: natural organic substances (mostly neurotransmitters) and other molecules (chemical substances or drugs). The natural organic neurotransmitters are released by neurons and they affect other cells, causing changes to the central nervous system. However, not every neurotransmitter is released naturally in every area. There are a variety of neurotransmitters, but the most common are monoamines (dopamine, norepinephrine, and serotonin), acetylcholine, glutamate, and GABA (γ-aminobutyric acid). The effects of neurotransmitters vary widely. For example, dopamine inhibits postsynaptic potentials, and its effects are linked to learning, motivation, and movement. It also plays an important role in general substance dependence as well as in nicotine and alcohol dependence. Norepinephrine, in turn, is involved in arousal and stress responses, while serotonin is related to regulation of mood, arousal, impulsivity, aggression, appetite, and anxiety. Serotonin is also involved in the effects of the central nervous system caused by nicotine, alcohol, and illicit drugs (cocaine and amphetamine). Acetylcholine plays an important role in the processes of learning and memory. It is also implicated in nicotine dependence and may even contribute to the effects of cocaine and amphetamine. Glutamate is important in learning as well, and it modulates neural responses to many psychoactive substances. GABA acts as an inhibitory neurotransmitter, and therefore, it directs the sedative and anxiety-reducing effects of alcohol, benzodiazepines, and barbiturates (World Health Organization 2004, Meyer & Quenzer 2004, Deutch & Roth 2003).

While neurotransmitters are natural organic psychoactive substances, there are also a variety of substances affecting natural neurotransmitter release or the second messenger system. In addition, these substances have the ability to affect an individual's perception, mood, thinking, and behavior by causing long-term changes

at the cellular level and further in complex physiological and behavioural changes in individuals' consciousness, mood, motivation, and thinking processes (Koob 2003, World Health Organization 2004). These combined with learned positive physical or psychological signs form substance use dependence. Therefore, psychoactive substances first reach the brain by absorbing into the brain from the blood plasma, thereafter binding to specific target sites (Meyer & Quenzer 2004). They then change the normally existing mechanism of the brain, causing substance use dependence after use (Koob 2003, Koob & Le Moal 2006). Substance dependence is often defined as follows: "When an individual persists in use of alcohol or other drugs despite problems related to use of the substance, substance dependence may be diagnosed. Compulsive and repetitive use may result in tolerance to the effect of the drug and withdrawal symptoms when use is reduced or stopped." (American Psychiatric Association 1994). Nevertheless, there are several ways to diagnose substance use dependence. According to the *ICD-10 classification of mental and behavioural disorders* (World Health Organization 1992), substance use dependence is examined with six criteria (including both physical and psychological symptoms); a diagnosis of "dependence" requires meeting at least three of these criteria. Alternatively, the *Diagnostic and Statistical Manual (DSM-IV)* (American Psychiatric Association 1994), which is similar to the ICD-10, can be used.

Psychoactive substances are divided into four major classes according to their mode of action in the nervous system: stimulants (e.g. caffeine), which act as adenosine receptor antagonists, depressants (e.g. alcohol), which act as GABA receptor agonists and NMDA receptor antagonists, hallucinogens (e.g. LSD), and opioids (e.g. heroin) ((Salaspuro, Kiianmaa & Seppä 2003, World Health Organization 2004). There are also substances, like the acetylcholine agonist nicotine, that can act as both stimulants and depressants depending on the dose (Henningfield, London & Pogun 2009). Responses to these substances vary between individuals (Davidson, Finch & Schenk 1993), and not all individuals develop dependence (Goldstein & Kalant 1990, Schuckit 2009). However, dependence on psychoactive substances is relatively common. One of the reasons why psychoactive substances are often used and the use is continued is to gain a physical or psychological experience of pleasure or to avoid pain or withdrawal symptoms (Koob 2003, World Health Organization 2004). Further, psychoactive substances, despite their biological effects, can also be categorized into three groups according to their purpose of use and legality: medications, legal psychoactive substances, and illegal or illicit psychoactive substances. This literature review focuses on three commonly used legal, non-medicinal psychoactive substances and their association with bruxism. These comprise nicotine as a component of tobacco products, ethanol as a component of alcoholic beverages like beer, wine, or spirits, and caffeine mostly derived from coffee consumption.

2.1. BRUXISM

2.1.1. DEFINITION OF BRUXISM

Bruxism is defined as "diurnal or nocturnal parafunctional activity that includes clenching, bracing, gnashing, and grinding of teeth" (American Academy of Sleep Medicine 2005). It is nowadays classified as a sleep-related movement disorder that may involve both grinding and clenching associated with excessive (intense) micro-arousals (Macaluso *et al.* 1998, Kato *et al.* 2001, De Laat & Macaluso 2002, Lavigne *et al.* 2003, American Academy of Sleep Medicine 2005, Lavigne *et al.* 2008). It may cause several problems, including abnormal tooth wear and fractures, failures of dental restorations, prostheses or implants, tooth mobility, and pain in the temporomandibular joint or jaw muscles, headaches, and even social problems (Kato *et al.* 2001, Lavigne, Manzini & Kato 2005). Still, not all bruxism necessarily causes notable problems, and the classification between normal behavior and parafunctional type is challenging for researchers and clinicians.

Bruxism may also be divided into primary and secondary bruxism based on potential etiological factors (Lavigne, Manzini & Kato 2005). Primary bruxism is a basic phenomenon that is not affected by any medical condition or medication. Secondary bruxism, by contrast, is affected by a distinct medical condition, medication or other external substance. Overall, the amount of bruxism explained by primary or secondary factors is difficult to study because of the many confounding factors that are often present. Further, pure bruxism may be rare in the adult population.

Bruxism may also occur during waking hours and is then called awake bruxism. It is, contrary to sleep-related bruxism, most commonly manifested as tooth clenching associated with psychosocial factors (Lavigne *et al.* 2008, Manfredini & Lobbezoo 2009) and there is debate whether or not these two forms of bruxism are independent disorders (Manfredini & Lobbezoo 2010). This literature review and study, however, concentrates on sleep-related bruxism only and awake bruxism is left outside of the review of the literature.

2.1.2. EPIDEMIOLOGY OF BRUXISM

The prevalence of bruxism varies among studies, but generally the prevalence of awake bruxism is thought to be about 20%, being more common among women, while the prevalence of sleep bruxism is about 8% in the adult population being same among sexes (Reding, Rubright & Zimmerman 1966, Glaros 1981, Lavigne

& Montplaisir 1994, Ohayon, Li & Guilleminault 2001, Lavigne, Manzini & Kato 2005). However, based on self-report studies, the prevalence of bruxism is highest in children, gradually decreasing with increasing age; from 14–18% in childhood to 3% in the elderly (Lavigne & Montplaisir 1994, Laberge *et al.* 2000, Ohayon, Li & Guilleminault 2001, Ng *et al.* 2005). The importance of factors like ethnicity on the prevalence of bruxism is uncertain, (Lavigne & Montplaisir 1994, Laberge *et al.* 2000, Ohayon, Li & Guilleminault 2001, Lavigne, Manzini & Kato 2005, Ng *et al.* 2005).

2.1.3. DETECTING BRUXISM

Previously, based on the idea of peripheral regulation of bruxism, bruxism was mostly detected clinically by looking at attrition patterns, i.e. bruxofacets, of dentition. Nowadays, bruxism is detected by using questionnaires or interviews and/or clinical examinations, including also direct measurement techniques of sleep laboratories. This direct measurement based on electromyography (EMG) and polysomnography (PSG) allows accurate diagnosis of current bruxism (De Leeuw 2008). However, the technique requires an experienced analyst due to difficulties in observing differences between oromandibular movements of interest and other types of oromandibular activities (Lavigne *et al.* 2008). Further, the major problems with a sleep laboratory setting are the high price of the method, the time-consuming analyses, the possible disturbances of sleep created by an atypical environment, and the potential long distances between the sleep laboratory and the homes of study subjects (Lavigne, Rompre & Montplaisir 1996, Manfredini & Lobbezoo 2010). Therefore, the sleep laboratory setting is best-suited to studies with small sample sizes, and large-scale epidemiological studies mostly rely on self-reporting methods (Manfredini & Lobbezoo 2010). Despite these difficulties, the best available method for detecting bruxism is the sleep laboratory setting because the main problem with self-reports is that not all individuals are aware of their bruxism, resulting in underreporting. However, based on the study of Rompré *et al.* (2007), over 74% of patients diagnosed with bruxism are aware of their condition. Therefore, self-report is currently the best available method for large-scale epidemiological surveys.

2.1.4. AETIOLOGY OF BRUXISM

The aetiology of bruxism is partly unknown, although many studies have explored the risk factors and mechanisms underlying the genesis of bruxism. Overall, several factors explaining the aetiology of bruxism have been suggested, including

morphological, pathophysiological, and psychosocial factors (Lobbezoo, Van Der Zaag & Naeije 2006). Further, two different aetiological theories exist to explain the unsolved nature of bruxism. These are peripheral (morphological) and central (pathophysiological and psychological) (Lavigne *et al.* 2008). In the early days of bruxism research, morphological factors alongside "neurotic tensions" were thought to be mainly responsible for the initiation of bruxism (Ramfjord 1961, Lobbezoo & Naeije 2001). Especially different disharmonies of occlusion were believed to induce bruxism in an effort to eliminate the interferences in occlusion. Later studies have failed to prove any significant association between morphological interferences and bruxism, any benefit of occlusal adjustment in the treatment of bruxism or evidence of a causal relationship between bruxism and peripheral factors (Lobbezoo & Naeije 2001, Lobbezoo, Van Der Zaag & Naeije 2006, Lobbezoo *et al.* 2012).

Therefore, at present, the theory of central regulation overwhelms the theory of peripheral regulation (Lobbezoo & Naeije 2001, Lobbezoo, Van Der Zaag & Naeije 2006). Nowadays, many pathophysiological and psychosocial factors seem to be related to bruxism. Also, age, gender, and genetic factors affect an individual's liability to bruxism (Hublin *et al.* 1998, Bader & Lavigne 2000, Kato *et al.* 2012). The current theory of central regulation of bruxism reflects the idea that certain aspects of central neurotransmitter systems, especially the dopaminergic system, may alter or initiate bruxism (Winocur *et al.* 2003, Lobbezoo, Van Der Zaag & Naeije 2006). Bruxism is associated with such pathophysiological factors as sleep disturbances and sleep apnea, disorders in dopaminergic system, reflux disease, use of certain medications, illicit drugs, and legal psychoactive substances like tobacco, alcohol, and coffee (Bader & Lavigne 2000, Lavigne & Manzini 2000, Lobbezoo & Naeije 2001, Ohayon, Li & Guilleminault 2001, Lavigne, Manzini & Kato 2005, Lobbezoo, Van Der Zaag & Naeije 2006). In addition, a role of certain medications in inducing, relieving, or worsening bruxism has been proposed, although evidence is weak because of small sample sizes or case-study aspects of these studies and because the disease being treated may itself affect bruxism (Winocur *et al.* 2003). Further investigations are warranted to elucidate the role of specific neurotransmitters and neurochemicals.

Psychosocial factors, including stress, anxiety, depression, and other personality traits, have been proposed to affect both awake and sleep-related bruxism (Pingitore, Chrobak & Patrie 1991, Fischer & O'toole 1993, Ahlberg *et al.* 2002, Lobbezoo, Van Der Zaag & Naeije 2006, Ahlberg *et al.* 2008, Manfredini & Lobbezoo 2009, Ahlberg *et al.* 2013). However, there is still a lack of evidence of their role in sleep-related bruxism (Lobbezoo, Van Der Zaag & Naeije 2006, Manfredini & Lobbezoo 2009), although some evidence of their relationship especially with self-reported sleep-related bruxism exist (Manfredini & Lobbezoo 2009). Ohayon *et al.* (2011) found that self-reported sleep-related bruxism associated significantly with mood, anxiety,

adjustment disorders, and hallucinatory phenomena, while Winocur *et al.* (2011) found that higher levels of emotional stress was more common among those who reported sleep-related bruxism. Manfredini *et al.* (2005) instead studied clinically diagnosed bruxism and found some association between clinically diagnosed sleep-related bruxism and certain psychopathological symptoms. Later, Manfredini *et al.* (2011) also reported that trait anxiety was related in the sleep-time masticatory muscle activity.

Psychosocial factors and psychoactive substances are related to each other. Many psychoactive substances affect an individual's perception, mood, thinking, and behavior (Koob 2003, World Health Organization 2004). Also, psychosocial factors may drive for the use of psychoactive substances (Patton *et al.* 1998, Sonntag *et al.* 2000) and therefore it remains unclear whether the role of psychosocial factors on bruxism is independent of the effect of psychoactive substances. Only, Ohayon *et al.* (2001) adjusted their models with multiple variables and in their results both psychosocial factors and psychoactive substances act as risk factors for bruxism. Therefore, further investigations of the possible link between psychosocial factors and psychoactive substances in the aetiology of bruxism are needed.

2.1.5. GENETIC FACTORS AFFECTING BRUXISM

Genetic factors affecting the genesis of bruxism or an individual's liability to bruxism remain unknown. Only a few questionnaire-based or large-scale twin studies reporting some genetic background for bruxism exist (Hublin *et al.* 1998, Lavigne, Manzini & Kato 2005, Lavigne *et al.* 2008). Some studies have indicated a hereditary component for bruxism, although most of these studies have been performed with only a few individuals. Multiple genes may be linked to the genesis of bruxism, and the exact genes are difficult to identify (Lavigne *et al.* 2008).

The earliest reports of a hereditary component of bruxism are from the 1960s and 1970s (Horowitz 1963, Reding, Rubright & Zimmerman 1966, Abe & Shimakawa 1966, Lindqvist 1974). These are based either on attrition patterns in dentition (Horowitz 1963, Lindqvist 1974) or on self-reports of sleep bruxism (Reding, Rubright & Zimmerman 1966, Abe & Shimakawa 1966). Both Horowitz (1963) and Lindqvist (1974) have studied twin pairs and found some evidence that monozygotic twins have higher concordance rates than dizygotic twins. In addition, Reding *et al.* (1966) studied individuals and their blood relatives and found a significant association between their reported bruxism. Similarly, Abe and Shimakawa (1966) evaluated children and their parents and noted that those children whose parents suffered from sleep bruxism were also more likely to experience sleep bruxism. However, all of these studies are based on the idea that bruxism is peripherally

regulated, and some of the studies diagnosed bruxism according to attrition patterns in dentition.

Later, Hublin *et al.* (1998) performed a large twin cohort study using middle-aged twins. They observed a strong association between bruxism in childhood and adulthood. They also found a notable hereditary component for the liability to bruxism in adulthood. The hereditary component differed among the sexes, with genetic factors explaining 39% of an individual's liability to bruxism in males and 53% in females. The rest of the phenomenon was explained by non-shared environmental factors. However, they could not determine whether genes specific to one sex, sex-specific common environmental effects, or sex-specific additive genetic effects affect the variation in bruxism due to the lack of opposite-sex pairs for the sex-limitation model. Thus, there is a need for studies to investigate gender differences in the genetic liability to bruxism.

Although genetic research on the genetic component and heredity of bruxism has been performed, only two studies on the molecular basis for bruxism exist (Nowakowska *et al.* 2010, Abe *et al.* 2012). Further, some suggestions about genetic markers for bruxism have been made, although these markers remain mainly unknown (Abe *et al.* 2012). Nowakowska *et al.* (2010) reported a case study of four young children with either deletions or mutations involving MEF2C in 5p14.3. They reported two of the four children to also suffer from bruxism. However, bruxism was not studied in further detail. Abe *et al.* (2012), on the other hand, analysed and genotyped 112 individuals for 13 polymorphisms in four genes related to serotonergic neurotransmission. According to their analyses, only the C allele carrier of HTR2A single-nucleotide polymorphism rs6313 was significantly associated with sleep bruxism, indicating that the serotonergic system may play a role in the genesis of bruxism. However, further molecular genetic studies on bruxism are warranted.

2.1.6. PSYCHOACTIVE SUBSTANCES AS RISK FACTORS FOR BRUXISM

Studies on the role of neurochemical substances exist (Winocur *et al.* 2003, Lobbezoo, Van Der Zaag & Naeije 2006), but the importance of these neurochemicals in the aetiology of bruxism is under debate. The relationship between neurotransmitters and bruxism is challenging to study, and no strong evidence has yet emerged of any single neurotransmitter, neurochemical mechanism, or a specific gene in the genesis of bruxism. Also the facts that most neurochemicals have several targets of action, neurotransmitters have several target receptors, and subtypes of receptors have many different types of action and also a high affinity for other substances and receptors make studying their detailed role in bruxism difficult.

Most studies have concentrated on common legal drugs and the psychoactive substances of nicotine, alcohol, and coffee, while studies on illegal psychoactive

substances, such as opioids, cocaine, and amphetamine, are less common. All of these psychoactive substances change the levels of natural neurotransmitters in the central nervous system (World Health Organization 2004). Further, most of these psychoactive substances affect the dopaminergic system and therefore may, despite their large variation in physiological effects, influence the genesis of bruxism (Winocur *et al.* 2003). A more detailed review of the role of the psychoactive substances of nicotine, alcohol, and coffee is provided in Sections 2.1.5.1.–2.1.5.3.

2.1.6.1. Tobacco and bruxism

Of the preventable causes of death, smoking remains a forerunner. Although smoking is decreasing in Western societies, it is increasing in developing countries. One-third of the adult population worldwide is estimated to smoke (Hammond 2009). Furthermore, nicotine is among the most commonly used highly addictive agents around the world (World Health Organization 2004), and according to the World Health Organization (2006) "Cigarettes are among the most deadly and addictive products ever produced by mankind". A large variety of tobacco products exist, including cigarettes, cigars, pipes, smokeless tobacco called oral snuff, water pipe tobacco, and biting tobacco (Hammond 2009). While smoking has decreased in Western societies over the past twenty years, it is still rather common (World Health Organization 2004, World Health Organization 2006). It is, however, more common among individuals in lower socio-economic groups, and the prevalence of smoking appears to decrease more slowly among these individuals (Giskes *et al.* 2005, Helakorpi *et al.* 2008). About 32% of the Finnish population smoked in 1990, while the corresponding proportion in 2010 was about 20% (Suomen virallinen tilasto 2005, Jääskeläinen 2011).) In addition, approximately 28% of the young adults (aged 15–24 years) smoked in 1990 (Suomen virallinen tilasto 2005), whereas in 2010 the proportion was 18% (Helakorpi *et al.* 2011). Altogether, smoking was more common in men (aged 15–64 years) than in women in 2010 (23% vs. 16%). However, 16-year-old girls smoke more than boys (22% vs. 21%). Of boys aged 15–24 years, 6% smoked occasionally; the corresponding proportion for girls was 8% (Jääskeläinen 2011).

   Tobacco products are noxious to the health; they cause untimely death and a variety of self-imposed diseases (Doll *et al.* 1994, Neubauer *et al.* 2006). They also increase work disability rate, shorten working age, and raise expenses incurred by society. They have a clear association with such oral health problems as increased risk for periodontal diseases (formation of pockets and loss of alveolar bone) (Walter, Kaye & Dietrich 2012), complications in the success of dental treatment (Levin, Schwartz-Arad 2005, Grossi *et al.* 2007, Heng *et al.* 2007), increased risk of oral cancers (Ram *et al.* 2011), discolouration of teeth (Alkhatib, Holt & Bedi 2005), and

even the sleep-related tooth grinding habit of bruxism (Lavigne *et al.* 1997, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Johansson *et al.* 2004, Ahlberg *et al.* 2004, Ahlberg *et al.* 2005, Kato *et al.* 2012, Abe *et al.* 2012).

Tobacco leaves contain over 2500 chemical constituents, and smoke from cigarettes contains over 4000 different toxic chemical substances (Haustein & Groneberg 2010). Of these chemicals, nicotine remains the main substance underlying dependence. Nicotine derives from the leaves of tobacco plants, where it acts as a botanical insecticide (Benowitz, Hukkanen & Peyton 2009), and is highly toxic in its pure form. In cigarettes, the nicotine content is about 1.5% by weight, and the amount of nicotine is similar in the smokeless tobacco called oral snuff (Benowitz, Hukkanen & Peyton 2009). The initiation of the effects of nicotine depends on the type of tobacco product, but overall nicotine absorbs quickly into the blood circulation and binds to the nicotinic acetylcholine receptors in the brain, where it causes a variety of physiological and psychological effects (Benowitz, Hukkanen & Peyton 2009, Djordjevic, Doran 2009).

Nicotine acts as an agonist for several types of nicotinic acetylcholine receptors (nAChRs) (Koob 2003). It affects various neurotransmitter systems by modulating presynaptic neurotransmitter release, and it also promotes dopamine synthesis, stimulates its transmission, and changes the ganglionic potentials (Henningfield, Keenan & Clarke 1996, Role & Berg 1996, Meyer & Quenzer 2004, Li, Mao & Wei 2008, Henningfield, London & Pogun 2009). The physical effects of nicotine comprise increased pulse rate and blood pressure and the secretion of glucocorticoids and vasopressin (Pomerleau *et al.* 1983). Because of its effects on the dopamine system, it causes several dose-related behavioural and psychoactive effects, including arousal, pleasure, increased attention and concentration, enhanced memory, reward, and euphoria, reduction of anxiety, and suppression of appetite (Koob 2003, World Health Organization 2004). It also reduces stress, causes mood changes, enhances performance, and acts as a self-stimulator (Goldberg & Henningfield 1988, World Health Organization 2004). Further, high levels of nicotine in the brain and plasma cause a rewarding effect, thus rapidly leading to tolerance, withdrawal, and dependence. However, the rewarding effect quickly vanishes when the nicotinic receptors desensitize and nicotine metabolizes (World Health Organization 2004). This creates a loop when an individual smokes to maintain nicotine levels and tries to avoid the negative effects of withdrawal, thereby controlling mood (Koob 2003, World Health Organization 2004). Not everyone develops nicotine dependence, which is influenced by different genetic factors as well as environmental factors (Niu *et al.* 2000, Feng *et al.* 2004). Of current smokers, approximately 53–76% can be classified as nicotine-dependent, depending on the test used, and twin studies have shown that genetic factors account for about 30–70% of the liability to develop nicotine dependence (True *et al.* 1997, Kendler *et al.* 1999, Lessov *et al.* 2004, Maes *et al.* 2004, Broms *et al.* 2006, Rose RJ. *et al.* 2009).

Nicotine dependence can be assessed using several questionnaire-based tests, the most common being the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association 1994), and the Fagerström Test for Nicotine Dependence (FTND) (Heatherton *et al.* 1991, Fagerström & Furberg 2008). Both of these tests consist of multiple questions measuring physiological and psychological dependence. However, these tests differ in their approach to nicotine dependence. The DSM criteria focus on both components of nicotine dependence extensively, with the wider aspects of the behavioral pattern of compulsive substance use and psychological dimensions of addiction, while the FTND focuses more on the behavioral components and less on the physiological components of tolerance and withdrawal. Thus, the DSM criteria approach dependence from a more general viewpoint than the narrow viewpoint examined by the FTND. The DSM-IV is used in the present study. To reach a diagnosis of "dependence", three of the seven criteria must be met within a 12-month period (presented later in section 4.2. *nicotine dependence*).

The role of smoking in the aetiology of bruxism is rather unknown. To date, only eight studies have investigated the association between smoking and bruxism (Lavigne *et al.* 1997, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Johansson *et al.* 2004, Ahlberg *et al.* 2004, Ahlberg *et al.* 2005, Kato *et al.* 2012, Abe *et al.* 2012). These earlier studies differ largely in study design, sample size, definition of smoking, assessment of bruxism, and control of covariates (Table 1). All have used subject self-reports of bruxism by questionnaire or by interview for the epidemiological analyses, while Lavigne *et al.* (1997), Johansson *et al.* (2004), Kato *et al.* (2012), and Abe *et al.* (2012) have done further analyses of bruxism (either clinical examination or sleep laboratory analyses). Although showing some degree of association between smoking and bruxism, none of these papers, with the exception of Abe *et al.* (2012), have looked at smoking in more detail, investigating, for instance, the amount smoked, the type of tobacco products used, or the role of former smoking. Instead they used a smoking versus non-smoking approach, providing evidence that smokers may be at a higher incidence of bruxism. In addition, the role of heavy smoking and nicotine dependence in the aetiology of bruxism is completely unexplored.

In the study of Lavigne *et al.* (1997) using questionnaires (n=2019) smokers reported more bruxism (OR 1.9) than non-smokers. They further studied a subsample of 15 individuals in the sleep laboratory and found smokers to have five times more bruxism episodes during sleep than non-smokers. Molina *et al.* (2001) observed that the smoking habit increased with the severity of bruxism and that the control group smoked less than the bruxism group. Consistent with the findings of Lavigne *et al.* (1997), Ohayon *et al.* (2001) using interviews (n=13057) revealed a higher odds of bruxism in smokers (OR 1.6), but after adjustment for covariates only light smokers had a significantly higher odds (OR 1.3) for bruxism. Johansson *et al.*

(2004) also used questionnaires (n=6343) and clinical examinations (n=941) in their cross-sectional study with 50-year-old males and females and noted a significant association between self-reported bruxism and daily tobacco use (either cigarette smoking or smokeless tobacco). Based on questionnaire and clinical examination, Kato *et al.* (2012) also found smoking to raise the risk of self-reported sleep bruxism almost twofold, OR 1.8. Similarly, Ahlberg *et al.* (2004) reported smokers (including all tobacco use: cigarettes, cigars, pipe, and smokeless tobacco) to be 2.4 (95% CI 1.2–4.9) times more likely than non-smokers to experience bruxism in a non-patient population of a media company (n=211). By contrast, in another survey in the same company (n=874), smoking frequency and frequent bruxism were weakly, albeit not statistically significantly associated (Ahlberg *et al.* 2005). Also Abe *et al.* (2012) in their questionnaire and sleep laboratory-based study failed to show any significant association between the amount of daily smoked cigarettes and bruxism.

Summing up, most existing studies have found some association between smoking and bruxism although few studies have failed to provide evidence of the association. The odds for bruxism have varied being about 1.0–2.4 times higher in smokers than in non-smokers.

Table 1. Previous findings of an association between smoking and bruxism.

First author and year	Study sample	Study design	Evaluation of bruxism	Evaluation of smoking status	Outcome/ OR
Lavigne, 1997	n=2019 22–73 years	Questionnaire and sleep laboratory	Yes/No	Yes/No	1.9
Molina, 2001	n=326 16–67 years	Questionnaire	Mild, moderate, severe	Yes/No	Habit increased with severity of bruxism
Ohayon, 2001	n=13 057 15–100 years	Telephone survey	Tooth grinding during sleep	0, ≤20, >20 cigarettes	1.3 (≤20 cigarettes)
Johansson, 2004	n=6343	Questionnaire, clinical examination	Yes/No	Daily/No	1.35
Ahlberg, 2004	n=1339 → 205 in final analyses, 30–55 years	Questionnaire	Frequent	All tobacco use Yes/No	2.4
Ahlberg, 2005	n=874 42.6–47.4 years	Questionnaire	Frequent (continually or often)	All tobacco use Yes/No	1.1, No significant association
Kato, 2012	n=1390 18–89 years	Questionnaire, clinical examination	Yes/No	Yes/No	1.88
Abe, 2012	n=120 22–69 years	Questionnaire, clinical examination, and overnight EMG recordings	Yes/No	Amount of smoked cigarretes, number/day	No significant association

2.1.6.2. Alcohol and bruxism

Alcoholic beverages have a long history worldwide, and evidence of the use of alcohol dates back thousands of years. Alcohol, which includes the psychoactive substance ethanol, is a legal substance, although its acquisition is restricted to persons over a certain minimum age in many countries (Hanson 1995). Alcohol is most commonly consumed in the form of various alcoholic beverages such as beer, wine, or spirits. Ethanol is quickly absorbed into the bloodstream and carried to brain. Alcoholic beverages are consumed for several different reasons: in social situations to refresh, relax, and provide courage and also for religious, medicinal, and analgesic use (World Health Organization 2004). Unfortunately, alcohol is also misused because of its effect on behaviour and mood and its addictive properties. The psychoactive properties of alcohol are in general dose-dependent, and excessive doses cause ataxia, blackouts, impaired reaction time, and sedation (World Health Organization 2004, Koob & Le Moal 2006). In addition, smoking often co-occurs with alcohol consumption (Grucza & Bierut 2006, Li *et al.* 2007).

Alcohol use in general may be divided into different forms of use; e.g. alcohol consumption (light, moderate, heavy), binge drinking, or alcohol abuse. Alcohol portion is defined as the amount of pure ethanol so that a standard drink equals 14 grams of pure ethanol, which as a drink is equal to 350 ml of beer, 150 ml of wine, or 44 ml (a "shot") of 80-proof distilled spirits or liquor. The definitions of alcohol consumption vary greatly between studies (Leeman *et al.* 2010). However, alcohol consumption is usually defined according to the number of drinks per week; light or moderate drinking when the consumption is no more than 7 drinks per week or 3 drinks on a single day for females, and 14 per week or 4 on a single day for males (National Institute on Alcohol Abuse and Alcoholism 2005). Heavy drinking reflects either higher overall use or occasions of high use.

According to the National Institute for Health and Welfare (THL) (Jääskeläinen & Virtanen 2011), the average total consumption of alcoholic beverages has risen about one litre of pure alcohol per resident from 1990 to 2010 in Finland. Further, alcohol use is common, with almost 90% of Finnish adults reporting alcohol consumption during the previous year (Helakorpi *et al.* 2011). However, the consumption has changed towards mild alcoholic beverages. Most of the consumption consists of beer and most of the consumed alcoholic beverages (86% in 2010) are derived from retail sale (Jääskeläinen & Virtanen 2011). The average starting age of alcohol use is rather young in Finland, being around 14–16 years, which is in line with the starting age of many other countries (Prescott & Kendler 1999, Rose *et al.* 1999, Rose *et al.* 2001, Young *et al.* 2002, Patton *et al.* 2007, Pitkänen *et al.* 2008, Eliasen *et al.* 2009). Furthermore, students and young adults aged between 18 and 22 years often consume large amounts of alcohol; this is often the period of the heaviest drinking during the lifetime (Kandel & Logan 1984, Chen & Kandel 1995, Grant & Dawson 1999, Clark 2004, Schuckit 2009). However, this does not necessarily mean that

alcohol dependence will develop because during early adulthood alcohol use and even binge drinking may be part of the social culture among young adults (Perkins 2002, Clark 2004, Kuntsche, Rehm & Gmel 2004).

The intoxicating substance in alcoholic beverages, ethyl alcohol or ethanol, is mainly responsible for the addiction-causing properties. Its action is mediated by GABA and NMDA receptors, and it also causes increasing release and firing of dopamine neurons when the blood concentration of ethanol rises (Moak & Anton 1999). Ethanol is produced in beverages by the fermentation of yeast, sugars, and starches. Its chemical structure is simple, and it easily crosses the blood-brain barrier. Although most effects of ethanol are depressant, it has a biphasic nature; at lower doses, it increases activity and reduces inhibitions and at higher doses it causes depression of cognitive, perceptive, and motor functions (World Health Organization 2004). As with nicotine, however, not all individuals experience the effects similarly, and especially the effects on mood and emotions vary greatly.

Only a few studies of the role of alcohol or ethanol in the aetiology of bruxism exist, and these present partly contradictory results (Hartmann 1979, Hartmann *et al.* 1987, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Bellini *et al.* 2011, Kato *et al.* 2012, Abe *et al.* 2012). Alcohol use in these studies has been analyzed using different alcohol quantities (Table 2). None of these studies used specific drinking patterns together with alcohol quantities. In his first study, Hartmann (1979) used self-reported alcohol consumption from one to four drinks per day as a measure of alcohol use. In their later clinical trial, Hartmann *et al.* (1987) used precisely measured doses of alcohol (dose = 226 mg/kg of ethanol) in a double-blind approach. Abe *et al.* (2012) also measured alcohol intake by ml/day. Ohayon *et al.* (2001), by contrast, classified alcohol consumption as glasses per day (zero, one or two, and at least three), while Molina *et al.* (2001), Bellini *et al.* (2011), and Kato *et al.* (2012) measured alcohol use only as yes or no.

In the first case study by Hartmann (1979), the role of alcohol as a risk factor for bruxism was analysed based on four patients and their bed partners' reports about their bruxism. On average, patients reported alcohol use of one to four drinks per day, and according to their bed partners' reports more episodes of bruxism occurred on the days with alcohol use. Further, using polysomnographic information about one patient, Hartmann reported more bruxism episodes on days with three drinks than on alcohol-free days. However, no statistical analyses were performed in their study. Later, Hartmann *et al.* (1987) performed a sleep laboratory-based double-blinded clinical trial with 16 patients. They gave patients 0 (placebo) to 4 alcoholic drinks to reveal possible effects of alcohol on sleep bruxism. However, they failed to find any significant effect of acute alcohol exposure on bruxism, although there was a slight trend towards higher levels of alcohol intake being associated with more bruxism.

Ohayon *et al.* (2001) estimated that alcohol use raises the risk of sleep bruxism by 1.5–1.8 depending on the daily consumption rate, while Molina *et al.* (2001), Kato *et al.* (2012), and Abe *et al.* (2012) found no significant association between bruxism and alcohol consumption. Further, Bellini *et al.* (2011) noted a trend for more alcohol consumers among bruxers than among non-bruxers in general.

Table 2. Previous findings of an association between alcohol and bruxism.

First author and year	Study sample	Study design	Evaluation of bruxism	Evaluation of alcohol use	Outcome/ OR
Hartmann, 1979	n=4	Interview	Yes/No	0, 1–4 drinks	Bed partners reported more bruxism after alcohol consumption
Hartmann, 1987	n=16	Clinical examination	Bruxism episodes	0,1,2,3,4 doses of alcohol	No significant association
Ohayon, 2001	n=13057 15–100 years	Telephone survey	Tooth grinding during sleep	0, 1–2, ≥3 glasses	1.5 (1–2 glasses) 1.8 (≥3 glasses)
Molina, 2001	n=326 16–67 years	Questionnaire	Mild, moderate, severe	Yes/No	No significant association
Bellini, 2011	n=132	Questionnaire	Yes/No	Yes/No	Alcohol consumers more frequent in bruxer group than in non-bruxer group
Kato, 2012	n=1390 18–89 years	Questionnaire, clinical examination	Yes/No	Yes/No	1.26, No significant association
Abe, 2012	n=120 22–69 years	Questionnaire, clinical examination, and overnight EMG recordings	Yes/No	Alcohol intake, ml/day	No significant association

Summing up, according to the existing studies, the role of alcohol as the risk factor for bruxism is unclear and the odds for bruxism among alcohol consumers seems to vary greatly between studies from no association to almost 2 times higher incidence.

2.1.6.3. Coffee and bruxism

Coffee is one of the most consumed beverages worldwide. Alongside many other substances, it contains caffeine, which acts as psychoactive substance (Minamisawa, Yoshida & Takai 2004). In Finland, coffee consumption is quite high relative to the average European consumption, being 12.2 kg of coffee (weight in green bean equivalent, 1 kg of green coffee beans = 0.84 kg of roasted coffee) per person in the year 2010 (International Coffee Organization 2010). The overall use of other beverages containing caffeine (tea, soft drinks with caffeine, energy drinks) together

with decaffeinated coffee is lower than coffee consumption. Both positive and negative health effects of coffee and caffeine have been widely studied, and caffeine is known to cause addiction and dependence (Laitala, Kaprio & Silventoinen 2008). Coffee consumption seems to have remained moderately stable over time in Finland, and it has an essential role in Finnish culture among adults, and thus, most adults are exposed to coffee regularly (Laitala, Kaprio & Silventoinen 2008). Genetic factors affect the consumption of coffee (Swan, Carmelli & Cardon 1996, Hettema, Corey & Kendler 1999, Kendler & Prescott 1999, Luciano *et al.* 2005, Reynolds, Barlow & Pedersen 2006, Laitala, Kaprio & Silventoinen 2008). There seems to be a common genetic pathway affecting the use of tobacco, alcohol, and coffee (Swan, Carmelli & Cardon 1996, Hettema, Corey & Kendler 1999), and according to Laitala *et al.* (2009), heavy coffee consumption is associated with female gender, a lower level of education, a higher BMI, and smoking.

Caffeine is a psychoactive substance that causes mainly stimulant effects (Salaspuro *et al.* 2003) and is one of the most consumed psychoactive substances in the world. Its stimulant effects include increased mental alertness, wakefulness, and faster information processing as well as alterations to sleep such as delayed sleep onset, reduced total sleep time, modified sleep stages, and deteriorated quality of sleep (Goldstein, Warren & Kaizer 1965, Heath *et al.* 1998, Harland 2000). Although coffee has a variety of other biological effects and contains many biologically active substances (Minamisawa, Yoshida & Takai 2004), the psychoactive effects mediated by caffeine cause the potential dependence.

Previous studies on coffee intake as a risk factor for bruxism are rare (Table 3). Only four studies were found (Bastien, Gale & Mohl 1990, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Abe *et al.* 2012) (Table 3). Bastien *et al.* (1990) performed a placebo-controlled study recording nocturnal masseteric muscle activity via a portable electromyograph recording unit. They gave either placebo or caffeine to 14 volunteers. However, they failed to show any significant association between rising muscle activities and caffeine ingestion. Later, Molina *et al.* (2001) found that the severity of bruxism worsens with increasing coffee consumption. Ohayon *et al.* (2001) estimated that the consumption of six or more cups of coffee daily raised the risk for bruxism 1.4-fold. However, in a questionnaire and sleep laboratory-based study, Abe *et al.* (2012) found no significant association between caffeine intake and bruxism.

Table 3. Previous findings of an association between coffee and bruxism.

First author and year	Study sample	Study design	Evaluation of bruxism	Evaluation of coffee use	Outcome/OR
Bastien, 1990	n=14, mean ages 26.2 and 26.5 years	Recordings by portable electromyograph recording unit	Masseteric activity associated with bruxism	Caffeine vs. placebo	No significant differences in masseteric muscle activity
Molina, 2001	n=326 16–67 years	Questionnaire	Mild, moderate, severe	Scale 1–10, values 8 and more considered as "excessive"	Frequency of coffee drinking increased with severity of bruxism
Ohayon, 2001	n=13057 15–100 years	Telephone survey	Tooth grinding during sleep	0, 1–2, 3–5, ≥6 cups	OR 1.4 (≥6 cups)
Abe, 2012	n=120 22–69 years	Questionnaire, clinical examination, and overnight EMG recordings	Yes/No	Caffeine intake, mg/day	No significant association

Summing up, in few existing studies, the results for the association between coffee consumption and bruxism have not been consistent and there have been great variation in study design and methods and thus, the evidence of coffee as risk factor for bruxism is unclear.

2.2 TWIN STUDIES AND HERITABILITY

A twin is an individual from a two-offspring pregnancy. Twins can be divided into identical or monozygotic (MZ) and non-identical or dizygotic (DZ) twins based on development as a zygote. MZ twins develop from a single egg cell or one zygote that splits, forming two embryos with identically inherited genetic material, and thus, MZ twins share 100% of their genes. DZ twins, by contrast, develop from two separate egg cells, forming two individual embryos, and therefore, DZ twins share on average only 50% of their segregating genes, like normal siblings do. Twins are further classified into five different zygosity-sex groups: monozygotic males (MZM), monozygotic females (MZF), dizygotic males (DZM), dizygotic females (DZF), and opposite-sex dizygotic twins (DZ-OS).

2.2.1. THE CLASSICAL TWIN METHOD

Human behavior and diseases are affected by both genetics and the environment. Individuals' differences from each other in relation to any phenotype may be caused by either genetic or environmental factors. Therefore, the twin situation can be exploited to estimate the heritability of a given trait using either intrapair

correlations or concordance rates (Boomsma, Busjahn & Peltonen 2002). Heritability (h^2) expresses the proportion of the phenotypic variance of the trait that is explained by genetic variance. Twin pregnancies are often considered normal singleton pregnancies in twin studies focusing on environmental and genetic factors. However, compared with actual singleton pregnancies, there may be developmental differences or differences in the intrauterine environment in twin pregnancies that affect the development of any given trait in later life (Hall 2003). Twins share varying amounts of genes while they also share a common environment if they are not reared apart. In addition, every twin individual has a unique environment apart from the one shared with the twin sibling. All of these can affect a given trait when the trait is not fully genetically regulated. Further, there may be some gene-environment interaction that affects the particular trait, meaning that genes may change the effects of exposure to environmental factors, certain genes may be more common in a certain environment, or environmental factors can alter gene expression (Plomin, DeFries & Loehlin 1977, Eaves 1984, Kendler, Eaves 1986, Boomsma, Busjahn & Peltonen 2002, Purcell 2002).

The extent of genetic variation determining the phenotypic variation of a given trait can be estimated by comparing the phenotypic resemblance of MZ and DZ twins. Any purely heritable disease will be more concordant among MZ than DZ twins, while any purely environmentally affected disease will be equally common between MZ and DZ twins (Boomsma, Busjahn & Peltonen 2002). When the trait is influenced by inherited genes as well as environmental factors, then the proportion of the shared environment can be estimated by deducting the genetically explained proportion from the total twin correlation. Because of the shared genetic background of MZs, any situation where one twin of the pair has a disease and his/her co-twin has not (discordant twin pair) could be explained by the different exposure to environmental risk factors. By contrast, in the case of DZ twins, where on average half of the genes are shared, an intrapair difference in a disease outcome could be explained by either environmental or genetic factors. Also, heritability can vary between sexes and the opposite-sex situation of DZ twins helps in the study of sex-specific factors affecting any trait being examined. Still, the result of heritability proportion affecting the trait does not tell whether the heritability derives directly from disease genes or whether it comes from the indirect effects of heritability (say acting on the risk factors for that disease). Despite this limitation, the twin case-control (twin vs. co-twin) situation creates an excellent situation for the evaluation of the importance of genetic variation to the susceptibility of a given trait.

2.2.2. THE DISCORDANT TWIN PAIR DESIGN TO TEST CAUSALITY

The situation of discordant twin pairs (where one twin is affected while the other is not) can be exploited when the focus of the study is on comorbidity or association of two characteristics. The classical twin method can be used to test whether this association is caused by genetic or environmental factors. Discordant twin pairs can also be used to control for genetic and environmental factors that may underlie the association by testing whether the association is present even after adjustment for unmeasured familial and genetic factors. Further, discordant twin pair design or the co-twin control design can be used to test causality (one trait causing the other) (Cederlof, Friberg & Lundman 1977, Kendler *et al.* 1993, Kujala, Kaprio & Koskenvuo 2002, Ligthart, Boomsma 2012). The design tests the intrapair risk for the other trait (B) when the twin pair is discordant for the first trait (A). If there is causality in the association of the studied traits (A raises the risk for B), then the twins of the pairs affected with the first trait (A) are also the twins with a higher risk of being affected with the other trait (B). In addition, discordant twin design results can be generalized to the general population so that individuals with trait A have an increased risk for trait B relative to individuals with no trait A (Ligthart & Boomsma 2012).

3. AIMS OF THE STUDY

The main aim of this study was to examine the role of genetic and environmental factors in sleep-related bruxism using young adult and middle-aged Finnish twins. A special emphasis was placed on three psychoactive substances (tobacco, alcohol, and coffee) as risk factors for sleep-related bruxism.

Specific aims of the study:

    I.   To quantify the relative roles of genetic and environmental factors in sleep-related bruxism (Study I)

    II.   To examine the role of smoking and nicotine dependence in the risk of sleep-related bruxism (Studies II-III)

    III.   To examine the role of alcohol use in the risk of sleep-related bruxism (Study IV)

    IV.   To examine the role of coffee consumption in the risk of sleep-related bruxism (Study IV)

4. MATERIALS AND METHODS

4.1. DATA SETS

The material of the present study originates from two large twin cohort studies: the *FinnTwin16* study and the *Finnish Twin Cohort* study, with a subsample of nicotine-dependent subjects (NAG Finland). Material for Substudies I-II derives from the *FinnTwin16* study and material for Substudies III and IV from the *Finnish Twin Cohort* study. The data and methods used in the substudies are presented in Table 4.

4.1.1. FINNTWIN16

FinnTwin16, a nationwide longitudinal Finnish twin cohort study of five birth cohorts born in 1975–1979, comprises 3065 twin pairs. Twins were identified from the Central Population Registry of Finland (Kaprio, Pulkkinen & Rose 2002). The study protocol was approved by the Ethics Committee of the Department of Public Health, University of Helsinki, Finland, and the Institutional Review Board of Indiana University, Pennsylvania, USA. Subjects were informed of the goals of the study and provided their informed consent.

Twins received comprehensive questionnaires about general health and lifestyle on four separate occasions. The first questionnaire was distributed when twins were 16 years of age in 1991–1995. Follow-up questionnaires were sent when the twins were aged 17 and 18.5 years, and a fourth wave at the stage of early adulthood in 2000–2002 (average age 24 years, range 23–27 years). The response rate was 88% in the fourth survey (Kaprio 2006). Oral health questions were asked only of twins born in 1975–1978; twins born in 1979 were thus excluded from the analyses of this study. Questionnaires included multiple health-related questions on general, mental, and oral health, as well as questions on common lifestyle factors such as smoking. The oral health question covered fillings, gingival bleeding, bruxism, and wisdom teeth, as well as experienced oral health and self-rated need for dental care.

4.1.2. FINNISH TWIN COHORT

The *Finnish Twin Cohort* is a nationwide longitudinal Finnish twin study. It comprises health questionnaires sent on four occasions to adult Finnish twins born before 1958. Questions about bruxism were posed in the third questionnaire sent to the twins in 1990. Twins (n=12 502 twin individuals) responding to the third questionnaire were born between 1930 and 1957, and their mean age was 44 years (Hublin *et al.* 1994, Hublin *et al.* 1997). The response rate to the third questionnaire was 77%. The Ethics Committee of the Department of Public Health, University of Helsinki, Finland, approved the study protocol. Subjects were informed about the goals of the study and provided their informed consent.

The third questionnaire consisted of 103 multiple choice questions about general health and health habits, tobacco and alcohol use, and sleep and vigilance matters, including also perceived bruxism in childhood and adulthood (Hublin & Kaprio 2003). Consumption of coffee was not included in the third questionnaire, but was asked about in the first and second questionnaires in 1975 and 1981.

SUBSAMPLE OF NICOTINE ADDICTION GENETIC (NAG)

For the studies of nicotine addiction, ever-smoking twin pairs concordant for heavy smoking (twin pairs where both twins are heavy smokers) from the Finnish Twin Cohort study were recruited to join the Nicotine Addiction Genetics Finland Study (NAG Finland) (Broms *et al.* 2007, Loukola *et al.* 2008). The subsample included both same-sex and opposite-sex twin pairs, their siblings, and some other family members (Kaprio & Koskenvuo 2002). The data were collected via telephone interview in 2001–2005 (Broms *et al.* 2007, Loukola *et al.* 2008). The mean age of the twins was 53.7 years. Altogether 445 twin individuals had answered the bruxism question in the 1990 questionnaire. Although the subsample focused on nicotine dependence, there were also question about major depressive disorder, alcohol dependence, and nicotine use. The Ethics Committee of the Hospital District of Helsinki and Uusimaa, Finland, approved the study protocol in 2001, and all subjects gave their written informed consent,

4.2. STUDY VARIABLES

BRUXISM

In the *FinnTwin16* study (Studies I-II), bruxism was evaluated with the following question: Do you grind your teeth? The response options were 1) every night, 2) weekly, 3) once in a while, 4) never, and 5) I do not know. Twins (n=3126) were classified into three groups, where alternatives 1) and 2) were classified as 'weekly bruxism', alternative 3) as 'rare bruxism', and alternative 4) as 'never bruxism', which was also our reference category. Those who were unaware of their bruxism habit (n=648) were excluded from the analyses. For some analyses, those responding to the first three alternatives were defined as having 'any bruxism'.

In the *Finnish Twin Cohort* study (Studies III and IV), bruxism was evaluated with the following question: Do you grind your teeth? The response options were 1) weekly, 2) monthly, 3) occasionally, 4) never, and 5) I do not know. Twins (n=10 229) were classified into four groups, where alternative 1) was classified as 'weekly bruxism', alternative 2) as 'monthly bruxism', alternative 3) as 'occasional bruxism', and alternative 4) as 'never bruxism', which was also our reference category. Those who were unaware of their bruxism habit (n=1817) were excluded from the analyses.

USE OF TOBACCO PRODUCTS

In the *FinnTwin16* study (Study II), smoking status was assessed with the following question: "Of the following options, which best describes your present smoking?" The response options were 1) I smoke at least 20 cigarettes a day, 2) I smoke 10–19 cigarettes a day, 3) I smoke no more than 9 cigarettes a day, 4) I smoke weekly or often but not on daily basis, 5) I smoke less than once a week, 6) I do not smoke at the moment or I have quit smoking, and 7) I have never smoked. Daily smokers were classified into two groups: heavy smokers (at least 10 cigarettes daily) and light smokers (less than 10 cigarettes daily and including those not smoking daily). Those who answered alternative 6) were classified as former smokers and those who reported never smoking were classified as never-smokers, and they were also the reference category in analyses. Other smoking habits where evaluated with the question: "Do you smoke cigars, cigarillos, or the pipe?" Response options were 1) never, 2) once in a while, and 3) regularly. There were only a few individuals who reported smoking regularly so we dichotomized the use of these other tobacco forms as cigar users (alternatives 2 and 3) vs. never. The third question related to

tobacco products evaluated the use of smokeless tobacco: "Have you tried smokeless tobacco (placed in the sulcus of the upper lip)? How many times?" The response options were 1) I have never tried, 2) I have tried once, 3) I have used 2–50 times, 4) I have tried more than 50 times, and 5) I use smokeless tobacco regularly. We then classified the use of smokeless tobacco as follows: never, occasional lifetime users (1–50 times), and regular users (> 50 times or use regularly by self-report).

In the *Finnish Twin Cohort* study (Study III), the use of tobacco was assessed with multiple questions. Never-smoker status was determined by asking "Have you smoked more than 5–10 packs of cigarettes during your entire life?". Those who reported smoking less than 5–10 packs (i.e. 100–200 cigarettes) in their entire life were categorized as never-smokers. The next question separated current smokers from occasional smokers; subjects who had never smoked regularly, but could not be classified as never-smokers were categorized as occasional smokers. Those categorized as former smokers indicated that they had smoked regularly, i.e. daily or almost daily, but had quit smoking later. The rest were categorized as current smokers. They were also asked to report the number of cigarettes smoked per day. The response options were 1) none, 2) less than 5, 3) 5–9, 4) 10–14, 5) 15–19, 6) 20–24, 7) 25–39, and 8) more than 40. We classified current smokers as light smokers (less than 10), smokers of 10–19 cigarettes daily, smokers of 20–24 cigarettes daily, and heavy smokers (at least 25 cigarettes daily). We also enquired about the age of starting to smoke regularly. Lifetime pipe or cigar smoking was categorized dichotomously, with a user defined as someone reporting having ever smoked at least 50 cigars, 75 cigarillos, or more than 3–5 packages of pipe tobacco (Hukkinen *et al.* 2009).

NICOTINE DEPENDENCE

Nicotine dependence (Study III) was assessed using a substudy of the *Nicotine Addiction Genetics* Finland Study (NAG; an international consortium among Finland, Australia, and USA). The participants needed to be ever-smokers because nicotine dependence requires a nicotine habit to develop. We categorized nicotine dependence dichotomously as either nicotine-dependent or non-dependent. Nicotine dependence was assessed with the DMS-IV scale in which participants meeting at least 3 of the 7 criteria within the last year were defined as dependent (American Psychiatric Association 1994). The 7 criteria of nicotine dependence in the DMS-IV scale are the following:

1. Tolerance, as defined by either a need for increased amounts of the substance in order to achieve the desired effect or a markedly diminished effect with continued use of the same amount

2. Withdrawal, as manifested by either the characteristic withdrawal syndrome for the substance or the same (or closely related) substance taken to relieve or avoid withdrawal symptoms

3. Substance often taken in larger amounts or over a longer period than intended

4. Persistent desire or unsuccessful efforts to cut down or control use

5. A great deal of time spent in activities necessary to obtain the substance or to recover from its effects

6. Important social, occupational or recreational activities given up or reduced because of substance use

7. Continued substance use despite knowledge of having a persistent or recurrent physical, psychological, or social problem that is likely caused or exacerbated by the use of the substance

ALCOHOL USE

The use of alcohol (Study IV) was assessed in the *Finnish Twin Cohort* study with four multiple choice questions dealing with information about the amount of alcoholic beverages consumed, the frequency of alcohol use, the frequency of binge drinking monthly, and the number of times passing out due to alcohol during the last year. The amount of alcohol beverages consumed was evaluated with the following question: How much on average do you consume of beer weekly, wine weekly, and spirits monthly? The frequency of alcohol use was evaluated with the following question: How often do you consume alcohol? Please give separate estimates for beer, wine, and spirits. According to the amount of consumed alcohol and the frequency of alcohol use, the answers were computed to derive the weekly alcohol intakes (Kaprio *et al.* 1987). The subjects were then categorized into four groups: abstainers, light drinkers (≤3 drinks per week), moderate drinkers (>3 to ≤7 drinks per week for women and >3 to ≤14 for men), and heavy drinkers (>7 drinks per week for women and >14 for men), as described elsewhere (Järvenpää *et al.* 2005). Binge drinking was assessed dichotomously with the following question: Do you drink more than five bottles of beer at least once a month, one bottle of wine, or half

a bottle of spirits (or the equivalent amounts of other alcoholic beverages) on the same occasion? The fourth question dealt with passing out due to excessive alcohol intake within the last year. The outcomes were categorized into three groups: never, once, and two or more times (Virta *et al.* 2010).

COFFEE CONSUMPTION

Coffee consumption (Study IV) was not asked about in the questionnaire in 1990 in the *Finnish Twin Cohort*. Instead, it was enquired about in the 1975 and 1981 surveys, and for this study we used information gathered in 1981 because it was chronologically closer to the 1990 survey. Coffee consumption was evaluated with the following question: "How many cups of coffee do you drink daily?". Participants who did not drink coffee daily were asked to record the answer zero. According to the answers, coffee consumption was divided into three categories: 0–3 cups per day, 4–8 cups per day, and more than 8 cups per day.

SOCIAL CLASS

Information about social class (Study IV) was assessed in the *Finnish Twin Cohort* study with an open question 'What is your occupation, or if you are not working at the moment: what was your earlier occupation? Describe it as precisely as possible.' According to the classification of the Central Statistical Office of Finland's using occupational information (Kaprio & Koskenvuo 1988, Broms *et al.* 2004, Ropponen *et al.* 2011, Official Statistics of Finland 2012), social class was then categorized as white-collar, bluecollar, or others.

DETERMINATION OF ZYGOSITY

Twins' zygosity was determined using an accurate and validated questionnaire method that focuses on twins' similarity and genetically influenced characteristics (Sarna *et al.* 1978). The validity of the method was further studied in a subsample using 11 blood markers (Sarna *et al.* 1978). This determination method leaves about 7% of twin pairs unclassified, while the probability of misclassification is as low as 1.7%.

4.3. STATISTICAL METHODS

The statistical analysis used was appropriate to the study design and the purposes of each original study (Table 4). Cross-sectional and longitudinal analyses as well as genetic modelling were used as in the original studies as follows:

–   Studies I: Quantitative genetic modelling based on the genetic
    similarity of identical and non-identical twins was used to calculate
    the most probable genetic model for bruxism.

–   Studies II-IV: Multinomial logistic regression was used to explore the
    relationships of frequency of bruxism with the psychoactive substances
    of tobacco, alcohol, and coffee. Conditional logistic regression models
    were used to obtain odds ratios (ORs) for the risk of bruxism in relation
    to the use of psychoactive substances in twin pairs discordant for
    bruxism.

4.3.1. DESCRIPTIVE STATISTICS AND ANALYSES BETWEEN BRUXISM AND RISK FACTORS IN INDIVIDUALS

Descriptive statistics and polychoric correlations are calculated with the Stata program (StataCorp 2005). The associations of the use of psychoactive substances and bruxism are assessed using cross-tabulations, the Pearson chi-square test of independence, and multinomial logistic regression models (Hosmer & Lemeshow 2000) adjusted for covariates. Odds ratios (ORs) and their 95% confidence intervals (CIs) of all models are adjusted for correlated observations within twin pairs by means of Stata 9.0 (StataCorp 2005) using a robust estimator of variance (Williams 2000). Conditional logistic regression models are used to obtain ORs for bruxism in relation to psychoactive substances in twin pairs discordant for bruxism.

Table 4. Data and methods used in substudies

	Study I	Study II	Study III	Study IV
Focus of substudies	Genetic and environmental factors in sleep-related bruxism	Smoking as risk factor for sleep-related bruxism	Nicotine dependence as risk factor for sleep-related bruxism	Alcohol and coffee as risk factors for sleep-related bruxsim
Data	*FinnTwin16* Collected in 2000–2002 n=3,126	*FinnTwin16* Collected in 2000–2002 n=3,126	*Finnish Twin Cohort* Collected in 1990 n=10,229	*Finnish Twin Cohort* Collected in 1981, 1990 n=10,229
Age and sex of participants	Range 23–27 years, mean age 24 years, men 46.1%	Range 23–27 years, mean age 24 years, men 46.1%	Range 33–60 years, mean age 44 years, men 45.6 %	Range 33–60 years, mean age 44 years, men 45.6 %
Method	Genetic modelling	Multinomial logistic and conditional regression analyses	Multinomial logistic and conditional regression analyses	Multinomial logistic and conditional regression analyses

4.3.2. GENETIC MODELLING

The comparison of monozygotic (MZ) and dizygotic (DZ) twins, based on the fact that monozygotic twins share 100% of their genes and dizygotic twins on average share only 50% of their segregating genes, provides estimates about the heritability. Twins are classified into five different zygosity-sex groups: monozygotic males (MZM), monozygotic females (MZF), dizygotic males (DZM), dizygotic females (DZF), and opposite-sex dizygotic twins (DZ-OS). The correlation expected for both additive and non-additive effects is 1.0 in MZ pairs and in DZ pairs the correlation expected for additive genetic effects is 0.5 and for non-additive effects 0.25.

We used the quantitative genetic methods based on structural equation modelling (Neale & Cardon 1992) to analyse the data. Quantitative genetic modelling compares different models to permit estimation of variance components. First, we assessed some of the assumptions of the twin model by comparing the fully saturated model (i.e. one where all model parameters were free to vary) with more constrained models, providing statistical tests for the assumption that the given characteristics do not differentiate in the subgroups of the population and the twins are thus representative. This was done by requiring the distributions of the bruxism to be: a) the same among first- and second-born twins, b) the same in MZ and DZ twins, and c) the same in men and women.

Next, the formal estimation of variance components was divided into four possible phenotypic variance components: additive genetic effects (A), non-additive genetic effects (D), shared environmental effects (C), including all experiences affecting both twins similarly (such as childhood diet), and non-shared environmental effects (E), including all experiences affecting only one member of the twin pair. The baseline model was the ACE/ADE model. We tested more restrictive two-parameter models (AE, CE) and the pure E model, which specifies that no familial aggregation exists for the trait being examined against the baseline model.

In addition, we estimated the possible sex-specific genetic variation by comparing same-sex twin pairs to opposite-sex twin pairs. The sex-limitation model (Neale & Cardon 1992) utilizes the information from opposite-sex pairs and tests whether genes specific to one sex, sex-specific common environmental effects, or sex-specific additive genetic effects affect the variation in bruxism. The model tests whether the magnitudes of A, D, and E are affected equally in the sexes and whether a constraint to this weakens the fit of the model. Sex-specific effects for the given character are expected if the correlations within opposite-sex pairs are smaller than those for same-sex pairs.

The best-fitting model is found by using the χ^2 difference test and degrees of freedom (*df*) between the more complex model and the more constrained model (e.g. ACE vs. AE tests for the presence of significant C effects). We calculated genetic modelling with the Mx program (Neale *et al.* 2003) to estimate the CIs for the pairwise tables grouped by sex and zygosity of the trait in twin 1 versus the trait in twin 2 as input.

5. RESULTS

5.1. The related roles of genetic and environmental factors in self-reported bruxism (Study I)

The genetic architecture of self-reported bruxism (Study I) was investigated using the *FinnTwin16* cohort study. Basic genetic modelling was carried out for the self-reported bruxism among young adults. All monozygotic polychoric correlations were higher than the dizygotic ones (Table 5). According to fully saturated models, the prevalence for the variables did not differ by sex. The best-fitting model for bruxism was the AE model, and according to sex-limitation analyses, no sex differences or sex-specific genes were found. The relative proportions of variance components are shown in Figure 1.

Table 5. Pairwise similarity of bruxism in young adults (*FinnTwin 16*). Polychoric correlations by sex and zygosity.

	Bruxism	
	Correlation coefficient	95% confidence interval
All monozygotic pairs	**0.55**	0.44–0.67
Male monozygotic pairs	**0.43**	0.21–0.65
Female monozygotic pairs	**0.61**	0.48–0.74
All dizygotic pairs	**0.20**	0.09–0.30
Male dizygotic pairs	**0.26**	0.05–0.47
Female dizygotic pairs	**0.10**	-0.12–0.33
Opposite-sex dizygotic pairs	**0.22**	0.07–0.37
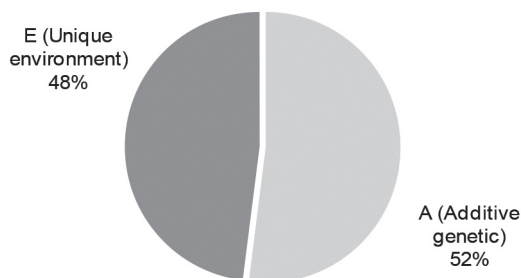
Figure 1. Relative proportions of variance components in bruxism (*FinnTwin16*).

5.2. Prevalence of bruxism (Studies I-IV)

Prevalence of bruxism was assessed in Studies I-IV using data from both the *FinnTwin16* study (adulthood bruxism) and the *Finnish Twin Cohort* study (childhood and adult bruxism). There were questions about both childhood and current bruxism in the *Finnish Twin Cohort* study and questions about current bruxism in the *FinnTwin16* study. Prevalence of childhood, adulthood, and adult bruxism is shown in Figures 2–4 separately for the sexes.

For the question on childhood bruxism, 11977 subjects responded and 27.3% of them did not know whether they had experienced bruxism in childhood. A significant gender difference was found in the prevalence of childhood bruxism ($p<0.001$) (Figure 2.). For the question on adulthood bruxism, by contrast, 3774 subjects responded and 17.2% of them were uncertain whether they experienced bruxism. No significant gender difference was seen in the prevalence of adulthood bruxism ($p=0.054$) (Figure 3.). Regarding bruxism in adults, 12 046 subjects answered the question and 15.1% of them could not tell whether they experienced bruxism or not. There was a significant gender difference in bruxism in adults ($p=0.003$) (Figure 4.). Again, prevalence of bruxism (childhood, adulthood, and adult) did not differ significantly between MZ and DZ twins ($p=0.1257$, $p=0.63$, and $p=0.64$, respectively).
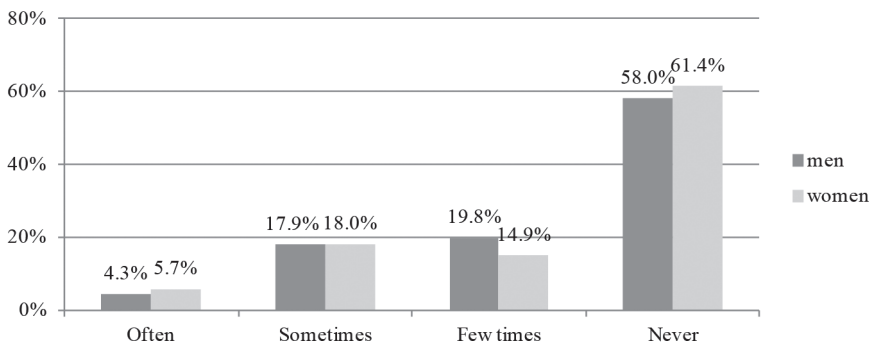
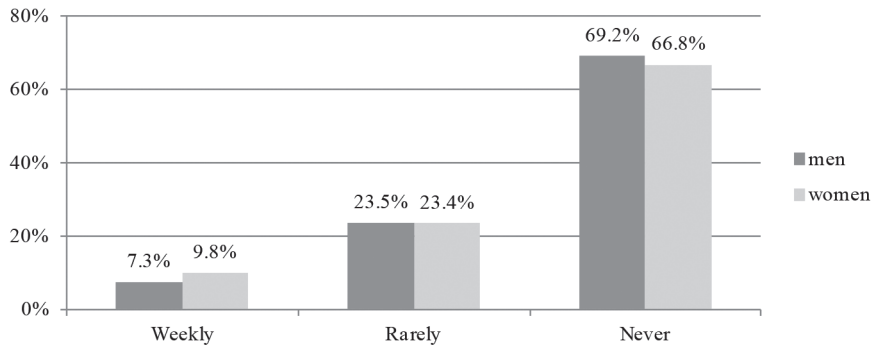**Figure 2.** Prevalence of childhood bruxism (*Finnish Twin Cohort*), n=8703.

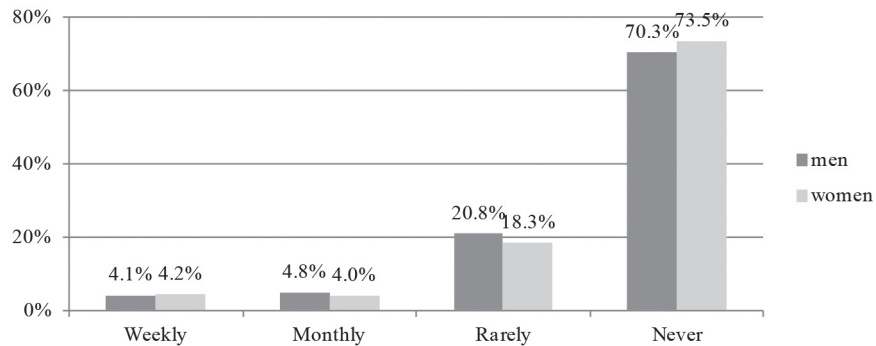**Figure 3.** Prevalence of adulthood bruxism (*FinnTwin16*), n=3126.

Figure 4. Prevalence of adult bruxism (*Finnish Twin Cohort*), n=10 229.

5.3. Prevalence of psychoactive substance use (Studies II-IV)

The prevalence of psychoactive substances (tobacco, alcohol, and coffee) was assessed in Studies II-IV using data from both the *FinnTwin16* study and the *Finnish Twin Cohort* study. In the *FinnTwin16* study, there were questions about smoking and the use of smokeless tobacco. In the *Finnish Twin Cohort* study, on the other hand, there were questions about smoking and nicotine dependence, alcohol use, and coffee consumption. The prevalence of psychoactive substances (smoking, alcohol use, and coffee consumption) is shown in Figure 5 and Table 6.
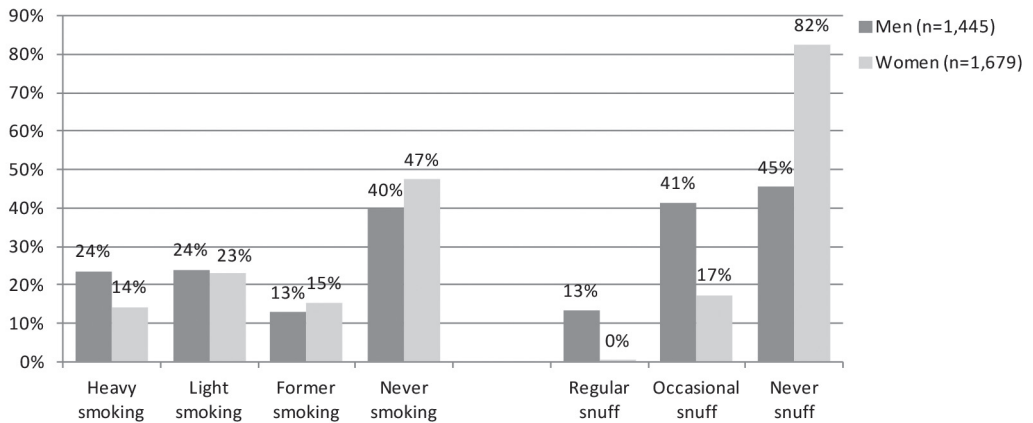
Figure 5. Prevalence of adulthood smoking and the use of smokeless tobacco (*FinnTwin16*), n=3124.

Table 6. Prevalence (%) of adult smoking and the amount smoked (cigarettes per day, CPD), alcohol use, and coffee consumption separately for men and women (*Finnish Twin Cohort*)

Psychoactive substance	Class of consumption/amount consumed			
Smoking	Current	Former	Occasional	Never
Men (n=5512)	31.4	29.4	4.0	35.1
Women (n=6601)	21.1	17.4	3.0	58.5
CPD	>24	20–24	10–19	<10
Men (n=2091)	14.9	24.7	30.7	29.8
Women (n=1619)	4.8	12.0	38.1	45.2
Alcohol consumption	Heavy	Moderate	Light	Abstainer
Men (n=5668)	19.8	48.2	23.3	8.8
Women (n=6748)	10.1	22.6	47.2	20.0
Binge drinking	Yes	No		
Men (n=5609)	44.9	55.1		
Women (n=6686)	12.2	87.8		
Passing out	2<	1	Never	
Men (n=5633)	12.5	8.91	78.6	
Women (n=6667)	2.85	4.14	93.0	

5.4. Association between bruxism and psychoactive substances (Studies II-IV)

5.4.1. SMOKING AND BRUXISM

In young adults (*FinnTwin16*), weekly bruxism was more common among heavy smokers and among those using snuff regularly (Figure 6). It was also significantly associated with smoking when age and gender were controlled. In addition, women reported more weekly bruxism when smoking was controlled (p<0.001). According to multinomial logistic regression, those with weekly bruxism were two times more likely to be heavy smokers than never-smokers (OR 2.5). Also, the use of smokeless tobacco raised the odds for bruxism. Detailed ORs and CIs of smoking and the use of smokeless tobacco in relation to weekly bruxism are shown in Figure 7. In young adults, the significant association of heavy smoking and smokeless tobacco with weekly bruxism held when the effects of other forms of tobacco use and psychoactive substance use (alcohol drinking to intoxication, drug use, and coffee consumption) were adjusted in the analyses. According to our analyses, both heavy smoking and smokeless tobacco raised the odds for weekly bruxism about twofold (heavy smoking OR 1.93 and smokeless tobacco OR 2.05). Conditional logistic regression analyses of young adults revealed that heavy smoking was strongly associated with any bruxism in opposite-sex dizygotic twin pairs (OR 2.4, 95% CI 1.2–4.8) (Table 7).
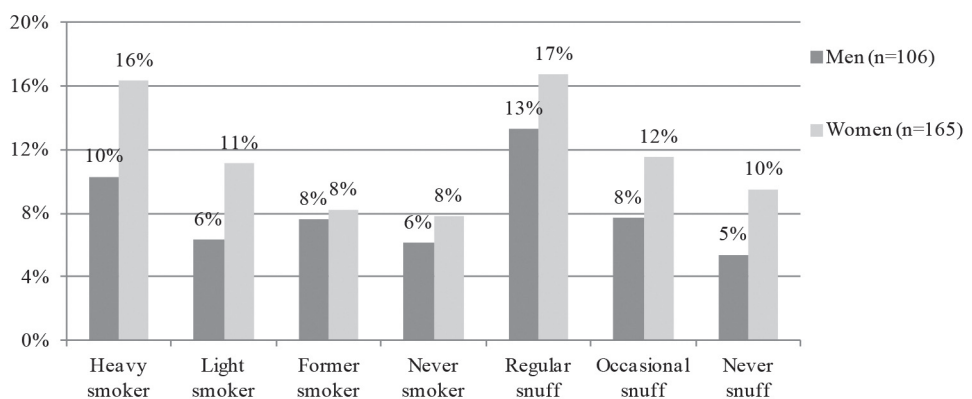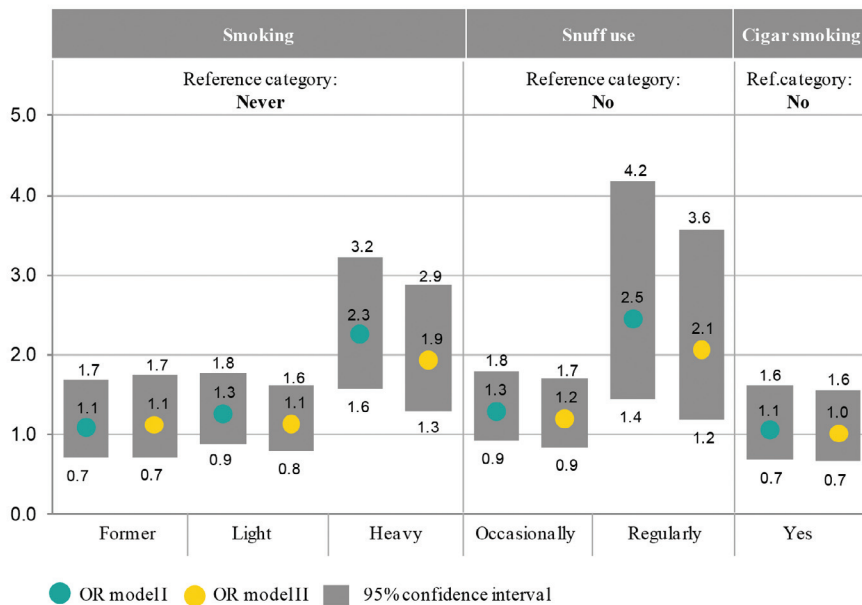

Figure 6. Proportion (%) of 'weekly' bruxism by smoking and snuff use status in young men and women (*FinnTwin16*).

In middle-aged adults, weekly bruxism was more common among both male and female smokers and also among current heavy smokers relative to current light smokers (Figure 8). According to multinomial logistic regression, weekly bruxism was associated with current smoking (OR 2.85). Of the current smokers, those smoking 20 or more cigarettes per day were more likely to report weekly bruxism than those with less cigarettes per day. Detailed ORs and CIs of smoking status and amount of current smoking in relation to weekly bruxism are shown in Figure 11. Also, current smoking with a nicotine dependence diagnosis raised the odds for weekly bruxism significantly (OR 2.50, 95% CI 1.06–5.87) compared with current smoking without such a diagnosis. Unlike in young adults, there was no significant effect of gender on bruxism. Contrary to weekly bruxism, both current smoking and former smoking were associated with monthly bruxism (OR 1.74, 95% CI 1.37–2.22 and OR 1.64, 95% CI 1.27–2.11, respectively).

Figure 7. Multinomial logistic regression: Detailed ORs and CIs of smoking, snuff use, and cigar smoking in relation to weekly bruxism (*FinnTwin16 Cohort*). Model I adjusted for age and sex, and model II adjusted for age, sex, and alcohol drinking to intoxication, RAPI score, illicit drug use, GHQ-21 and coffee use*.

Table 7. The odds ratios (OR) for the risk of bruxism in relation to cigarette smoking in young adult twin pairs (*FinnTwin16* study) discordant for 'weekly' and 'any' bruxism. Conditional logistic regression. (n= number of pairs).

	Twins, all pairs			Monozygotic			Dizygotic, same sex			Dizygotic, opposite sex		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Weekly	n=101			n=22			n=38			n=38		
Former	0.69	0.25–1.88	0.47	1.44	0.11–18.64	0.78	0.34	0.04–2.87	0.32	0.32	0.06–1.72	0.19
Light	0.53	0.22–1.29	0.16	0.32	0.02–5.81	0.44	0.24	0.04–1.39	0.11	0.85	0.25–2.92	0.8
Heavy	1.64	0.64–4.26	0.31	1.35	0.07–27.28	0.84	1.48	0.23–9.53	0.68	1.72	0.47–6.39	0.42
Any	n=414			n=96			n=148			n=153		
Former	0.95	0.60–1.50	0.84	1.67	0.54–5.10	0.37	0.58	0.26–1.30	0.19	0.88	0.43–1.79	0.72
Light	1.17	0.78–1.74	0.45	1.17	0.47–2.96	0.73	0.85	0.44–1.63	0.62	1.47	0.76–2.84	0.25
Heavy	1.53	0.98–2.38	0.06	1.59	0.47–5.36	0.45	0.86	0.41–1.78	0.68	2.4	1.20–4.77	0.01

*Weekly discordant pairs are such that one twin in a pair reports at least weekly bruxism, while the co-twin reports never-bruxism. Twins reporting less often than weekly are excluded, likewise are all concordant pairs. For any bruxism, discordant pairs have one twin with any frequency of symptoms and the co-twin has no symptoms.
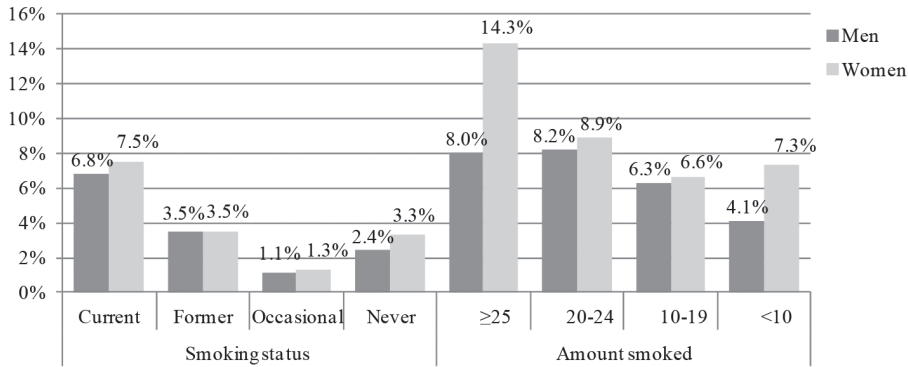
Figure 8. Proportions of 'weekly' bruxism in adults by smoking status (n=9955) and the amount smoked by current smokers (n=2604), with men and women shown separately (Finnish Twin Cohort).

The risk of bruxism was further analysed using twin pairs discordant for smoking status to test whether the association exists even when the unmeasured familial and genetic factors are adjusted. We used twin pairs in which either the twin with tobacco use reports also bruxism while the other twin reports neither tobacco use nor bruxism or the pairs in which the one with tobacco use reports no bruxism and the co-twin reports no tobacco use but does report bruxism. In middle-aged adults, there were 142 discordant twin pairs. Of the monozygotic twin pairs, there were 13 pairs where one twin reported weekly bruxism and the other reported never-bruxism and where one twin reported current smoking and the other was a non-smoker. In all of these pairs, the twin who reported weekly bruxism was also the one who reported current smoking (McNemar Chi-square test, p=0.0003).

5.4.2. ALCOHOL USE **AND BRUXISM**

Weekly bruxism was more common among heavy drinkers than among moderate drinkers or abstainers (7% vs. 4% vs. 3%). Proportions of weekly bruxism by alcohol use are shown in Figure 9. Also, the severity of bruxism increased with an increasing number of alcoholic drinks, and when alcohol consumption was calculated as grams of alcohol per day (log-transformed) it was also associated with weekly bruxism (p=0.017). This association with bruxism held even when smoking status was controlled. In age- and gender-adjusted multinomial logistic regressions, moderate and heavy drinking, binge drinking, and passing out were associated with weekly bruxism. Detailed ORs and CIs of alcohol use in relation to weekly bruxism are shown in Figure 11. When smoking status was adjusted in the model, heavy drinking, binge drinking, and passing out at least two times during the last year retained their statistical significance, although the ORs decreased (Figure 11). When social

class was added to the model, heavy drinking, passing out at least two times, or binge drinking did not lose their significance (OR 1.9, 95% CI 1.21–2.86; 1.5, 95% CI 1.09–2.19; 1.7,95% CI 1.28–2.15, respectively), although social class itself did not have a significant association with weekly bruxism. Binge drinking was strongly associated with weekly bruxism, and it retained its statistical significance even after alcohol consumption and passing out were added to the model. In this model, however, alcohol consumption and passing out lost their statistical significance when smoking status was accounted for, while binge drinking retained a significant association with bruxism (OR 1.5; 95% CI 1.17–2.01). In addition, when multinomial logistic regression analyses were performed separately for non-smokers and all current smokers, binge drinking remained significant in both groups (2.1 and 1.5, respectively), while other forms of alcohol use lost their statistical significance in all current smokers.
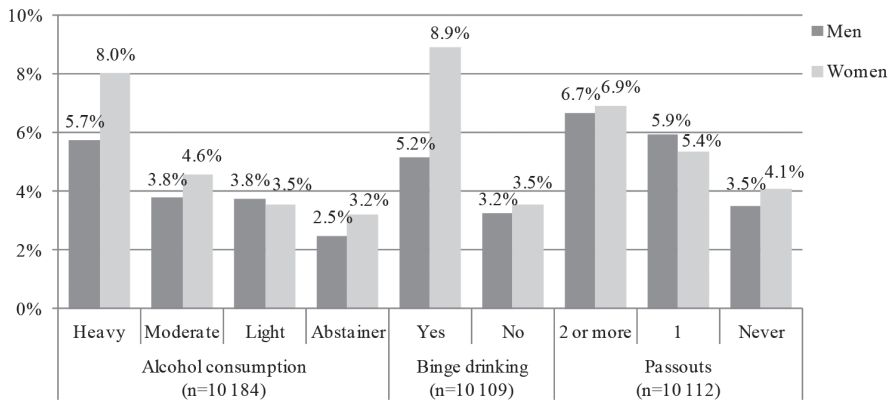

Figure 9. Proportions of weekly bruxism by alcohol use in men and women (*Finnish Twin Cohort*).

The risk of bruxism was further analysed using twin pairs discordant for alcohol use status to test whether the association exists even when the unmeasured familial and genetic factors are adjusted. Alcohol intake raised the odds for any bruxism within the twin pairs in pairwise analyses and conditional logistic regressions, and the ORs increased in all twin pairs in association with more risky health habits. There were altogether 77 discordant MZ twin pairs where one twin experienced bruxism while the other did not and one reported binge drinking while the other did not. Of these, 45 were pairs where the twin with bruxism was also the one with binge drinking and 32 were pairs where the twin with bruxism was not the one with binge drinking (McNemar Chi-square test, p=0.14).

5.4.3. COFFEE CONSUMPTION AND BRUXISM

Weekly bruxism was more common among those consuming more than 8 cups of coffee daily than in those consuming less coffee (Figure 10). Moreover, the odds for weekly bruxism were higher among those consuming more than 8 cups of coffee daily (OR 1.9). This association held when smoking status was controlled (OR 1.4). Detailed ORs and CIs of coffee consumption in relation to weekly bruxism are shown in Figure 11. Multinomial logistic regression performed separately for non-smokers and all current smokers revealed that coffee consumption of more that 8 cups per day lost statistical significance in non-smokers, while it remained significant in all current smokers (OR 2.0, 95% CI 1.25–3.22). Pairwise analyses and condition logistic regression indicated that coffee consumption raised the odds for any bruxism within twin pairs.
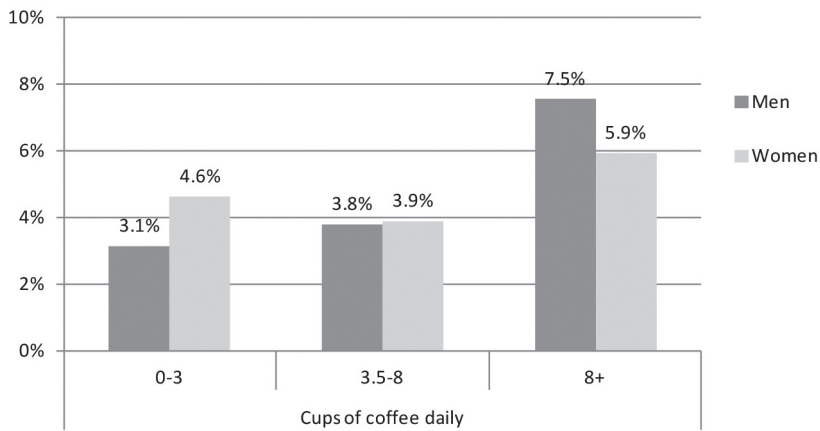

Figure 10. Proportions of weekly bruxism by coffee consumption in men and women (*Finnish Twin Cohort*).

Figure 11. Multinomial logistic regression: Detailed ORs and CIs of smoking, alcohol use, and coffee consumption in relation to weekly bruxism (*Finnish Twin Cohort*). Model I adjusted for age and sex, and model II adjusted for age, sex, and smoking status.

*Alcohol consumption: light drinker (>0-3), moderate drinker (>3-14 men, >3-7 women), heavy drinker (>14 men, >7 women).
**Binge drinking: i.e. drinking at least once a month more than 1 bottle of wine, half a bottle of spirits, or the equivalent amount of other alcoholic beverages on the same occasion.
***Passouts: passing out as a result of excessive alcohol intake.

6. DISCUSSION

This work rests on two large research projects based on population-wide Finnish twin cohorts. The first part of this work (Studies I-II) derives from the *FinnTwin16* study on young adult twins and the second part (Studies III and IV) from the *Finnish Twin Cohort* study on middle-aged twins, which also included a substudy, the *Nicotine Addiction Genetics* Finland Study. The general aim here was to investigate the genetic and environmental factors affecting bruxism and the risk factors for bruxism.

6.1. Main results and comparison with previous studies

The results indicated that both genetic and environmental factors affect bruxism and psychoactive factors seemed to play an important role as risk factors for bruxism.

6.1.1. ROLE OF GENETIC AND ENVIRONMENTAL FACTORS IN BRUXISM

The first aim of the study was to analyse the role of genetic and environmental factors in bruxism. The results indicate that genetic factors account for about half (52%) of the phenotypic variance in liability to bruxism, with no gender difference. This means that about half of the phenotypic difference is explained by genetic factors. A novel finding is that there was no gender difference in the liability to bruxism, meaning there is a common genetic background for bruxism in men and women, and no gender-specific genes or different proportions of genetic and environmental factors affect the liability. These findings are important in the rather unknown aetiology of bruxism, shedding new light on it.

The earlier questionnaire-based studies or large-scale twin studies have also reported some genetic background for BRUXISM (Hublin *et al.* 1998, Lavigne, Manzini & Kato 2005, Lavigne *et al.* 2008). However, the earliest reports of the hereditary component of bruxism are derived from the 1960s and 1970s, when bruxism was thought to be mainly peripherally regulated. These studies were largely based on attrition patterns in dentition (Horowitz 1963, Lindqvist 1974), although a few studies were also based on self-reports of sleep bruxism (Abe & Shimakawa 1966, Reding, Rubright & Zimmerman 1966). These earliest studies reported higher concordance rates for bruxism in monozygotic than dizygotic twins (Horowitz 1963, Lindqvist 1974), a significant association between current bruxism and reported

bruxism in blood relatives (Reding, Rubright & Zimmerman 1966), and children whose parents experience sleep bruxism being more likely to suffer from bruxism than children whose parents do not experience bruxism (Abe & Shimakawa 1966). Regardless of the different approaches to determination of bruxism, these early findings parallel the findings in this study.

The results of this study are in line with the earlier findings of Hublin *et al.* (1998), who reported a significant effect of genetic factors, but also reported a gender difference in the liability to bruxism in an adult population (genetic factors explaining 38.9% of the phenotypic variation in males and 53.2% in females). Although Hublin *et al.* (1998) also used data from Finnish twins, the twins in their study were older and were derived from a different cohort study (*Finnish Twin Cohort* study). But because they lack opposite-sex twin pairs, they could not perform a sex-limitation model, and thus, their results of a gender difference may differ from the results here. In any case, our results indicate that a common genetic background for bruxism exists in men and women. Interestingly, the best-fitting model in their study was also the AE-model, indicating that the same genetic and environmental factors may affect individuals' liability to bruxism throughout their life. The main conclusion based on our data together with the results from Hublin *et al.* (1998) is that the relative role of genetic factors in the liability to bruxism may be age-dependent. While there is no gender difference in young adults, there is likely to be a gender-dependent genetic influence or a different relative magnitude of genetic effects by gender in middle-aged adults.

6.1.2. ROLE OF LEGAL PSYCHOACTIVE SUBSTANCES IN THE RISK OF BRUXISM

The general aim of the study was to examine the role of three legal psychoactive substances (tobacco, alcohol, and coffee) in the risk of bruxism. The results indicate that the legal psychoactive substances of tobacco, alcohol, and coffee seem to have independent effects on bruxism. Although the basic analyses were performed using twins as individuals, the twin approach strengthened the evidence of psychoactive substances as risk factors for bruxism. At the moment, no other studies using a twin approach to evaluate the association between psychoactive substances and bruxism exist. The use of twins enables the exclusion of the disturbing effect of shared genes between siblings (Boomsma, Busjahn & Peltonen 2002) because twin analyses adjust for familial factors shared by both co-twins. Thus, this twin approach provides additional adjustment even for unmeasured confounding factors. Therefore, regardless of the cross-sectional nature of this study, the results for discordant pairs suggest a causal association and analyses with genetically identical twin pairs provide further evidence that this association is independent of genetic background.

The present study focused on psychoactive substances while the effect of psychosocial factors was left out of the study. However, it is known that psychosocial factors, like stress or anxiety, and psychoactive substance use are often related (Koob 2003, World Health Organization 2004, Patton *et al.* 1998, Sonntag *et al.* 2000). It is also unclear whether these factors have interactions with each other that affect their independent effects on bruxism. Previously, Ohayon *et al.* (2001) explored the association of bruxism with both psychosocial factors and the use of psychoactive substances in the same model. Further, in their adjusted model the use of psychoactive substances (tobacco, alcohol and coffee) and both high life stress and DSM-IV anxiety disorder diagnoses were all associated with bruxism although the odds decreased slightly. At the present study, social class was added into some analyses dealing with alcohol use. Other psychosocial factors, instead, were not investigated. According to the analyses, the adjustment of the model with social class did not affect the statistically significance of the alcohol variables indicating that alcohol use affect bruxism regardless of social class status. In addition, social class itself did not associate with bruxism. Nevertheless, there is a lack of studies dealing with both psychosocial factors and psychoactive substances and their possible interactions and therefore there is a great need for further studies exploring the possible link between psychosocial factors and psychoactive substances in the etiology of bruxism.

The mechanism underlying the relationship between psychoactive substances and bruxism is still unknown. The dopaminergic system (both hyper- and hypo-dopaminergic states) has been linked to bruxism, but the evidence is weak (Lobbezoo *et al.* 1997, Lavigne *et al.* 2001, Lobbezoo, Van Der Zaag & Naeije 2006). In addition, some neurochemicals and their interactions with the dopaminergic system have been proposed to affect bruxism, but this evidence is also weak (Lobbezoo & Naeije 2001, Chen *et al.* 2005, Lobbezoo, Van Der Zaag & Naeije 2006). Because psychoactive substances affect the central nervous system and many of them also affect the dopaminergic system, their mechanism of action may arise from this link. However, the mechanism of action varies depending on the psychoactive substance, warranting more detailed neurological studies of the association between psychoactive substances and bruxism. Despite the fact that the detailed mechanism of the pathogenesis of bruxism is unknown and the specific mechanism of the actions of psychoactive substances in relation to bruxism remains unsolved, the present study indicates that bruxismis centrally regulated and may be linked to specific neurochemicals and systems of the brain.

6.1.2.1. Role of cumulative smoking and use of smokeless tobacco in the risk for bruxism and the association between nicotine dependence in ever-smokers and bruxism

The second aim of the study was to examine the role of tobacco in the risk of bruxism. One of the main findings was that both cumulative smoking and use of smokeless tobacco are important risk factors for bruxismin adults. They increased the odds strongly even when the other study variables and possible interactions were taken into account in both young adults and middle-aged adults using large-scale epidemiological data sets. Also nicotine dependence seemed to be associated with increased odds for bruxismin middle-aged ever-smokers.

Previously, only eight studies have investigated the role of smoking in bruxism and most of them have reported some degree of association between these (Lavigne *et al.* 1997, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Johansson *et al.* 2004, Ahlberg *et al.* 2004, Ahlberg *et al.* 2005, Kato *et al.* 2012, Abe *et al.* 2012). Although smoking has been shown to be a risk factor for bruxism in these studies, the study approach has mainly been dichotomous, and study design, sample size, definition of smoking, assessment of bruxism, and control for covariates have varied greatly. However, most of these studies have concluded that smoking increases the odds for bruxism significantly, with odds ratios varying from 1.35 to 2.4 (Lavigne *et al.* 1997, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Johansson *et al.* 2004, Ahlberg J. *et al.* 2004, Kato *et al.* 2012). Ahlberg *et al.* (2005) and Abe *et al.* (2012), by contrast, failed to find a significant association. In any case, our findings related to smoking and nicotine intake and dependence are in line with most of the previous studies, and thus, improve the evidence that nicotine and smoking are important risk factors for bruxism. The approach of the present study also supports the significance of nicotine itself, rather than other chemicals (such as carbon monoxide), as an instigator of the association because a significant association was found with both forms of tobacco (smoked and smokeless), a clear dose-response relationship was shown, and nicotine dependence itself was associated with bruxism.

6.1.2.2. Role of alcohol use and effects of different forms of alcohol use in the risk of bruxism

The third aim of the study was to examine the role of alcohol in the risk of bruxism. The results indicated that alcohol is an important risk factor for bruxism. Also, according to the present findings, the role of alcohol use is significant even when smoking is taken into account. Multiple alcohol use patterns, especially heavy drinking, binge drinking, and frequently passing out due to excessive alcohol intake, seem to increase the odds for bruxism. Previous studies have shown varying

outcomes, with only some finding a significant association between alcohol use and bruxism. Alcohol consumption has been estimated to raise the odds for bruxism from 1.5 to 1.8 (Ohayon, Li & Guilleminault 2001), depending on the dose. Overall, alcohol consumption seems to be more common among individuals with bruxism (Bellini *et al.* 2011). However, most studies have focused on alcohol quantities as the main measure of alcohol use and none of the previous studies have examined specific alcohol use patterns, and thus, our results provide new information about the nature of the relationship.

This study had a broad approach to alcohol use, which allowed detailed evaluation of the impact of alcohol on bruxism. The results indicated that there is a dose-response relationship between alcohol consumption and bruxism, and also binge drinking has specific effects on bruxism. The effect of binge drinking on bruxism may derive from the toxic effects of ethanol on the brain. Binge drinking and passing out due to excessive alcohol intake are common signs of alcohol dependence. Although we did not investigate alcohol dependence in this study, the results together with the results of nicotine dependence emphasize the need for further studies of the role of common psychoactive substance dependence in the genesis of bruxism. In addition, alcohol consumption is known to be strongly associated with smoking (Li *et al.* 2007), but none of the previous studies have examined the possible confounding effect of smoking on the association between alcohol use and bruxism in detail. We analysed the effect of an interaction variable smoking-alcohol and found that the effects of alcohol use are independent of smoking status, which further strengthens our results that alcohol is an important independent risk factor for bruxism.

6.1.2.3. Role of coffee consumption in the risk for bruxism

The fourth aim of the study was to examine the role of coffee in the risk of bruxism. According to our results, coffee consumption of more than 8 cups per day increases the odds for bruxism almost two-fold. This, however, decreases to 1.4 when smoking status is taken into account. The results indicate that coffee as a psychoactive substance affects bruxism, probably in a dose-dependent manner.

Although previous studies (Hartmann 1979, Hartmann *et al.* 1987, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Bellini *et al.* 2011, Kato *et al.* 2012, Abe *et al.* 2012) have yielded varying results, the findings here combined with those of Molina *et al.* (2001) and Ohayon *et al.* (2001) provide new information about the role of psychoactive substances in the risk for bruxism. Similar to alcohol use, coffee consumption is often related to smoking, which may affect the relationship between coffee and bruxism. We therefore added interaction variables to the analyses and found no interaction between coffee consumption and smoking. This

further indicates that substantial coffee consumption is an independent risk factor for bruxism.

6.2. Methodological considerations

6.2.1. DATA AND DESIGN

The data used in the present studies derive from unique large-scale twin cohort studies of Finnish adolescents and adults, namely the *FinnTwin16* study and the *Finnish Twin Cohort* study, which have several strengths because of their twin design. The data are representative of the general Finnish population because all twin pairs of a given birth cohort around Finland were invited to participate. The data are also optimal for quantitative genetic modelling because of the twin design. In addition, the older cohort (*Finnish Twin Cohort*) does not differ in mortality risk from the general population, supporting the representativeness of the data (Kaprio 2013). The comprehensiveness of the questionnaire enabled the use of many variables as confounders. The fact that participants were also twins created the unique opportunity to analyze the role of genetic and environmental factors and further clarify the independent role of, for example, psychoactive substances in bruxism. The study was cross-sectional, although the large number of participants strengthens the value of our results remarkably. In addition, usually the causal nature of the association between an exposure (like the use of a given psychoactive substance) and a supposed outcome (like bruxism) is analysed in most epidemiological studies by examining potential confounding variables that may eliminate the observed association. If a multivariate model reveals no significant confounders affecting the association being investigated, it supports the evidence of causality regardless of the cross-sectional nature of the data. Further, an alternative way to test possible causality is the use of discordant twin pairs, which tests whether the association exists even after adjustment for unmeasured familial and genetic factors. Therefore, the present twin study provides novel evidence for a possible causal link between psychoactive substance use and bruxism, and quantitative genetic modelling revealed important knowledge about the hereditability of oral health parameters and bruxism. Certainly, longitudinal analyses would add more specific information, and replication of the study in other twin data sets would be valuable. Prospective studies about the incidence of new cases of bruxism among users of psychoactive substances compared with non-users are also needed to strengthen knowledge about causality.

The measurement and categorization of study variables were performed in line with commonly used measures. In addition, in the genetic modelling the possible underestimation of the genetic component caused by a measurement error is incorporated into the environmental component as factors uncorrelating between twins. For example, the data of smoking is similar to the smoking behaviour of the Finnish population in other studies (Verkasalo *et al.* 1999, Suomen virallinen tilasto 2005, Helakorpi *et al.* 2008, Jääskeläinen 2011). This was previously studied by Verkasalo *et al.* (1999), who found that lung cancer incidence was an excellent indirect measure of smoking behaviour. Using the Finnish Twin Cohort linked to the Finnish Cancer Registry and the Central Population Register, the authors revealed that lung cancer incidence did not differ from that in the general population, indicating that the data used in part of our study as well are representative of the Finnish smoking population. However, according to the study of Broms *et al.* (2007), the heaviest smokers were somewhat underrepresented in the NAG study, likely indicating some underreporting. The situation is probably similar with alcohol intake. Especially heavy drinking and regular binge drinking are socially not acceptable in adults and may thus be underreported. Binge drinking is more common among students and young adults, whose reports may be therefore more reliable, if not indicating actual misuse of alcohol or alcohol dependency. Coffee consumption, by contrast, is not as likely to yield underreporting because it is a commonly accepted habit in Finland and a rather common practice in the adult population. The measurement and categorization of bruxism are somewhat problematic based on questionnaires alone; optimally, they would be based on sleep laboratory analyses. Nevertheless, this study yielded a similar prevalence to those previously found in Finland and elsewhere (Lavigne & Montplaisir 1994, Partinen & Hublin 2000, Lavigne, Manzini & Kato 2005). Because of the large number of participants, the high response rate, and the good representativeness of the general population, the use of a questionnaire here was justified. Furthermore, the general finding of the overall prevalence of weekly bruxism has been that the occurrence is higher among young adults, and it gradually decreases in the elderly (Lavigne & Montplaisir 1994, Ohayon, Li & Guilleminault 2001). Because the prevalence in our data with both young adults and middle-aged adults was similar, it supports the use of the self-reporting methodological approach and ensures the overall representativeness of the data with respect to the general population.

6.2.2. GENERALIZABILITY OF RESULTS

The results of both the quantitative genetic modelling and the risk factor analyses can be generalized to the Finnish population of young and middle-aged adults because

the study samples were derived from the Finnish Twin Register with complete birth cohorts of twins born in Finland in the given years. The response rates were also high, improving the representativeness of the sample. Previous studies have found similar prevalence rates for the same variables in the Finnish population and in other countries, also supporting generalization of the results (Reding, Rubright & Zimmerman 1966, Glaros 1981, Lavigne & Montplaisir 1994, Hublin *et al.* 1998, Ohayon, Li & Guilleminault 2001, Lavigne, Manzini & Kato 2005, Suomen virallinen tilasto 2005, Jääskeläinen 2011, Jääskeläinen & Virtanen 2011). Generalization is further assisted by the variables being categorized in commonly used ways, thus allowing results to be compared and the study protocol to be repeated easily to obtain findings for other populations.

6.2.3. STRENGTHS AND LIMITATIONS

The study was based on self-reports gathered by questionnaires in large cohorts of twins with high response rates. This supports the reliability and generalizability of the results, even though the information was gained from self-reports. The FinnTwin16 study collected data from almost 3000 twin individuals and Finnish Twin Cohort study from about 12 500 twin individuals; these are both very large samples compared with previous dental surveys on the subject matter. Although self-report is known to yield some biases (Stone *et al.* 2000) because the information is subjective not objective, it is widely used and accepted as an efficient method in large population-based epidemiological surveys, where the gathering of information with exact laboratory or clinical methods from a vast number of participants would not otherwise be possible. Specific limitations with studying bruxism in conjunction with ICSD criteria-based diagnoses and standardized sleep laboratory settings are the high costs and logistic challenges (Lavigne, Rompre & Montplaisir 1996, Manfredini & Lobbezoo 2010), especially when the study population arrives from all over the country to broadly represent the general population. Generally, the major limitation with self-reports and questionnaires is, however, that some participants may answer in socially accepted ways, e.g. underreporting when asked about undesirable behaviours such as smoking and alcohol consumption. Participants may also give incorrect answers under distress (Turner *et al.* 2001) or if they are unsure of the situation, e.g. awareness of bruxism behaviour may arise only from a story told by a bed partner or by information given by the dentist based on clinical signs in the oral cavity and not an accurate clinical diagnosis. However, although the information on smoking behaviour is based on self-reports and no biochemical verification was available for subjects, earlier population-based study in Finland from 1992 have indicated that current smokers do report their smoking status

very accurately (Vartiainen *et al.* 2002). Also, because of the large sample size, the prevalence of items studied correlated well with prevalence in earlier studies. The accuracy of answers is somewhat improved by the use of a categorized scale to facilitate estimation of dental variables, bruxism, and use of psychoactive substances.

The major strength of the study was the twin design. Basically, in the analysis performed using twin data the method allows possible confounding effects of genes to be observed. Familial aggregation of a given trait may be due to genes or the environment shared by family members. For example, previous findings together with our results illustrate that genetic components affect both smoking (Rose *et al.* 2009) and bruxism (Hublin *et al.* 1998). Earlier studies have also shown a clear association between smoking and bruxism (Lavigne *et al.* 1997, Molina *et al.* 2001, Ohayon, Li & Guilleminault 2001, Johansson *et al.* 2004, Ahlberg *et al.* 2004). This, however, may be due to the independent effect of smoking on bruxism or to underlying genetic effects common to both, i.e. two different phenotypes resulting from pleiotropic effects of genes. Notwithstanding many similarities to our results, Hublin *et al.* (1998) in their twin study on bruxism failed to find any shared familial effect, which suggests that the association between smoking and bruxism cannot be explained by shared family effects common to these two phenotypes. Further, the analysis on discordant pairs taking the family background into account showed that an association between smoking and bruxism exists. However, to elucidate the exact contribution of genes and the environment, multivariate quantitative genetic modelling is required.

7. CONCLUSIONS

7.1. Scientific conclusions

The results of this questionnaire-based study using genetic modelling confirm that genetic factors play an important role in the phenotypic variation of bruxism. However, the exact mechanism underlying these genetic factors remains unknown, and there is a need for further research to reveal whether a specific gene, a mechanism coded by a group of genes, or some indirect genetic effect underlies the development of bruxism.

This study, in addition, confirms that legal psychoactive substances, mainly tobacco, alcohol, and coffee, are strongly associated with self-reported bruxism. It also gives evidence that the relationship is cumulative and dose-dependent in nature and that the psychoactive substances have independent roles as risk factors, independent also of shared genes. Nevertheless, further research is required to establish causality and also to examine whether there is a common genetic background for psychoactive substance use and bruxism; the latter can be ascertained with bivariate quantitative genetic modelling of twin data. The strong relationship between psychoactive substances and bruxism may give clues for future research into the exact mechanism underlying the genesis of bruxism and differing individual liability to bruxism.

7.2. Practical implications

These results have significant clinical relevance in light of better understanding the risk factors affecting bruxism. Because curing bruxism is not possible based on current knowledge and the treatment of bruxism mostly consists of providing symptomatic relief and preventing complications, the practical implications of this study are mainly improving the clinical guidance and understanding of patients suffering from problems caused by bruxism. A clinically important finding is that psychoactive substance use may worsen bruxism. This creates a window of opportunity to offer general health advice and tobacco and alcohol interventions, possibly helping to reveal heavy substance use problems. Further, when there is suspicion about heavy psychoactive substance use, clinicians themselves can provide information and support, e.g. for the treatment of tobacco or alcohol dependence,

and help in the cessation process or refer the patient to an addiction specialist if needed. This may not only relieve the symptoms of bruxism, but most importantly, improve the patient's general health.

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