

Public Health Genomics : translation of genomic research on smoking behaviour into evidence synthesis and guidelines for public health

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PUBLIC HEALTH GENOMICS:
TRANSLATION OF GENOMIC RESEARCH ON SMOK-
ING BEHAVIOUR INTO EVIDENCE SYNTHESIS AND
GUIDELINES FOR PUBLIC HEALTH

SYLVIANE DE VIRON

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PUBLIC HEALTH GENOMICS:
TRANSLATION OF GENOMIC RESEARCH ON
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HEALTH

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*If you understand what you are doing,
you are not learning anything*
– Unknown

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MAJOR ABBREVIATIONS

ADHD	Attention Deficit Disorder with Hyperactivity
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic Acid
GABA	Gamma Aminobutyric Acid
GWAS	Genome Wide Association study
HWE	Hardy Weinberg Equilibrium
mRNA	Messenger Ribonucleic Acid
nAChRs	Nicotinic Acetylcholine Receptors
NAcc	Nucleus Accumbens
NRT	Nicotine Replacement Therapy
PHG	Public Health Genomics
PHGEN	Public Health Genomics European Network
RDS	Reward Deficiency Syndrome
SES	Socioeconomic Status
SNP	Single Nucleotide Polymorphism
TUD	Tobacco Use Disorder
VTA	Ventral Tegmental Area

INTRODUCTION

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Introduction

Smoking and Public Health Genomics

Translation of genomic research on smoking

Communication of genome-based information about smoking

Aims and outline of the thesis

Genomic research and knowledge rapidly grew since the completion of the Human Genome Project in 2003. Different areas of genomic research have been developed from bench to bedside and beyond from bench to healthcare including, for example, fundamental research in systems biology, the Personal Genome Project, molecular epidemiology and new challenges for Public Health Genomics (PHG), personalised, and individualised healthcare.

In 1997 the institutionalisation of PHG started with the establishment of the Office of Public Health Genomics within the Centre for Disease Control and Prevention (CDC) in the USA and with the foundation of the Unit of Public Health Genomics within Cambridge University in the UK. At the same time, PHG was established as a new field in Germany as well. However, it was not institutionalised. In 2003, the first international cooperation group followed by the first international meeting on PHG took place in Bielefeld, Germany and was coordinated by Prof. Dr. Angela Brand.

PHG, as defined during the Bellagio workshop in 2005, in which all of the above mentioned groups participated, is *'the responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health'* [1, 2]. According to that definition, the major aim of PHG is to translate research from basic sciences into health policies and healthcare to improve population health. To date, the most important problem is the lack of translation from basic research to the healthcare system, as only around 2% of research is effectively translated based on the amount of funding and activities [3]. In Europe, the Public Health Genomics European Network (PHGEN), funded by the General Directorate for Health and Consumer Protection (DG SANCO), from the very beginning specifically worked on the translating knowledge 'from cell to society'. The second phase of the PHGEN project ended with the first edition of 'European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies' [4]. These guidelines have been endorsed in 2012 by key European institutions and organisations like the European Medicines Agency (EMA) and the European Science Foundation (ESF) as well as by the European Member States. They will guide the Member States within the next few years in the field of PHG and personalised healthcare.

This thesis uses smoking as a case study to apply PHG. Smoking is still a major public health problem worldwide despite the widespread knowledge of the risks of morbidity and mortality. Both, preventing smoking initiation and enhancing smoking cessation are the best way to reduce risks of smoking related disorders. In a public health point of view, different approaches are used to prevent smoking initiation and enhance smoking cessation such as taxation, bans and media campaigns [5]. However, these interventions have shown some limitations in reducing smoking prevalence. Therefore, genomics may be an innovative and useful way to promote public health. Although no applications are currently ready for practice, potential applications of genomics are investigated in the prevention, the control and the cessation of smoking. It is why including genomic knowledge is a more holistic and

useful approach leading to personalised interventions taking the advantage of the supportive environment [5]. Interventions may include (1) genomic risk notification of smoking initiation, nicotine addiction, smoking cessation or smoking related disorders or (2) genomically adapted treatments in drugs, dose and duration, which may enhance both personalised and individualised treatments [6].

The aim of the present thesis is to apply PHG on smoking. To achieve this objective, two main goals were developed: firstly, to improve healthcare for smokers, and secondly to propose new approaches to enhance the communication of genomic risks about smoking in the general population.

The general introduction of this thesis starts with theories on PHG. After that, the application of PHG concepts on smoking is developed.

PUBLIC HEALTH GENOMICS

Public Health Genomics mission

The initial idea of PHG is to devise effective preventive interventions targeted at individuals with specific genotypes [7]. Its main attempt would, therefore, not primarily concern the new technological advances like gene therapy [8] but subcategorise populations compatible to the effectiveness of preventive environmental interventions stratified according to their genetic risk. The motivation behind this strategy is that the molecular and cellular processes, which are encoded in the gene sequence, are susceptible to influence from the external environment.

Causation of complex diseases — Role of epidemiology

At this moment, however, clear applications of PHG in the prevention of disorders remain distant. We still do not understand the complexity of diseases in the causation of a certain common disorder. Very few common genetic variants are known to increase the risk of complex disorders substantially [9]. Even when a genetic risk is substantial, knowledge of the risk contributes to improved health outcomes only if effective measures are available for preventive or early treatment [2]. Similarly, genetic testing is of uncertain value when the available interventions are not genotype-specific. Furthermore, for a genetic test to be useful in the management of a common disorder, it must have predictive powers over and above accepted risk factors, which can easily be measured [9]. Genetic testing will have its greatest public health value when it identifies individuals who would benefit from specific interventions based on their risk [2, 7]. However, the major limitation is that genetic tests mostly do not take the environment into account.

To better understand the cause of complex disorders by taking notice of the genetic contribution is one of the main thrusts of genetic epidemiology [10]. To date, most proposed advances resulted from genetic epidemiological research using methods like the investigation of familial clustering, twin, adoption, and migration studies. The specific genetic determinants have been identified through linkage

analysis and, more recently, through pathway analyses and genome-wide association studies (GWAS). A GWAS is defined as a study of common genetic variation across the entire human genome designed to identify genetic associations with observable traits [11]. These studies use high-throughput genotyping technologies to assay hundreds of thousands of single nucleotide polymorphisms (SNPs) and relate these genetic variants to disorders or health-related traits [11]. However, a GWAS is prone to false-positive and false-negative associations, which demands for the replication of the study results in an independent population sample [11].

Although the GWAS often offer robust associations between certain SNPs and complex disorders, the population implications of those findings are mostly unclear because the basic population-based genetic prevalence data are mostly unevaluated [12]. Population-based research is essential to quantify the population prevalence of genetic variants, the magnitude of disorder risk associated with these variants (in relative and absolute terms), the contribution of these variants to the occurrence of disorder in different populations (attributable risk), the existence of gene-environment and gene-gene interactions and the validity of genetic tests based on such variants in predicting disorder risks [13, 14]. The Human Genome Epidemiology Network (HuGENet) is a global collaboration of individuals and organisations to assess population health impact of human genomic variation and how it can be used to improve health and prevent disorders in populations. Their main aim is to conduct rigorous systematic, peer-reviewed reviews and meta-analyses of genetic associations and of the epidemiological aspects of variation in particular genetic variants, the HuGE reviews [15].

The necessity of translation

Obviously, the relation between genes and a phenotype is far from simple. Thus, there is a need to translate the information about genes into information about genomic susceptibility for disorders, the interaction between these susceptibilities and the impact of this knowledge on population health. Khoury *et al.* presented a framework for the continuum of multidisciplinary translation research in genomic medicine [3]. The purpose is to move promising genomic applications to clinical and public health practice for population health benefit. The framework consists of four phases from T1 to T4. T1: gene discovery to candidate health application; T2: health application to evidence-based practice guidelines; T3: practice guidelines to health practice and T4: practice to population health impact [3]. It is based on genomic epidemiology findings.

Lal *et al.* also proposed a new model (Learning Adapting Leveling, LAL model) aiming to enhance the translation and mostly focusing on the translation of genome-based technologies. This model includes both the technology transfer activity and public health assessment technologies in relationship to public-private partnerships to promote relevant technologies. Currently, the LAL model is the most holistic approach, since it covers the whole pipeline 'from cell to society', i.e. from basic sciences into implementation in healthcare systems [16].

Although moving scientific discoveries into practice and the delivery of population-level health benefit has always been slow and difficult at best, many believe that this is a doable project when all relevant stakeholders on all levels are involved [9].

The broader scope of Public Health Genomics

PHG is a task and has a broader scope than only biomedical sciences like the molecular research, pharmacogenomics or genomic epidemiology. It aims to achieve the understanding of systems medicine, which incorporates both environmental and genomic factors, to promote truly personalised healthcare based on the individual rather than populations of patients. This also implies future modifications in disease classifications based on diseasesomes [17]. One of the challenges in the evaluation of genomic applications to healthcare is the integration of studies of the ethical, legal, and social implications (ELSI). A 2003 report by the Institute of Medicine in the US identified genomics as a priority for the training of all public health professionals in the 21st century [18]. Therefore, the public health community has a major role to play in raising the level of general genomic literacy, developing targeted messages about the uses of genome-based information in disorder prevention and coordinating communication strategies with stakeholder groups [10].

Two working concepts for Public Health Genomics

All these concepts are grouped together in two concepts where the PHG research can be fit in: the PHG enterprise and the wheel of the ten essential PHG functions.

The Public Health Genomics enterprise

This enterprise was developed on consensus by the international key experts of the Bellagio meeting to demonstrate how to translate genome-based science and technology, together with the human sciences, into improvements in population health [1, 2]. Figure 1.1 shows the PHG enterprise. It represents a way of working or approaching problems, rather than a discrete subject that includes certain topics and excluded others. This means that any new development in modern genomics or in molecular and cell biology fits within the scope of the enterprise. Figure 1.1 shows the fundamental role of genome-based science and technology and the achievement of improvement in population health as an ultimate goal [1, 2]. Besides the genome-based science and technology, the enterprise acknowledges the need to incorporate research and knowledge from the population sciences and from the humanities and social sciences as important inputs. Knowledge integration plays a central role, not only within but also across disciplines and is therefore the driving force of the PHG enterprise. It is defined as the process of selecting, storing, collecting, analysing, integrating, and disseminating information both within and across disciplines for the

benefit of population health. It further includes the methodological developments too, and is the means by which information is transformed into useful knowledge.

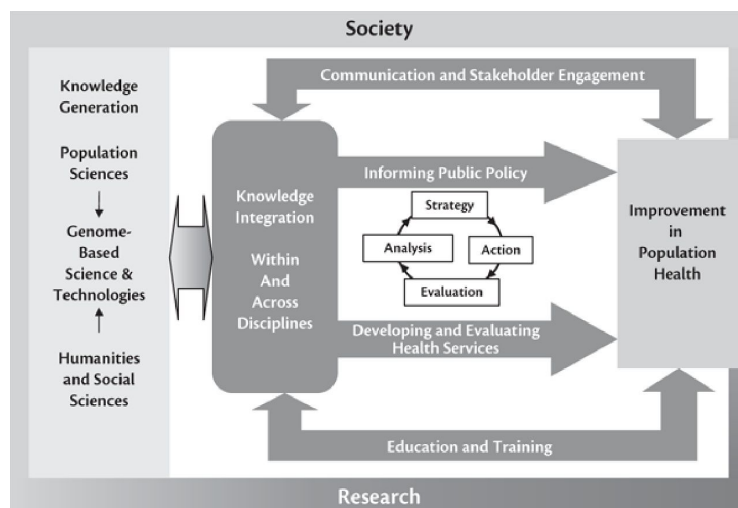


Figure 1.1: The Public Health Genomics enterprise (Adapted from the report of an expert workshop held at the Rockefeller Foundation Study and Conference Centre Bellagio, Italy, 2005 [1])

The integrated multidisciplinary knowledge generated from an effective PHG enterprise supports four core activities. First, informing public policy includes the whole range of legal, philosophical, and social analyses, development of regulatory frameworks, engagement in the policy-making process, promoting relevant research, seeking international comparisons, and working with governments and relevant public institutions. Second, developing and evaluating preventive and clinical health services includes development of policies, programmes and services in the health sector, strategic planning, service organisation, manpower planning and capacity building, service review and evaluation and guideline development. The third core activity of the enterprise is communication and stakeholder engagement. Relevant activities include promoting general genomic literacy in society, public dialogue, and engaging with industry, which is seen as a key player in the development of new genomic-based clinical interventions. At last, education and training will involve promoting programmes of genomic literacy for health professionals and generally within society, specific training for public health specialists, and development of educational materials, courses, workshops and seminars.

The dynamic and interactive nature of the enterprise is visualised by the double-headed arrows. It is informed by societal priorities, generates knowledge as well as using it, and is modulated by the effect of its own outputs and activities. Thus, PHG incorporates a cycle of analysis-strategy-action-evaluation, which describes how the enterprise carries out its activities.

The wheel of essential Public Health Genomics' activities

Beskow *et al.* developed genomic-related definitions for the core functions and essential services of public health [10] based on the ten essential public health functions as described first by the Institute of Medicine (IoM) of the US in 1988. This 'blueprint' for integrating genomics into the complete range of public health activities is depicted in Figure 1.2.



Figure 1.2: The integration of genomics into public health (Adapted from Beskow *et al.* [10])

The wheel indicates that performance of public health functions and services is neither linear, nor discrete. It is composed of three major parts, which are the core functions of public health ('public health trias'): assessment, policy development, and assurance. Assessment activities provide the knowledge base for policy development including genomics knowledge and for assuring the proper implementation of programs and services that involve genomic components. Policy development activities help identify gaps in scientific knowledge and form the foundation of assuring the effectiveness, accessibility and quality of programs and services. The assurance function, in addition to ensuring that genomics is properly integrated into health-related services, also supplies evaluative information for continuing efforts in assessment and policy development.

Those three core functions are further subdivided in different essential services, which are described in Table 1.1.

In conclusion, the wheel demonstrates the important role for genomics not as a separate specialty but as a fundamental component of existing public health programs and includes also prevention and health promotion programs.

The European best practice guidelines on PHG, which had been developed by the Public Health Genomics European Network (PHGEN) are based on the public health wheel and the ten essential public health tasks (www.phgen.eu).

Table 1.1: Essential services for PHG (Adapted from Beskow *et al.* [10])

Assessment	<p><i>Core function</i> The regular systematic collection, assembly, analysis and dissemination of information, including human genome epidemiologic information, on the health of the community.</p> <p><i>Related essential services</i></p> <ul style="list-style-type: none"> * Epidemiologic and laboratory research: quantifying the impact of gene variants on human health and identifying and quantifying the impact on human health of environmental risk factors that interact with gene variants. * Monitoring health: monitoring health status, including genetic factors, to identify health problems within the community. * Diagnosing and investigating: investigating the distribution of genetic and modifiable risk factors within the community to determine their contribution to identify health problems and to improve health outcomes.
Policy development	<p><i>Core function</i> The formulation of standards and guidelines, in collaboration with stakeholders, which promote the appropriate use of genetic information and the effectiveness, accessibility and quality of genetic tests and services.</p> <p><i>Related essential services</i></p> <ul style="list-style-type: none"> * Policy and communications research: identifying and analysing the economic, social, ethical and political implications of advances in human genetics, including the information and communications needs of stakeholders. * Informing, educating, empowering, facilitating communication and education about the integration of genomics into health promotion and disease prevention programs. * Mobilising partnerships: fostering collaboration between public and private agencies and constituent groups to promote effective and efficient communication and policy making about genomics. * Developing policies: establishing standards and guidelines for when and how genetic information should be applied to promote health and prevent disease.
Assurance	<p><i>Core function</i> Assuring constituents that genetic information is used appropriately and that genetic tests and services meet agreed-upon goals for effectiveness, accessibility and quality.</p> <p><i>Related essential services</i></p> <ul style="list-style-type: none"> * Health services research: identifying and analysing the factors that influence the impact of genetic information and the delivery, utilisation and quality of genetic tests and services. * Enforcing laws: promoting the enforcement of policies and standards enacted to ensure the appropriate use of genetic information and the effectiveness, accessibility and quality of genetic tests and services. * Linking to/providing care: ensuring the availability and accessibility of genetic tests and services and associated interventions to improve health and prevent disease. * Assuring a competent workforce: ensuring that present and future health professionals have training and skills in the appropriate use of genetic information to promote health and prevent disease. * Evaluating: evaluating the impact of genetic information and the effectiveness, accessibility and quality of genetic tests and services.
System management	<p>Building and maintaining the capacity of the public health infrastructure to integrate genomics into public health research and practice.</p>

APPLICATION OF PUBLIC HEALTH GENOMICS ON SMOKING

Introduction

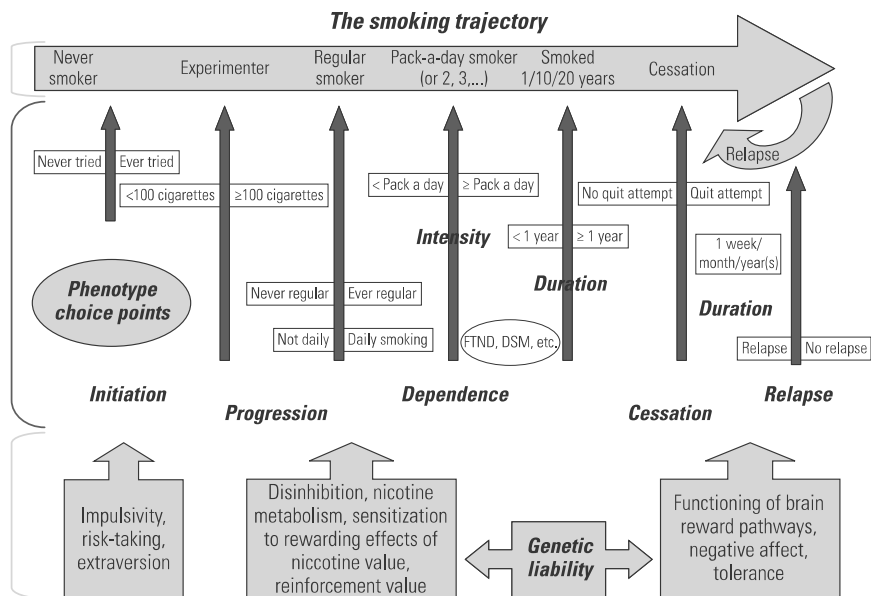
In European countries, the prevalence of smoking is still around 30% in the population of 15 years and over [19]. Smoking, which is the single most preventable cause of death, killed around 6 million people worldwide in 2011 with major occurrence in countries of low and middle income. Of these deaths around 5 million are directly due to tobacco use and 600,000 are attributable to second-hand smoking [19].

Smoking is known to be an important risk factor in the incidence of the 4 leading non-communicable disorders (cardiovascular disorders, diabetes, cancers, and chronic respiratory disorders) [19]. It is estimated that smoking is responsible for 71% of the lung cancer deaths, 42% chronic respiratory disorders and around 10% of the cardiovascular disorders. Smoking is not only an important factor in non-communicable disorders but also in communicable disorders such as tuberculosis or respiratory infections [20]. In 2003, in Germany the total cost of cigarette smoking was about 21.0 billions euros including 7.5 billions of direct costs (cares and drugs) and 13.5 billions euros of indirect costs (mortality and morbidity) [21]. In 2000, the WHO estimated that smoking accounted for 12.3% of the total years of life lost due to premature mortality and years lived in disability (DALYs) in European regions [22].

Smoking behaviour is a multifactorial trait including both non-genomic and genomic factors. Non-genomic factors are also called environmental. In genetic medicine, environmental factors include all non-inherited factors (e.g. psychological, social or socioeconomic factors). Regarding genomics, twin studies determined that genetic factors influence around 50% of smoking initiation [23], 75% of nicotine dependence [24] and around 40 to 60% of smoking cessation [25]. More specifically, nicotine metabolism and the cascade theory of reward are the two main groups of genes influencing smoking behaviour. Nicotine metabolism indicates how nicotine is absorbed in the organism. The major gene influencing nicotine metabolism is the Cytochrome P450 2A6 (*CYP2A6*). The cascade theory of reward, which is responsible for the amount of pleasure someone gets when smoking, is based on the action of four different neurotransmitters (serotonin, opioid, gamma-aminobutyric acid (GABA), and dopamine) each containing many genes. (i) Serotonergic neurons release serotonin (5-HT). This activates (ii) opioidergic neurons that, at the same time, release endogenous opioid. The opioid inhibits the release of (iii) GABA and this inhibition increases the release of (iv) dopamine in the nucleus accumbens (NAcc) in the brain [26]. In a meta-analysis, Munafo *et al.* reported an association between *DRD2* Taq1A, a dopamine receptor, and smoking initiation as well as smoking consumption. Moreover, one variant from the serotonin (*SLC6A4* 5-HTTLPR) and another influencing the nicotine metabolism (*CYP2A6*) were associated with smoking cessation [27].

Not only smoking initiation, dependence, and cessation are influenced by genomic factors but also smoking related disorders. Multiple genes have, for example, been associated to chronic obstructive pulmonary disease (COPD) and lung cancer such as *CHRNA3*, *CHRNA5* and *CYP1A1* [28]. *CHRNA3* and *CHRNA5* are nicotinic acetylcholine receptors and *CYP1A1* is a cytochrome P450 protein. In complex disorders such as smoking, most genomic variables are likely to contribute only to a small part of the phenotype variance. Smoking trajectory from initiation to cessation is made of successive phenotypes as presented on Figure 1.3. For example, the phenotype 'smoking initiation' is assessed by the choice point, never or ever tried cigarette [29].

Therefore, both genomic and environmental factors as their interactions should be taken into account in smoking prevention and cessation. Moreover, cigarette smoking induces, for example, epigenomic and transcriptomic alterations [30, 31]. Methylations are correlated with smoking status and the number of cigarettes per day (e.g. in *F2RL3* and *GPR15*). However, some DNA methylations seem to be reversible after smoking cessation [31].



Note. FTND = Fagerström Test for Nicotine Dependence; DSM = Diagnostic and Statistical Manual of Mental Disorders.

Figure 1.3: Phenotype choice points along the smoking trajectory (Adapted from Wanke *et al.* [29])

Smoking behaviour and Public Health Genomics

In the case of smoking, as in most complex disorders, far less attention has been given to translating genomic information into public health applications in comparison to basic research associating smoking to specific SNPs.

Currently, genomic information is not used in the daily clinical practice as intervention or prevention of smoking. Two main directions of research need further development (i) translation of genomic research on smoking to improve the health of smokers and healthcare interventions, and (ii) to enhance the communication of genome-based risks associated with smoking (initiation, dependence and cessation) and smoking related disorders in the general population.

Translation of genomic research

Genomic research includes both research on genes and 'omic' features. The translation of genomic research may be conducted through different tools. Firstly and probably one of the most important use is *'employing the power of genetic (and genomic) studies in understanding the underlying biological, behavioural, and environmental factors that will enhance research on etiology, treatment, and prevention for these complex diseases'* [32]. Therefore, a better understanding of the biological mechanisms leading to smoking initiation, addiction, cessation, or smoking related disorders is crucial to implement future public health interventions in an effective and efficient way. Indeed, genomic testing has to be used as additional information to environmental factors [33], such as smoking history of the family, history of depression or social support. Considering genomics, environment, and interactions between those two factors is of high importance to improve the motivation and the success in, for example, preventing and quitting smoking and, therefore, on public health outcomes.

In smoking, pharmacogenomics is an approach having high potential. Targeted interventions (in drugs, dose and duration) based on genomic factors can enhance smoking cessation through more precise and personalised interventions [34]. As smoking is a complex disorder, it is unlikely that only one gene will be sufficient to develop personalised interventions [35]. Moreover, the integration of genome-based information, i. e. genome-environmental interactions, into public health policies and practice needs strong evidence of causation, efficacy and cost-effectiveness [35]. Clinical utility and clinical validity are, therefore, of high importance. However, currently there is a lack of evidence supporting both clinical utility (lack of evidence that genomic tests will improve smoking prevention or cessation) and clinical validity (lack of replication in the gene-disorder association studies) [36]. Currently, most personalised interventions in smoking cessation do not include genomic information except in the study of Rose *et al.*, where interactions between nicotine dependence, dose of treatment and quit-success in genotype score were reported. In that study, a score based on 12,058 SNPs indicated interactions with smoking cessation [37]. Prediction models of smoking initiation, addiction, cessation or smoking

related disorder risks are one specific example of personalised medicine and health-care. These models could either contain only genomic factors or both genomic and environmental factors, and the latter being more comprehensive of the real problem. To date, few prediction models were developed due partly to the complexity of the mechanisms leading to smoking initiation, addiction, cessation, smoking related disorder risks. However, recently, a model was developed for lung cancer risk in a Chinese population [38]. This prediction model included four different SNPs previously identified in GWAS (rs2736100, rs402710, rs4488809 and rs4083914). However, only moderate discriminatory accuracy was obtained using weighted genetic risk score [38].

Communication of genome-based information

Communication of genome-based information is necessary for both health professionals and patients. The need is even growing with the availability of direct-to-consumer genetic testing [39]. However, to date, there is an underutilisation of the communication sciences to exchange information on a regular basis [33, 40]. This is why it has been set as one of the priorities for translational research during a 2-day workshop organised by the National Human Genome Research Institute in 2008 [33]. Communication of genome-based information should be used both in health promotion strategies on smoking (e. g. health campaigns) as well as in preventive interventions (e. g. notifying a genomic risk of smoking related disorders in smokers attempting to quit smoking).

The genomic literacy is a relatively new field assessing the knowledge and understanding about genomics in the population. To date few studies assessed the genomic literacy of the general population but due to the specialised and recent topic of genomic, it is suggested to be reasonably low. Therefore, this field needs to be further developed in the near future. In a Japanese study, the term 'genome' appeared unfamiliar with only 14.9% of the participants answering that they knew the meaning of 'genome'. However, the meaning of the terms 'gene', 'DNA', and 'chromosome' was most widely known [41]. The medium of communication delivery (e. g. television, Internet or information from healthcare providers) may influence the outcome based on the characteristics of the individual. The choice in the type of medium is also susceptible to change over time. The Internet has the potential to become an important tool of communication due to the easiness in sharing and retrieving information and the low-cost in the development of information. Moreover, a very large audience is reached through that kind of media [42]. Moreover, health information on social media, which is a tool dedicated to communication, is suspected to grow dramatically in the next years. Blogs are one example of social media. They allow the spread of information to lay public and health professionals as well as interactions with the public through the commentary's options [42]. However, the most important challenge will be to control the accuracy of the information displayed on such media [33]. To date, most communication-based research on smoking did not take genomics into account except research on genetic risk noti-

fication of smoking related disorders [43–52]. However, genome-based information is essential to modify health behaviour (e. g. smoking) through different intermediate factors such as emotional factors, self-efficacy or response efficacy [33].

Personalised communication through, for example, genomic notification via web-based communication will not only influence one single individual. Individuals receiving the information will most likely share the information to their circle (e. g. peers) and social network. Therefore, improving genome-based risk communication to a single individual is suggested to have a health impact on the social network of the individual as well [33, 49].

AIMS AND OUTLINE OF THE THESIS

The main objective of the thesis is to describe how genomics contribute to the prevention and the treatment of smoking. Thus, the thesis meets a key task of the 21st century, which is to synthesise and disseminate information [53]. This major objective can be clustered in two parts: (i) to improve healthcare for smokers and (ii) to enhance the communication of genomic risks about smoking in the general population.

The **FIRST PART** of the thesis focuses on improving the health of smokers and healthcare interventions on smoking. **Chapter 2** provides an overview of genomic predictors for smoking initiation and cessation. **Chapter 3** presents a literature review including environmental factors, genomic factors and interventions influencing smoking cessation. Based on the literature review, a working model of smoking cessation including all these factors was developed. Moreover, the genetic similarities between tobacco use disorders and other disorders are explored in **Chapter 4**, based on the observation that genes influencing tobacco use disorders are also associated with many other disorders.

The **SECOND PART** of the thesis describes the high potential of communicating genome-based information about smoking to the population. The impact of genetic notification of smoking related disease risk on smoking cessation is described in **Chapter 5**. The availability of information about genetics and smoking on three different social media (YouTube, Facebook and Twitter) is assessed in **Chapter 6**. **Chapter 7** describes the Internet tools and factors influencing the search of information about health, smoking and genetics on the Internet in university students.

Part I

IMPROVING HEALTHCARE FOR SMOKERS

GENETIC PREDICTORS FOR SMOKING INITIATION AND
CESSATION

Sylviane de Viron

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ABSTRACT

Preventing smoking initiation and improving smoking cessation has been a major interest of public health for years. Despite this, only 20% of smokers succeed in quitting smoking with an adequate treatment. Predictors of smoking initiation and cessation have traditionally been focusing on environmental factors such as motivation to quit, age or gender. However, there is more and more evidence that also genetic factors influence smoking initiation and cessation. This chapter provides an overview of the current knowledge on genetic predictors for smoking initiation and cessation.

INTRODUCTION

Smoking behaviour (initiation, persistence and cessation) is a complex trait, and depends, just like other behavioural traits and common diseases, on environmental factors, genetic factors and interventions, as well as on the interactions between these different factors (Figure 2.1). For example, not all monozygotic twins have the same smoking status, which demonstrates an impact of environmental factors. The heritable risk was studied in twin studies due to their sharing of genetic factors. In this kind of studies, monozygotic twins are compared to dizygotic twins. Theoretically, monozygotic twins are sharing approximately 100% of their genes instead of around 50% for dizygotic twins. Thus, improved correlation of the phenotype might rather be found in monozygotic than in dizygotic twins [54]. Twin studies determined that genetic factors influence around 50% of smoking initiation [23], 75% of nicotine dependence [24] and around 40 to 60% of smoking cessation [25]. The remaining percentage is explained by the shared and non-shared environmental factors. This highlights the high importance of both genetic factors and environmental factors [54].

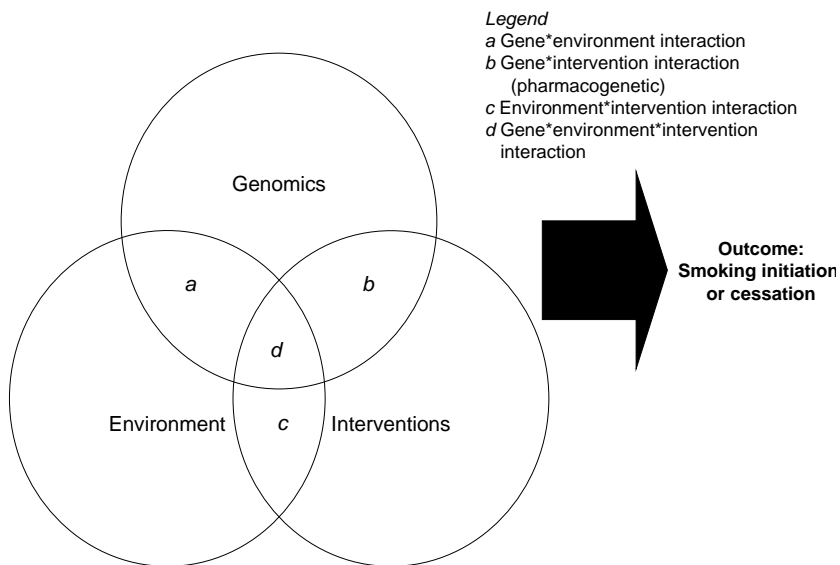


Figure 2.1: Schematic diagram of the multifactorial factors influencing smoking initiation and cessation

Genetic factors are identified through two different ways. First, genetic association studies are looking for potential genetic markers that are based on well established physiologic pathways. Secondly, genome wide association studies (GWAS) are dealing with a large number of single nucleotide polymorphisms (SNPs) across

the whole genome in a broad sample of participants [55]. This approach is considered as 'hypothesis-free' and consequently, it goes beyond the current knowledge of physiological pathways.

Specific neural pathways are involved in nicotine addiction. Upon inhalation of cigarette smoke, nicotine passes into the bloodstream and, within seconds, crosses the blood-brain barrier to enter the brain. Nicotine binds principally to $\alpha_4\beta_2$ and α_7 nicotinic acetylcholine receptors (nAChRs) located on dopaminergic, glutamatergic and GABAergic neurons in the ventral tegmental area (VTA) of the midbrain, which in turn modulate the release of extracellular dopamine in the nucleus accumbens (NAcc). The activity of dopamine neurons in the VTA is modulated by excitatory glutamatergic and inhibitory GABAergic neurons. The release of dopamine in the nucleus accumbens (NAcc) is responsible for the rewarding and addictive effects of nicotine. Over time, the repeated exposure to nicotine alters the properties of individual neurons and circuits, and this leads to complex behaviours including dependence, tolerance, sensitisation, and craving [56].

GENETIC AND INTERETHNIC DIFFERENCES

Interethnic differences are of high importance in genetic studies. Some disorders and behaviour occur more frequently in population involving ancestries from the same geographic area. People from the same ethnicity share allelic variations of their genes. If one of these allelic variations is causing a specific disorder or behaviour, the frequency of this particular disorder or behaviour will be more present in that population [57]. Table 2.1 presents an example of the *DRD2* C957T, variant in the D2 dopamine receptor. In this example, the frequency of the C allele of the *DRD2* C957T variant is about 0.40 in the European population, 0.91 in the African-American and 0.94 in the Asian population (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=rs6277), which could influence the risk of a common disease or the effect of a specific treatment among the different ethnicities. Differences in allele frequencies between ethnicities are found in multiple other genes. Thus, mixing populations could lead to the introduction of confounding in the analyses as the population correlate with both smoking cessation (the outcome) and allele frequency in specific population (the exposure).

Table 2.1: Allele frequency of *DRD2* C957T

ETHNICITY	C ALLELE	T ALLELE
European	0.396	0.604
African-American	0.913	0.087
Asian	0.938	0.062

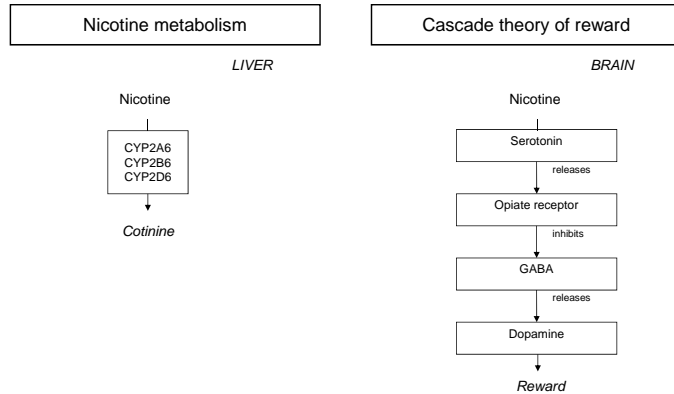
C and T correspond to the 2 possible alleles of the *DRD2* C957T variant

Adapted from http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=rs6277

GENETIC PATHWAYS OF INTEREST

Research on smoking focuses mainly on 2 types of candidate genes (Figure 2.2):

1. Genes influencing the metabolism of nicotine or the pharmacokinetics of nicotine;
2. Genes influencing the reward action induced by nicotine or the pharmacodynamics of nicotine;



(A) Nicotine metabolism; (B) Cascade theory of reward. CYP, Cytochrome p450

Figure 2.2: Genetic pathways influencing smoking initiation and cessation

Nicotine metabolism

The major gene influencing the metabolism of nicotine is the hepatic enzyme cytochrome P₄₅₀ 2A6 (*CYP2A6*) and to a lower proportion cytochrome P₄₅₀ 2B6 or 2D6. These enzymes mainly metabolise nicotine into cotinine. Cotinine is a well-known factor that determines the exposure to nicotine [58]. Multiple smoking phenotypes are influenced by *CYP2A6* such as smoking status, nicotine dependence, and smoking cessation [58]. In comparison to normal metabolisers (with 100% activity), smokers with a genetically poor nicotine metabolism (with <50% activity) are often less prone to develop nicotine dependence. Moreover, they may quit smoking more easily possibly due to reduced side effects of smoking abstinence [58].

Cascade theory of reward

'Reward' is defined in the Merriam Webster's dictionary as being a '*stimulus administered to an organism following a correct or desired response that increases the probability of occurrence of the response*'. The cascade theory of reward is based on the action of four different neurotransmitters.

- Serotonin;
- Mu-opioid receptor;
- Gamma-aminobutyric acid (GABA);
- Dopamine;

(i) Serotonergic neurons release serotonin (5-HT). This activates (ii) opioidergic neurons that, at the same time, release endogenous opioid. The opioid inhibits the release of (iii) GABA and this inhibition increases the release of (v) dopamine in the NAcc in the brain [26]. The release of dopamine is responsible for the feeling of pleasure. Smokers with a genetically increased release of dopamine are plausibly more affected by the reward pathway. Consequently, they are more susceptible to become regular smokers when they initiate smoking and are less likely to achieve smoking cessation. These four neurotransmitters have also other functions than the ones mentioned here. The major roles of *serotonin* are the control of temperature, mood, sleep, locomotion and sensory perception. Studies reported, for example, associations between serotonin genes and depression or addictions (e. g. alcohol, nicotine, gambling or drug). Different treatments are modulating the serotonin release, such as e. g. selective serotonin re-uptake inhibitors [59]. The *mu-opioid receptor* is the major site of action of opioids (e. g. morphine, heroine or methadone). Studies reported an impact of mu-opioid receptor genes in the reinforcement of learning, in pain response and in addictions [60]. *GABA* is a major inhibitory neurotransmitter. Associations with schizophrenia and drug addictions were reported in studies [61]. The main role of *dopamine* is the control of locomotion and emotion as well as reward. Dopamine release has also an important role in other diseases, such as Parkinson's or Alzheimer's disease [59]. Glutamate and nAChRs also play a role in smoking reward. The *glutamate* synthesises GABA and plays an important role in training and memory. Glutamate has been related to other diseases such as schizophrenia and epilepsy [62]. Different roles of *nAChRs* are defined such as neuronal development, memory, learning, and, of course, reward. Until now, most studies assessing the influence of nAChRs were based on smoking. However, some studies assessed the changes in nAChRs in different neuropsychiatric diseases (e. g. Alzheimer diseases, Parkinson diseases, or depression). Some treatments are modulating nAChRs such as e. g. selective $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonists [60].

PHARMACOGENETICS

Pharmacogenetics is studying genes influencing the pharmacokinetics and pharmacodynamics of treatments regarding the outcome of interest. Pharmacogenetics is of high interest to improve personalised interventions of smokers regarding their own genotypes by targeting specific drug, dose and duration. Different pharmaceutical interventions are used for smoking cessation, the most important one are the following:

- Nicotine replacement therapies (NRTs);
- Bupropion;
- Varenicline;

Nicotine replacement therapies (NRTs) substitute nicotine and are available in different forms (e.g. patch, spray or gum). As NRTs mimicked nicotine from the cigarette, pharmacogenetic interactions are susceptible with the genetic pathways influencing smoking, thus the pharmacokinetics and the pharmacodynamics of nicotine [63]. *Bupropion* is an antidepressant used to reduce nicotine withdrawal. Pharmacogenetic interactions with smoking cessation are susceptible as Bupropion inhibits dopamine and norepinephrine reuptake and also influences the action of the serotonin pathway. Moreover, it has also some actions on nAChRs [64]. *Varenicline* is a partial agonist for nAChRs (partial for $\alpha_4\beta_2$ and full for α_7 nAChRs). It stimulates the release of dopamine, thus reduces craving and withdrawal. Pharmacogenetic interactions are thus conceivable regarding the genes influencing nAChRs (e.g. *CHRNA4* or *CHRNA7*) and the release of dopamine [65].

PROGRESS IN THE IDENTIFICATION OF GENES INFLUENCING SMOKING INITIATION AND CESSATION

Genes included in Table 2.2 were based on prospective or retrospective studies for smoking initiation and only prospective studies for smoking cessation. Indeed, few studies assessed smoking initiation prospectively. Included studies were based on the general population without mixed background ethnicities for the reasons explained in the 'Genetic and interethnic differences' section. We excluded specific subpopulations such as people with mental illness, pregnant women, hospitalised smokers, or referring to another addiction. All candidate genes with at least one significant reported association were selected. Significance was assessed with a p-value lower than 0.05 for the association studies and through the genome-wide significance for GWAS. As in GWAS multiple genetic factors are assessed, correction for multiple testing is important to avoid significant results obtained by chance. A level of significance of 5×10^{-8} was proposed (based on the correction of Bonferroni for 1 million SNPs because of the fishing expedition approach).

Smoking initiation

For smoking initiation, we considered studies comparing initiators versus non initiators. Only four SNPs demonstrated an association with smoking initiation in the literature. Two SNPs from the serotonin pathway (*5-HTTLPR* C-759T and *5-HTTLPR* G-697T) were associated with smoking initiation in populations of European ancestries [66]. And one SNP influencing the dopamine pathway, *CALY* (rs2298122), was associated with smoking initiation in an Asian and in a European population [67]. The last association was observed in a GWAS with the *BDNF* polymorphism (rs6265) [68]). *BDNF* was demonstrated to modulate the reward pathway, and more specifically the activity of $\alpha 7$ nAChRs [69].

Smoking cessation

Eleven SNPs from 6 different pathways demonstrated an association with smoking cessation and/or an interaction with intervention.

GENES INFLUENCING SMOKING CESSATION. Smoking cessation was reported to be associated with nicotine metabolism (*CYP2B6* C1459T) [70], and different neurotransmitters of the reward pathway: the mu-opioid receptor (*OPRM1* A118G) [71, 72], different dopamine receptors (*DRD2* Taq1A, *DRD2-141C*, *DRD2* C957T, *DRD4* VNTR) as well as one enzyme that degrades dopamine (*COMT* Val^{108/158}Met) [73–78] and two different nAChRs (*CHRNA3* rs1051730 and *CHRN2* rs2072661) [79–81]. Finally, a GWAS study reported an association of *DBH* (rs3025343) with smoking cessation [68]. This variant is responsible for the translation of dopamine into norepinephrine.

PHARMACOGENETICS OF SMOKING CESSATION. *NRTs* interacted with the mu-opioid receptors (*OPRM1* A118G) [72], a dopamine receptor (*DRD4* VNTR) [77] and one nAChR (*CHRN2* rs2072661) [81]. As *NRTs* mimic nicotine from tobacco the different pathways influencing nicotine are susceptible to influence *NRTs*. However, to our knowledge no studies reported an interaction with genes influencing nicotine metabolism despite its plausible influence. *Bupropion* interacted with a gene from the nicotine metabolism (*CYP2B6**6 haplotype composed of two loci, *CYP2B6* G516T and A785G) [70, 82], with a variant of the serotonin neurotransmitter (*SLC6A4* 5-HTTLPR) [83] as well as with two different variants of the dopamine D2 receptors (*DRD2* Taq1A [73, 74] and *DRD2-141C* [76]). Serotonin and dopamine neurotransmitters were highly plausible given their implication in the metabolism of *Bupropion*. To our knowledge, *varenicline* has not demonstrated any pharmacogenetic interactions with smoking cessation for the moment. Finally, in an Asian population, an interaction between *acupuncture* and a polymorphism in the D2 receptor of the dopamine pathway (*DRD2* Taq1A) was also reported [75]. This could be in line

with the suggestion of Yoon *et al.* that acupuncture could modulate the release of Dopamine [84].

Table 2.2: Candidate genes with associations reported at least once in the literature

SNP	ETHNICITY	IMPACT ON SI	IMPACT ON SC	INTERACTION WITH INTERVENTION	REF.
Nicotine metabolism					
<i>CYP2B6</i> C1459T	European	No	Yes	No	[70]
<i>CYP2B6</i> *6 (G516T and A785G)	European	No	No	Bupropion	[82]
Serotonin					
<i>5-HTTLPR</i> C-759T	European	Yes	No	No	[66]
<i>5-HTTLPR</i> G-697T	European	Yes	No	No	[66]
<i>SLC6A4</i> 5-HTTLPR	European	No	No	Bupropion	[83]
Mu-opioid receptor					
<i>OPRM1</i> A118G	European	No	Yes	NRT	[71, 72]
Dopamine					
<i>DRD2</i> Taq1A	Asian	No	No	Acupuncture	[85]
	European	No	Yes	Bupropion	[73–75]
<i>DRD2-141C</i>	European	No	Yes	Bupropion	[76]
<i>DRD2</i> C957T	European	No	Yes	No	[76]
<i>DRD4</i> VNTR	European	No	Yes	NRT	[77]
<i>COMT</i> Val ¹⁰⁸ /Met ¹⁵⁸	European	No	Yes	No	[78]
<i>CALY</i> rs2298122	Asian	Yes	No	No	[67]
	European	Yes	No	No	[67]
Nicotinic acetylcholine receptors (nAChRs)					
<i>CHRNA3</i> rs1051730	European	No	Yes	No	[79]
<i>CHRNA3</i> rs2072661	European	No	Yes	NRT	[80, 81]
Other from GWAS					
<i>BDNF</i> rs6265	European	Yes	No	No	[68]
<i>DBH</i> rs3025343	European	No	Yes	No	[68]

GWAS, Genome-wide association study; NRT, Nicotine replacement therapy; SC, Smoking cessation; SI, Smoking initiation

Gene-gene interactions

To our knowledge, no gene-gene interactions were reported for smoking initiation. However, in smoking cessation two studies reported gene-gene interactions. In 2006, Dahl *et al.* demonstrated an interaction between the *FREQ* gene (rs1054879) and *DRD2-141C* [86]. The *FREQ* gene has a role in the regulation of D2 receptor signaling. Another study reported a gene-gene interaction between *SLC6A3* and *DRD2* Taq1A [87]. Gene-gene interactions might have a key role, as smoking cessation is not a monogenic behaviour.

CONCLUSION

Identifying genes influencing smoking initiation and smoking cessation as well as the different interactions (gene-environment, gene-intervention and gene-gene interaction) is still of main importance to understand the mechanism leading to modification of smoking behaviour. For the moment, there is a lack of replication of studies that demonstrate the influence of genetic factors on smoking initiation and cessation in different populations of the same background ethnicity and from different ethnicities, as we observed on Table 2.2. Most studies were based on populations of European ancestries and only two studies explored other ethnic populations (always Asian population). This raises the question on how to activate studies in other parts of the world.

Few studies demonstrated the influence of genetic factors on smoking initiation, probably because smoking can be initiated at any time, which increases the difficulty of testing this, both prospectively and retrospectively. Most studies in this field have focused on the influence of genetic factors on the age of smoking initiation [68]. Moreover, the real starting point of smoking initiation may be strongly influenced by environmental factors. Genetics and gene-environment interactions may then play a central role in the continuation of smoking initiation.

Studies on smoking cessation mainly focused on the neurotransmitter of dopamine, probably because it is the most important molecule leading to the reward or pleasure. From the nicotine metabolism, no studies demonstrated an impact of *CYP2A6* on smoking cessation, despite its high implication in the metabolic inactivation of nicotine into cotinine. Especially in European ancestries, this may also be due to the low frequency of poor metabolisers in the studies. Although serotonin is the first neurotransmitter responsible for the reward pathway, no studies were identified in which a significant impact on smoking cessation was found, even though there are several candidate genes (e. g. *SLC6A4* 5-HTTLPR, *TPH1* A779C or *HTR1A* C-1019G). Finally, no associations were reported for GABA or glutamate. Smoking cessation and relapse during smoking cessation are mainly related to nicotine dependence but also to behavioural, gestural and ritualistic components of smoking behaviour. These components may be partly due to genetic factors. However, for the moment, no studies investigated these factors.

For the moment, few studies reported gene-environment, gene-gene interactions that could influence smoking initiation or smoking cessation. Most studies lack the power to detect these kinds of interactions due to an insufficient sample size. The required sample size depends on different factors (e. g. the type of study, the allele frequency or the prevalence of the environmental factor of interest).

Studies observing the genetic predictors of smoking initiation and cessation mostly focused on the nicotine compound of cigarette. However, in Europe around 600 additives are allowed in cigarettes and are susceptible to increase the addiction through, for example, the improvement of the taste or the reduction of the side effects (e. g. irritability) of the cigarette. The principal effects of these additives are

bronchodilatation, anti-inflammation, analgesia, inhibition of neoplastic cells, antipyretic effect and addiction [88]. Tobacco is also composed of more than 4,000 chemical substances. From these 4,000 chemical substances at least 50 are carcinogenic and 250 noxious. The impact of chemicals on addiction is twofold. First, some chemicals are reinforcing the effect of nicotine (e.g. acetaldehyde). Others are inhibiting enzymes influencing the nicotine metabolism (*CYP2A6*) (e.g. gamma-valerolactone) [89]. Increasing the knowledge of the different compounds influencing smoking initiation, addiction and cessation could improve the comprehension of physiological and genetic pathways influencing smoking initiation, nicotine addiction and smoking cessation.

Genes influencing the nicotine metabolism and the cascade of reward are also associated with different comorbidities and with personality traits of smoking behaviour. As an example for the comorbidities, 3 different neurotransmitters of the reward pathway (serotonin, GABA, and dopamine genes) are also associated with depression (HuGENet). Personality traits are influenced through 4 different neurotransmitters of the reward pathway, serotonin, opioid receptor, GABA and dopamine (HuGENet). Trait theory in psychology is an approach to the study of human personality. Trait theorists are primarily interested in the measurement of traits, which can be defined as habitual patterns of behaviour, thought, and emotion [90]. According to this perspective, traits are relatively stable over time, differ across individuals and influence behaviour. Five traits are used to describe personality [91, 92]. Proponents of the five-factor approach [91, 92] assume a role of genetics and environment (on personality traits) but offer no explicit causal explanation.

In the future, genetic factors should provide new insights for the prevention of smoking initiation and could also improve interventions and more specifically personalised interventions regarding smoking cessation in tobacco control policies. Informing populations on genetic risk modifying the susceptibility of smoking initiation and cessation as well as smoking related disease risk, could improve the awareness on that problematic. This could both increase the motivation to quit smoking or in the opposite, lead to fatalism and consequently decrease the intention to quit smoking. To improve smoking cessation, genetic factors should be used through different ways:

- Personalised interventions (e.g. more intensive interventions for highly genetically addicted smokers);
- Pharmacogenetic analyses (e.g. targeted interventions in drug, dose and duration depending on alleles of different variants);
- Genetic notification of smoking related disease (e.g. giving genetic notification of smoking related disease risk as a part of the intervention of smoking cessation). Recently, a meta-analysis suggested that genetic notification of cancer risk improved smoking cessation in comparison to control [93];

As demonstrated with the examples above, the most important strengths in using genetic factors for smoking cessation is to improve personalised and individualised

cares. And at the same time, using genetic factors would enhance global care. Indeed, genetic factors will be only part of the treatment for smoking cessation, other factors such as social support, weight concerns or health status might also be taken into account. Regarding the limitations, genetic factors may just be taken as a part of the factors influencing smoking initiation or smoking cessation. These factors might be studied, as we already mentioned, with environmental factors and interactions. Future studies might also focus on epigenetics and on ‘-omics’. Epigenetics is the link between genetics and phenotype making gene-environment interactions measurable. In the opposite of genomic factors, it evolves during time. Two main types of epigenetic factors are DNA methylation and histone modification. Most studies observed DNA methylation or histone modification leading to smoking related disease or smoking status (never versus current versus former smokers). However, Wan *et al.* recently reported that different sites of methylation were associated with current smoking, cigarettes consumption (pack-years) and time since quitting smoking [31]. Different levels of ‘-omics’ are available (Figure 2.3):

- Genomics (referring to DNA);
- Transcriptomics (referring to mRNA);
- Proteomics (referring to proteins);
- Metabolomics (referring to metabolites);

Most researches on ‘-omics’ regarding smoking behaviour are focusing on changes leading to smoking related diseases such as chronic obstructive pulmonary disease (COPD) or lung cancer rather than on the impact on smoking initiation and cessation.

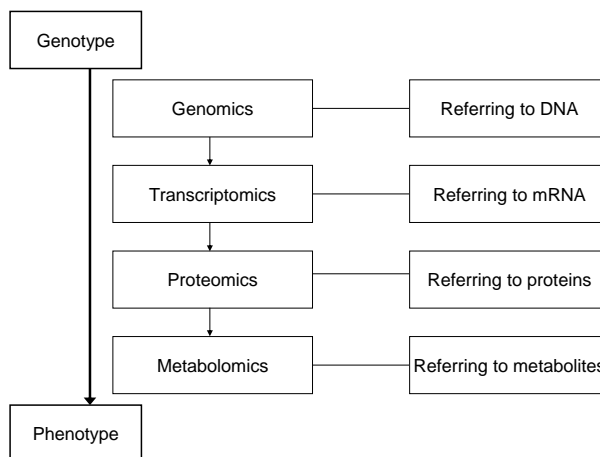


Figure 2.3: Schematic diagram of the hierarchy in the ‘-omics’

CHAPTER SUMMARY

The genetic impact of smoking initiation and smoking cessation is mainly linked with nicotine

- How genes influence the metabolism of nicotine (e. g. *CYP2B6*).
- How genes influence the reward feeling caused by nicotine.

Implications for future research

- Different additives and other chemicals than nicotine are susceptible to influence genetic predictors of smoking initiation and smoking cessation.
- Increased sample sizes are needed to explore gene-gene and gene-environment interactions.
- Investigation of the epigenetics and '-omics' implications in smoking initiation and cessation might give new insights.

Implications of genetic predictors for clinical practice

- Smoking initiation: Genetic predictors could help in the prevention of smoking initiation.
- Smoking cessation: Genetic predictors could be used for personalised interventions, pharmacogenetic assessment and genetic notification of smoking related disease risk.

3

ENVIRONMENTAL AND GENOMIC FACTORS AS WELL AS INTERVENTIONS INFLUENCING SMOKING CESSATION: A SYSTEMATIC REVIEW OF REVIEWS AND A PROPOSED WORKING MODEL

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ABSTRACT

Background Smoking behaviour is a major public health problem worldwide. Several sources have confirmed the implication of genomic factors in smoking behaviour. These factors interact both with environmental factors and interventions to develop a certain behaviour.

Objectives (1) To describe the environmental factors, the genomic factors as well as the interventions influencing smoking cessation (SC) and (2) to develop a working model incorporating the different factors influencing SC.

Methods Two systematic reviews were conducted using articles in English from the Cochrane library, PubMed and HuGENet from January 2000 to September 2012: (1) a systematic review of systematic reviews and meta-analyses and (2) a systematic review of original research for genomic factors. The proposed working model was developed by making use of previous models of SC and applying iterative process of discussion and re-examination by the authors.

Results We confirmed the importance of the four main factors influencing SC: (1) environmental factors, (2) genomic factors, (3) gene-environment interactions (4) evidence-based interventions. The model demonstrates the complex network of factors influencing SC.

Conclusion The working model of SC proposed a global view of factors influencing SC warranting future research in this area. Future testing of the model will consolidate the understanding of the different factors affecting SC and will help to improve interventions in this field.

INTRODUCTION

Smoking is a major public health problem worldwide and the most preventable cause of morbidity and mortality. Five million people die from tobacco consumption every year [94]. Successful smoking cessation (SC) reduces the incidence of comorbidities as well as mortality among smokers [95–97].

Smoking behaviour (smoking initiation, dependence and cessation) is influenced by a high number of both genomic and non-genomic factors. According to twin studies, around 60 to 70% of the variance of nicotine dependence is explained by inherited factors [98, 99]. Genomic factors are explored in 3 types of studies: candidate association studies, genome-wide association studies (GWAS) and 'omics' studies (including transcriptomic, proteomic, and metabolomic studies). To assess the correlation of a particular locus with smoking behaviour in candidate association studies, two main hypotheses are used: (1) the cascade theory of reward and (2) the nicotine metabolism. First, based on the 'cascade theory of reward', a number of target genes can be identified that are related to the central behaviour control system. Many different neurophysiological processes are controlled by the modulation of four interlinked compounds: serotonin, opioids, gamma-aminobutyric acid (GABA), and dopamine. In short, serotonin (5-HT) release activates opioids secretion which inhibits the release of GABA. Due to GABA decrease, the release of dopamine is stimulated [100]. Genetic changes in the pathways controlling the synthesis of these compounds may be involved in the susceptibility to smoking. Second, modifications in genes that influence the 'nicotine metabolism' may also have an impact on smoking behaviour as they define the degradation and the level of nicotine in the body.

Non-genomic factors, also called environmental factors, encompass a broad range of aspects, including cultural, economic, psychological, nutritional, and social factors [101]. SC is reported to be influenced by sociodemographic characteristics, psychological factors and policy decisions [102, 103].

Epigenetic mechanisms, such as methylation, histone modification, miRNAs, and chromatin remodelling are induced by tobacco components. Up to now, epigenetic studies have mostly focused on the development of smoking related disorders, such as lung cancer, chronic obstructive pulmonary disease and cardiovascular disease [104]. However, some methylations appear to be correlated with smoking status and increase with smoking intensity (e. g. *RARB* and *FHIT*) [104].

Every year, around 40% of smokers try to quit smoking for at least one day. Unfortunately, most of them relapse due to nicotine dependence [105, 106]. This high rate of relapse supports the need to further improve care for people who want to stop smoking. In the last decades, plenty of interventions have been implemented in SC (e. g. pharmacotherapy and counselling). However, the rate of relapse after SC is still high. A knowledge synthesis of all factors and interventions influencing SC will give a more global view of this public health problem. A visual overview of the current knowledge, through the development of a conceptual or a working model,

is particularly relevant. This visual overview illustrates the complex relationships at multiple levels (e. g. psychological, biological and macro-social level) and the relation between the various factors that are involved [107]. Each factor influencing SC is a single component of a causal mechanism, but a given disorder or trait (e. g. SC) may be the result of more than one causal mechanism. Most causes of SC are neither sufficient nor necessary [108].

The models on SC that were developed up until now had 4 different focuses: (1) application of a general model of behavioural changes on SC [109], (2) impact of tobacco policies [102], (3) social classes [110], and (4) environmental factors and interventions [103, 111]. These models mostly targeted specific populations (e. g. women, adolescents) and environmental factors. Only one model considered genomic factors focusing mainly on pharmacogenetics [111]. However, the conceptual model assessing tobacco use and dependence includes both non-genomic and genomic factors [112]. The introduction of genomic factors led to a more comprehensive and global model of SC and thus improved the knowledge of both providers and smokers.

In this paper, we present the results of a literature review on factors involved in SC. In the last decade, the dramatic increase of the number of molecular analyses at the genetic level has led to recent GWAS and other 'genetic test'-based approaches that could shed a new light on the role of particular factors in SC. The aims of this paper were (i) to review the environmental and the genomic factors as well as the interventions influencing SC reported in the recent literature, and (ii) to develop a working model of SC integrating all relevant factors based on the existing data and the current models.

METHODS

In a first step, we conducted 2 systematic reviews of factors influencing SC: the first one based on systematic reviews and meta-analyses (*the main review*), the second one on original research (*review on genomic factors*). In the latter review, the rationale to focus specifically on genomic factors was based on the hypothesis that most genomic studies were new and, therefore, more often missed out in reviews that were not very recent. Both systematic reviews were used to develop our working model of SC.

Literature review of factors influencing SC

Outcome

SC was defined in the Medical Subject Heading (MeSH) index as the discontinuation of the habit of smoking, the inhaling and exhaling of tobacco smoke. This could be self-reported and/or biochemically verified.

Eligibility criteria

For the main review, eligible studies consisted of systematic reviews and meta-analyses published in English. The target population included adults from the general population. Studies had to be prospective with a follow-up period of at least 6 months.

The review of genomic factors was restricted to prospective studies in English with a 6-months follow-up period. To avoid confounding, we restricted this review to populations of European ancestries. People from the same ethnicity share allelic variations of their genes. Consequently, frequencies of genetic variants differ among different ethnicities [57].

Articles restricted to a population with a specific disorder (e. g. alcohol addiction or cardiovascular disease) other than smoking were excluded from both reviews. This was also the case for hospitalised patients and pregnant women.

Search strategy (Figure 3.1)

For the main review, we searched the Cochrane library and PubMed for articles from January 2000 until September 2012 using the term: 'smoking cessation' (PubMed search in Supplementary material - Chapter 3). For the review on genomic factors influencing SC, we searched in PubMed for the same period of time using the terms: 'smoking cessation', 'genetic', 'genomic', 'transcriptomic', 'proteomic', 'metabolomic', 'methylome', and 'epigenome' (PubMed search in Supplementary material - Chapter 3). In addition, we searched for 'smoking cessation' in HuGENet, and we manually reviewed the reference lists of relevant articles and reviews.

One author (SDV) screened the title and electronic abstract identified by the search for relevance and eligibility criteria. Articles that passed this initial screening were further examined.

To make analyses manageable, choices had to be made in the eligibility criteria and the search strategy. Nevertheless, all factors influencing SC were expected to be included in this systematic review, and we presume that the inclusion of other databases would not have contributed to the identification of other factors.

Data extraction

Factors influencing SC were extracted from reviews and then classified, based on existing models, as follows [102, 103, 109–111]: smoking behaviour, demographic factors, social factors, socioeconomic status (SES), psychological factors, biological factors, health factors, genomic factors, and interventions.

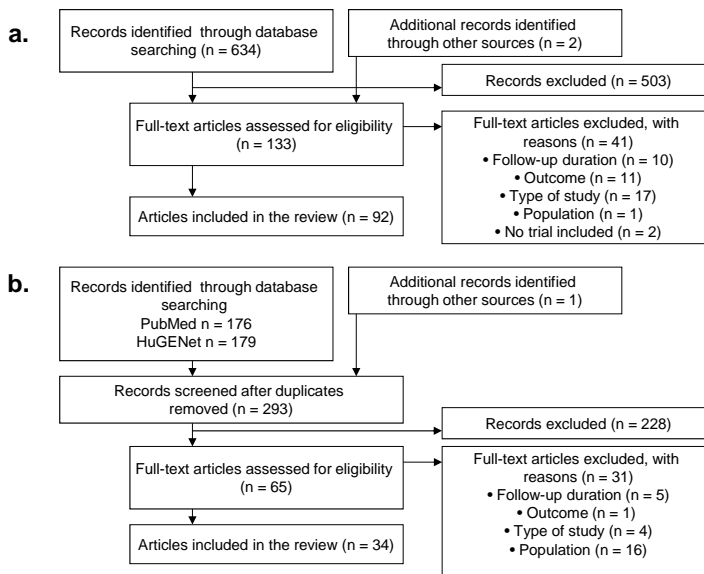
For the interventions, we distinguished three target levels: the individual, the neighbourhood (e. g. household or workplace) and the society (e. g. community or national level). Target levels interact with each other and are at the same time influenced by environmental and genomic factors.

For the factors identified in the meta-analyses, the overall risk ratio (RR) or odds ratio (OR), the 95% confidence interval (CI) and the I^2 statistics (indicating the level of heterogeneity) were extracted (Table 3.1).

From eligible papers on genomic factors of SC, we extracted information, where available, on the study design, inclusion and exclusion criteria, sample size, interventions, characteristics of participants, outcome length of follow-up, and Hardy-Weinberg equilibrium (HWE). The HWE assesses the consistency of the genotype frequency of a specific single nucleotide polymorphism (SNP) and other genetic variants (e. g. copy number variation) in the population from generation to generation.

Model formulation

Building upon the classification of factors extracted from the literature review, we developed the working model of SC (Figure 3.2). The development of this working model was an iterative process based on existing models of SC and discussion and re-examination by the authors.



(A) Flow chart of the study selection process of factors influencing SC in reviews, meta-analyses and guidelines. (B) Flow chart of the study selection process of genomic factors influencing SC in original studies.

Figure 3.1: Flow chart of the study selection process

RESULTS

Description of studies

Regarding the main review, among the 636 publications screened in the Cochrane library, PubMed and hand search, 92 met our inclusion criteria (Figure 3.1A.). None of the systematic reviews and meta-analyses discussed genomic factors influencing SC. Actually, meta-analyses mainly assessed the effect of interventions on SC. The overall results (OR, RR and 95% CI) of the meta-analyses for the different categories of factors are presented in Table 3.1.

Regarding the systematic review of genomic factors influencing SC, out of 293 publications, 34 studies met our inclusion criteria (Figure 3.1B.). Four were based on GWAS, and the other 30 were genetic association studies. None of the selected studies reported an 'omics' association with SC.

Table 3.1: Overall results of the selected meta-analyses

VARIABLE	RR/OR	95% CI	FOLLOW-UP	REF.
Environmental factor (Individual level)				
Gender (male versus female)	1.33 ^a	[0.91 – 1.95]	≥ 6 m	[113]
Low income (female)	1.28 ^b	[0.96 – 1.72]	≥ 6 m	[114]
Low income (male)	1.58 ^b	[0.96 – 1.72]	≥ 6 m	[114]
Higher cotinine level	0.80 ^a	[0.79 – 3.14]	≥ 6 m	[113]
Smoking within 30 minutes after waking up	0.40 ^a	[0.63 – 0.92]	≥ 6 m	[113]
Not having other smokings in the household	1.43 ^a	[0.25 – 0.62]	≥ 6 m	[113]
Longest previous quit attempt (female)	1.23 ^a	[1.25 – 1.65]	≥ 6 m	[113]
Longest previous quit attempt (male)	1.09 ^a	[0.68 – 1.02]	≥ 6 m	[113]
Male initiating smoking before the age of 16 (versus later age)	2.10 ^a	[1.40 – 3.00]	≥ 6 m	[113]
Smoking reduction before cessation	2.06 ^b	[1.34 – 3.15]	≥ 6 m	[115]
Pharmacotherapy (Individual level)				
NRT	1.56 ^a	[1.16 – 2.11]	3-6 m	[116]
	1.94 ^a	[1.70 – 2.20]	6 m	[117]
	1.72 ^a	[1.61 – 1.84]	6 m	[118]
	2.06 ^{b,c}	[1.34 – 3.15]	≥ 6 m	[119]
	1.58 ^b	[1.50 – 1.66]	≥ 6 m	[120]
NRT over-the-counter	2.5 ^a	[1.8 – 3.6]	2.5-6 m	[121]
NRT (female)	1.61 ^a	[1.29 – 2.00]	6 m	[122]
	1.76 ^a	[1.48 – 2.10]	6 m	[117]
NRT (male)	2.20 ^a	[1.75 – 2.76]	6 m	[122]
	2.16 ^a	[1.80 – 2.59]	6 m	[117]
NRT gum	1.71 ^a	[1.35 – 2.21]	6-12 m	[123]
	1.66 ^a	[1.52 – 1.81]	6-12 m	[118]
	1.43 ^b	[1.33 – 1.53]	≥ 6 m	[120]
NRT inhaler	2.08 ^a	[1.43 – 3.04]	6-12 m	[118]
	1.90 ^b	[1.36 – 2.67]	≥ 6 m	[120]
NRT intranasal spray	2.27 ^a	[1.61 – 3.20]	6-12 m	[118]
	2.02 ^b	[1.49 – 3.73]	≥ 6 m	[120]
NRT patch	1.74 ^a	[1.57 – 1.93]	6-12 m	[118]
	1.66 ^b	[1.53 – 1.81]	≥ 6 m	[120]
	1.95 ^a	[1.65 – 2.34]	6-12 m	[123]
NRT tablet	1.73 ^a	[1.07 – 2.80]	6-12 m	[118]
	2.00 ^b	[1.63 – 2.45]	≥ 6 m	[120]
NRT preloading	2.17 ^a	[1.46 – 3.22]	6 m	[124]
	1.16 ^b	[0.97 – 1.38]	6-12 m	[125]

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VARIABLE	RR/OR	95% CI	FOLLOW-UP	REF.
Bupropion	2.07 ^a	[1.73 – 2.55]	6-12 m	[123]
	1.69 ^b	[1.53 – 1.85]	6-12 m	[126]
Nortriptyline	2.03 ^b	[1.48 – 2.78]	≥ 6 m	[126]
Varenicline	2.41 ^a	[1.91 – 3.12]	≥ 6 m	[123]
	2.27 ^b	[2.02 – 2.55]	6-12 m	[65]
Cytisine	1.83 ^a	[1.12 – 2.99]	3-6 m	[127]
	3.98 ^b	[2.01 – 7.87]	≥ 6 m	[65]
Naltrexone	1.26 ^a	[0.80 – 2.01]	≥ 6 m	[128]
Clonidine	1.89 ^a	[1.30 – 2.74]	≥ 3 m	[129]
Combined therapy	2.14 ^a	[1.28 – 3.60]	6-12 m	[130]
	2.19 ^a	[1.7 – 2.8]	6-12 m	[131]
	1.54 ^b	[1.19 – 2.00]	6 m	[132]
Counselling (Individual level)				
Individual counselling	1.39 ^b	[1.24 – 1.57]	≥ 5 m	[133]
	1.20 ^{a,c}	[0.72 – 2.00]	6-9 m	[116]
	1.49 ^a	[1.08 – 2.07]	6-12 m	[134]
Group counselling	1.98 ^b	[1.60 – 2.46]	≥ 6 m	[135]
	1.76 ^a	[1.11 – 2.93]	6-12 m	[134]
Telephone counselling	1.37 ^{b,c}	[1.26 – 1.50]	≥ 6 m	[136]
	1.58 ^a	[1.15 – 2.29]	6-12 m	[134]
Call-back counselling	1.41 ^{b,c}	[1.27 – 1.57]	6-12 m	[137]
Motivational interviewing	1.35 ^a	[1.02 – 1.78]	≥ 6 m	[138]
	1.45 ^a	[1.14 – 1.83]	1-12 m	[139]
	1.70 ^{b,c}	[1.32 – 2.21]	≥ 5 m	[140]
Brief advice	1.74 ^{b,c}	[1.37 – 2.22]	≥ 5 m	[140]
	1.47 ^b	[1.24 – 1.75]	≤ 12 m	[141]
Intermediate advice	1.71 ^{b,c}	[1.39 – 2.09]	≥ 5 m	[140]
Intensive advice	1.60 ^{b,c}	[1.13 – 2.27]	≥ 5 m	[140]
Counselling by provider (Individual level)				
Counsellor	1.82 ^b	[0.84 – 3.96]	≥ 6 m	[142]
Trained professional	1.60 ^a	[1.26 – 2.03]	≥ 6 m	[143]
Physician	1.76 ^b	[1.58 – 1.95]	≥ 6 m	[144]
	1.87 ^b	[1.42 – 2.45]	≥ 6 m	[142]
Nurse	1.28 ^{b,c}	[1.18 – 1.38]	≥ 6 m	[145]
	1.45 ^{a,c}	[1.17 – 1.80]	≥ 6 m	[146]
	1.76 ^b	[1.21 – 2.57]	≥ 6 m	[142]
Nurse - High intensity	1.28 ^{b,c}	[1.18 – 1.39]	≥ 6 m	[145]
	1.46 ^{a,c}	[1.12 – 1.89]	≥ 6 m	[146]
Nurse - Low intensity	1.27 ^b	[0.99 – 1.62]	≥ 6 m	[145]
	1.43 ^a	[0.96 – 2.14]	≥ 6 m	[146]
Psychologist	1.94 ^b	[1.04 – 3.62]	≥ 6 m	[142]
Other intervention (Individual level)				
Biomedical risk assessment (CO measure + spirometry)	2.45 ^a	[0.73 – 8.25]	≥ 6 m	[147]
CO measure	1.07 ^a	[0.83 – 1.39]	≥ 6 m	[147]
	1.06 ^b	[0.85 – 1.32]	6-12 m	[148]
Aversive therapy	1.98 ^a	[1.36 – 2.90]	≥ 6 m	[149]
	4.26 ^a	[1.26 – 14.38]	6-12 m	[150]
Acupuncture	3.53 ^{a,c}	[1.03 – 12.07]	6-12 m	[150]
	1.79 ^b	[0.98 – 3.28]	6-12 m	[151]
Hypnotherapy	4.55 ^a	[0.98 – 21.01]	6-12 m	[150]
Web-based intervention	1.93 ^b	[1.44 – 2.60]	6 m	[152]
	1.93 ^b	[1.27 – 1.64]	3-12 m	[153]
Minimal clinical intervention	1.50 ^a	[0.84 – 2.78]	6-12 m	[134]
Self-help intervention	1.28 ^b	[0.89 – 1.82]	≥ 5 m	[142]
	1.08 ^b	[0.99 – 1.17]	6-12 m	[154]
Written self-help material	1.59 ^{b,c}	[1.22 – 2.07]	≥ 5 m	[140]
Genetic notification	1.55 ^b	[1.06 – 2.21]	≤ 6 m	[93]
	1.87 ^a	[1.20 – 2.92]	≤ 6 m	[155]

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VARIABLE	RR/OR	95% CI	FOLLOW-UP	REF.
	0.68 ^a	[0.57 – 1.30]	≥ 6 m	[155]
	1.03 ^b	[0.64 – 1.65]	≤ 12 m	[93]
Intervention (neighbourhood level)				
Partner support	0.99 ^b	[0.84 – 1.15]	6-9 m	[156]
	1.08 ^a	[0.81 – 1.44]	6-9 m	[157]
Incentive in workplace	1.44 ^a	[1.01 – 2.01]	6 m	[158]
Workplace interventions	2.03 ^a	[1.42 – 2.90]	6 m	[159]

Reference group for the risk ratios and odds ratios were placebo or no intervention; ^a OR Odds ratio; ^b RR Risk ratio; ^c heterogeneity in the analyses ($I^2 \geq 50\%$)

Environmental factor 1: Smoking behaviour

Factors determining smoking behaviour such as nicotine dependence or past cessation attempts are leading factors influencing the success of SC. Men initiating smoking before the age of 16 have a reduced SC rate in comparison to men starting at a later age (OR = 2.10, CI = 1.40-3.00) [113, 160, 161]. Higher nicotine dependence, indicated for example in those who start smoking within 30 minutes after waking up, reduces SC success [113, 162]. Moreover, a longer duration or a higher number of past cessation attempts is positively associated with SC [113, 162]. Compared to abrupt cessation, smoking reduction doubles the probability of SC [115, 161]. A positive association with SC is reported for intention-to-quit smoking and the confidence level in quitting [160, 162–164]. Negative beliefs about smoking and health benefit expectancy increase cessation [160–162]. By contrast, a negative impact on SC is reported when enjoying smoking [162] and having easy access to cigarettes [160, 161].

Environmental factor 2: Demographic factors

Gender does not influence SC (OR = 1.33, CI = 0.91-1.95) [113], despite hypotheses that women might have lower SC rates due to, for example, more weight concerns or emotional sensitivity [113, 160, 162]. Regarding age, although in the review of Vangeli *et al.* [162], 5 studies did not yield significant results, two other studies presented a positive association between age and SC. Gender and age might be moderated by other factors such as e. g. menstrual phase, age at smoking initiation and mortality.

Environmental factor 3: Social factors

Social factors are especially important due to transmission of social norms between peers. In most studies, being married, couple living together [113, 160, 162], or having children at home [160–162] has no impact on SC. However, living with both biological parents is suggested to enhance SC [160]. Not having friends who smoke

and the absence of other smokers in the household are positively associated with SC [113, 160, 161].

Environmental factor 4: Socioeconomic status (SES)

SES is mainly assessed through education, employment (e. g. employed versus un-employed, blue versus white collar) and income. A lower SES may be associated with reduced SC due to limited information about health concerns, lower access to SC therapy, increased risk of daily stress, and weaker social unacceptability of smoking [103]. However, the relation between SC and the 3 aforementioned socioeconomic factors does not prove to be statistically significant in most studies [161, 162]. Even a meta-analysis was not able to demonstrate an impact of low income on SC either in men (RR = 1.58, CI = 0.79-3.14) or in women (RR = 1.28, CI = 0.96-1.72) [114].

Environmental factor 5: Psychological factors

Psychological factors such as anxiety (OR 2.2 = for males and 2.6 for females) are likely to reduce SC ability [113]. By contrast, both self-efficacy and intrinsic motivation to quit smoking improve SC [113, 162, 165]. Therefore, mood and stress management programmes are thought to improve SC [166].

Environmental factor 6: Biological factors

Smoking is known to increase energy expenditure and to reduce appetite. Therefore, a higher weight and more weight concerns may lower SC [166]. Weight concern is linked to psychological and biological factors. A low physical activity is also negatively associated with SC [161]. For women, choosing the target quit day in relation to the menstrual phase, more specifically during the follicular phase, improves SC [166].

Environmental factor 7: Health factors

Health factors, such as alcohol addiction or depression, may have an important impact on SC due to a reduction of the dopamine release. Indeed, smoking induces the release of dopamine. Alcohol use is negatively associated with SC [113, 161]. A better perceived mental and physical health status enhances SC [160, 161]. However, in most studies there is no significant relation with improved knowledge of health risks associated with smoking [161, 162].

Table 3.2: Genes influencing SC and reported interactions with interventions

GENE	GENETIC VARIANT	EFFECT ON CESSATION	REF.
Serotonin			
SLC6A4	5-HTTLPR	No effect	[83, 167–169]
		Interaction with bupropion	[83]
	rs25531	No effect	[83]
	Stin2 (intron 2 VNTR)	No effect	[83]
TPH1	A779C	No effect	[168]
HTR1A	C-1019G	No effect	[168]
Opioids			
OPRM1	A1148G	A1-allele: ↑ cessation	[71]
		G-allele (women): ↑ cessation (EOT of NRT)	[72]
		AA genotype (men): ↑ cessation	[72]
		Interaction with NRT patch	[72]
Dopamine			
DRD2	Taq1A	A1-allele: ↓ cessation	[75]
		AzA2-genotype: ↓ cessation (among CYP2B6 1459 CC carriers)	[74]
		No effect	[73, 77, 87, 170–172]
		Interaction with bupropion and rimonabant	[73, 77, 172]
	Taq1B	No effect	[75]
	-141C	Del-Allele: ↑ cessation (EOT)	[76]
		No effect	[75, 76]
	C957T	Interaction with bupropion	[76]
		TT-genotype: ↑ cessation	[76]
		No effect	[75, 76]
	VNTR	Long-allele: ↓ cessation	[77]
		No effect	[173]
SLC6A3		Interaction with NRT and bupropion	[77, 173]
	C-521T	No effect	[77]
	VNTR	9/9 and 9/10-genotype: ↑ cessation (EOT) (among DRD2 Taq1 A2/A2 carriers)	[87]
		No effect	[74]
COMT	Val ¹⁰⁸ /158Met	Met/Met-genotype: ↑ cessation	[78, 174]
		No effect	[175, 176]
		Interaction with NRT	[175]
	rs165599	No effect	[176]
	rs737865	No effect	[176]

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GENE	GENETIC VARIANT	EFFECT ON CESSATION	REF.
Nicotinic receptors			
<i>CHRNA3</i>	rs1051730	No effect	[79]
<i>CHRNA4</i>	rs1044396	No effect	[177]
	rs2273504	No effect	[177]
	rs2236196	No effect	[177]
	rs2273502	No effect	[177]
<i>CHRNA7</i>	rs2133965	No effect	[177]
	rs4779969	No effect	[177]
<i>CHRNB2</i>	rs2072661	A-allele: ↑ cessation	[80]
		GG-genotype: ↓ cessation	[81]
		No effect	[177]
	rs2072660	No effect	[177]
Nicotinic metabolism			
<i>CYP2B6</i>	* 6	No effect	[82]
	C1459T	Interaction with bupropion	[82]
		T-allele: ↓ cessation (EOT)	[70]
		No effect	[74]
Other			
<i>GALR1</i>	rs2717162	C-allele: ↓ cessation	[178]
		Interaction with treatment (NRT, bupropion)	[178]
<i>HINT1</i>	rs3852209	T-allele: ↑ cessation	[179]
	rs2278060	No effect	[179]
<i>ARRB2</i>	rs1045280	No effect	[179]
	rs2036657	No effect	[179]
	rs3786047	No effect	[179]

EOT End of Treatment; NRT Nicotine Replacement Therapy; ↑ increased; ↓ decreased

Genomic factors (Table 3.2 and Table 3.3 in Supplementary material - Chapter 3)

Regarding the cascade theory of reward, no study reports a significant impact of serotonin and GABA on SC [83, 167–169]. In opioids, contradictory results are obtained concerning the *OPRM1* A118G variant. One study reports that the G-allele improved SC [71]; another confirms this in women but reports an increased SC in men with AA-genotype [72]. Dopamine influences SC through some variants, but some results could not be replicated in different studies [73, 75–77, 87, 170–173, 175, 176]. The A1-allele of *DRD2* Taq1A [75] and the long-allele of *DRD4* VNTR [77] appear to reduce SC. By contrast, the Del-allele of *DRD2*-141C [76], the TT-genotype of *DRD2* C957T [76], the 9-repeats of *SLC6A3* VNTR [87] and the MetMet-genotype of *COMT* Val^{108/158}Met [78, 174] improve SC. Gene-gene interactions are reported between *DRD2* Taq1A-*SLC6A3* VNTR [87] and *DRD2* Taq1A-*CYP2B6* C1459T [74]. The variant *CHRNA2* rs2072661, which encodes for a nicotinic receptor is associated with SC [80, 81]. However, this finding is not replicated in the study of Spruell *et al.* [177].

Regarding the nicotine metabolism, only one study reports a significant association with *CYP2B6**6 in a population of European ancestry [70].

Different genes that belong neither to the cascade of reward nor to the nicotine metabolism are also associated with SC: the C-allele of *GALR1* (rs2717162) decreases SC [178] and the T-allele of *HINT1* (rs3852209) increases SC at 6-month follow-up [179].

In none of the GWAS [180–183] a significant association was found (level of significance in GWAS is $\alpha = 5 \times 10^{-8}$). Also in three (non-GWAS) studies that included many different SNPs, no significant result was found after correction for multiple testing [184–186].

Interventions

Individual level

At the individual level, two kinds of interventions can be distinguished: (1) pharmacological interventions and (2) non-pharmacological interventions.

Meta-analyses (Table 3.1) indicate that various pharmacological treatments improve SC: nicotine replacement therapy (NRTs), substitutes of nicotine [117–120, 123], Bupropion and nortriptyline (antidepressants) [123, 126, 129, 187–189], and varenicline, cytisine and mecamylamine (agonists of the nicotine acetylcholine receptors) [65, 123, 127, 190, 191]. Naltrexone, an opioid antagonist, has no significant impact on SC [128]. Cannabinoid type I receptors (rimonabant and taranabant) appear to improve SC at 12-month follow-up, but no result is observed at 6-month follow-up [192].

Different types of non-pharmacological interventions indicate a substantial improvement in SC: individual counselling (although in contrast with 2 other meta-analyses, Coleman *et al.* [116] did not report any benefit of individual counselling,

$I^2 = 68\%$) [116, 133, 134], group counselling [134, 135], web-based interventions [153, 193–195], telephone counselling (with pro-active telephone counselling being even more effective than simple telephone counselling) [134, 136, 137, 196, 197], motivational interviewing [138–140, 198], and genetic notification of smoking related disease risk [93, 155]. Other interventions described in the meta-analyses do not demonstrate statistical significant differences. It concerns: self-help material [142, 154], biomedical risk assessment (e.g. CO or spirometry measurement) [147, 148, 199], incentive-based interventions [158, 193, 200], and hypnosis (even if men were more likely to respond than women) [150, 201, 202]. Positive associations are observed for acupuncture [150, 151], increased physical activity [161, 166, 203, 204] and aversive therapy [149, 150], but the results are not significant. Improvement of SC is also related with the type of provider; e.g. physicians nearly doubled SC in comparison to control [142, 144, 205] and this is also the case for nurses [142, 145, 146], psychologists [142] and trained health professionals [143].

Combining pharmacological and/or non-pharmacological interventions appears to improve SC in comparison to no intervention [130–132] or to monotherapy (RR 1.54, CI 1.19–2.00) [132].

Genetic factors may influence the response to an intervention and, consequently, the success in SC. Some gene-treatment interactions have been reported in European ancestries. Interactions with NRTs are observed for *OPRM1* A118G [72], *DRD4* VNTR [77], *COMT* Val¹⁰⁸/Met¹⁵⁸ [175], *CHRNA2* rs2072661 [81] and *GALR1* rs2717162 [178]. Bupropion interacts with *SLC6A4* 5-HTTLPR [83], *DRD2* TaqIA [73, 74], *DRD2*-141C [76], *DRD4* VNTR [173], *CYP2B6**6 [82], and *GALR1* rs2717162 [178]. Finally, rimonabant interacts with *DRD2* Taq1A [172] (Table 3.2).

Neighbourhood level

At the neighbourhood level, only non-pharmacological interventions are available. Enhancing partner support does not demonstrate any efficacy in improving SC [156, 157]. However, the use of a buddy (when someone is appointed to support a smoker) may be of some benefit in the context of a smokers' clinic [206]. Home smoking restrictions have a positive impact on SC [162]. At workplace, no conclusion can be drawn regarding the efficacy of the interventions, due to their heterogeneity of the interventions [207].

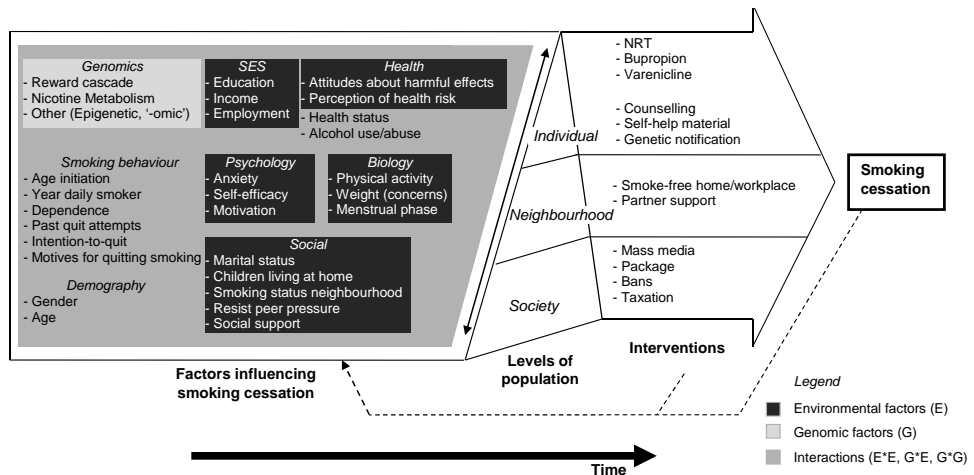
Society level

Policy-makers launch different actions to reduce smoking prevalence at the society level. Increased taxation [161, 208] and mass media campaigns [161, 208–210] appear to improve SC. However, in lower socioeconomic groups, mass media are more effective when also other interventions are included such as free NRT and telephone counselling or when there is a policy to change the social and structural context of cigarette use [210]. Other interventions such as bans (e.g. banning advertising and

sponsorship or smoking in public places) [208, 211] and health warnings [208] could help to modify SC through health belief modification.

Smoking cessation working model

Based on the literature review, we developed a working model of SC consisting of 3 components: (1) factors influencing SC, (2) interventions and (3) SC (Figure 3.2). Each factor in the two first components may influence SC success. Therefore, when attempting to quit smoking all these factors and interventions need to be considered.



Based on the literature review, we developed a conceptual model of SC consisting of 3 components: (1) factors influencing SC including both genomic and non-genomic factors and interactions (the different factors are interacting as indicated by the light grey background), (2) interventions based on the 3 levels of population (individual, neighbourhood and society level) and, (3) SC (the actual outcome). Interventions are always part of the success of SC. At least unconsciously, interventions at the society level play a role as they are part of our daily life. These 3 components are linked together (indicated by the different arrows) and evolve with time (indicated by the timeline at the bottom of the figure). SES, socioeconomic status; NRT, nicotine replacement therapy.

Figure 3.2: Working model of Smoking Cessation

(1) Factors influencing SC – Eight dimensions are included: smoking behaviour, demography, SES, psychology, social situation, health, biology, and genomics. The eight dimensions cover all factors influencing SC described before, except for the interventions. They constantly evolve and influence one another (indicated by the light grey box covering all factors). For example, smoking induces epigenetic modifications (e. g. methylations) which could influence health [212].

(2) Interventions – Three target levels are defined to classify the interventions: the individual, neighbourhood and society level. Even if smokers do not want to receive specific interventions, some interventions based on the neighbourhood and society level (e. g. smoke-free workplace and taxation) are present in the daily life

of smokers. Interventions are the most important link between factors influencing SC and SC (represented by the broad arrow).

(3) SC – The actual outcome. SC dynamically interacts with the previous boxes (indicated by the dashed arrows). The success of SC by an individual depends on the different factors influencing SC, neighbourhood and the society in which he lives (e. g. social unacceptability, availability of treatments and bans).

Additionally, the model also takes into consideration the evolution of the environmental and the genomic factors and the interventions over time (represented by the time-line).

DISCUSSION

To our knowledge, this study is the first to propose a literature review-based working model of SC taking into account environmental factors, genomic factors and interventions. Compared to other models focusing on specific factors such as environmental factors [103] or policy [102], our model is more comprehensive.

Conceptual models are useful for summarising and integrating knowledge. The model demonstrates the importance of research that studies the impact of environmental factors, genomic factors and interventions on SC in the general population in an integrated way. It assumes that SC is a dynamic phenomenon depending on many factors, including interventions at the 3 population levels that we described and environmental factors. For example, a health campaign to stop smoking (intervention) leads to changes in the social acceptability (environmental factor), which could further influence the use of interventions and thus also SC itself.

Our actual model focused on the general population. In a further step, it would be interesting to adapt the model to more specific populations such as smokers with comorbidity or mental illness. The major factors influencing SC will probably be the same, but the effect size might differ. For example, in pregnant women, social pressure will most likely be an important factor. Moreover, for some populations, additional factors appear. In hypertensive smokers, for example, these could be e. g. treatment of hypertension and other cardiovascular risks.

Factors included in the working model of SC were quite similar to the one used in the integrative model of tobacco use and dependence developed by Swan *et al.* [112] in 2003. In that model, seven dimensions were used to consider tobacco use and dependence: (1) environmental risk factors (e. g. SES and peer smoking), (2) vulnerability factors (e. g. family history of smoking and early smoking experiences), (3) tobacco use trajectory features (e. g. speed of transition to regular use and use of other tobacco substances), (4) motivations (e. g. psychosocial and addictive), (5) nicotine dependence (e. g. the Fageström test for nicotine dependence and nicotine metabolism), (6) nicotine reinforcement (e. g. positive reinforcement and relief from withdrawal), and (7) genetic risk factors in relevant biological pathways (e. g. dopamine and serotonin). Although the seven dimensions used in the integrative model of tobacco use and dependence were classified in a different way than in the

working model of SC, the included variables were mostly the same. The main difference between the two models is the 'interventions' component. This component is not included in the model of tobacco use and dependence, as dependence does not involve an intervention.

Some factors in the working model could be considered as moderators or confounders (e. g. age could be a confounder in the relation between age at smoking initiation and SC). However, we decided that all factors should be taken into account, as they are part of the causal mechanism leading to SC [108]. A future statistical validation of the model could help to verify this.

A statistical validation of the model is indeed needed. This validation should assess the interactions between the different factors and the size of the effect of each factor. A way to validate this model would be to develop a prospective cohort of smokers that are willing to stop smoking and to observe them for at least 6 months after having stopped. The statistical technique to deal with this is structural equation modelling, in which the number of observations is based on the number of variables. In the proposed working model, around 40 variables are included, which implies that the minimum number of observations should be 820. The strength of that kind of model would be that it allows evaluating the effect of each single factor and consequently quantifying the effect of the components [108]. Model testing through simulations under different conditions will also help in understanding complex system behaviour in an unexpected fashion [107].

We observe in Table 3.1 that most significant factors influencing SC had a RR or an OR between 1.26 and 2.56. This indicates that none of these factors had a predominant effect on SC, and therefore, all factors may be taken into account when someone wants to quit smoking. Probability helps in the assessment of the contribution of each single component of a causal mechanism. Therefore, it gives a better approximation and more support in public health interventions [213]. However, the interpretation of probabilities often reflects our ignorance about the causal mechanism of a disorder or a trait [213].

Regarding the selection of genomic studies, we focused on European populations because allele frequencies differ among ethnicities. For example, *CYP2A6**2 and *CYP2A6**3 alleles are much more frequent in Asian than in Caucasian populations [214]. Environmental factors are also modified by ethnicity; this is e. g. the case for tobacco use, perception of health risk, or social unacceptability [215]. However, in non-genomic studies, ethnicity is usually not considered as a factor of interest; either mixed ethnicities are used or there is no information on it.

A positive correlation has been reported between the time since quitting and methylation at two

different loci (*F2RL3* and *GPR15*), even though no epigenetic study reported an effect on SC. Methylations are found to be rapidly reversible, and therefore, remethylations are suggested after SC [31]. Not only exposure to smoking during childhood and adulthood might influence smoking behaviour. Also exposure to smoking during intra-uterine life is known to induce methylations that increase the risk of disorder

ders in later life [216]. These methylations might also influence smoking behaviour in a later stage.

The link between psychology and genomic factors influencing SC could be enhanced as the same genomic pathways are implicated. Munafo *et al.* [217] reported in their meta-analysis that: (i) a genetic variant of the serotonin (5-HTTLPR) was associated with avoidance and aggression traits; (ii) dopamine genes were associated with approach traits (*DRD3*) and avoidance traits (*DRD4*). This supports the hypothesis that some personalities are more at risk of having problems to quit smoking.

Multiple interactions (gene-gene, gene-environment and environment-environment interactions) influence individual chances to achieve SC. Because of these complex interactions and the association of the same genomic and environmental factors with other disorders, it is still difficult to recognise the influence individual genes have on SC. Even if some studies demonstrated an association of genomic factors with SC, there is still a lack of replication in the literature. Moreover, up to now, only a few studies assessed the multiple interactions (environment-environment, gene-gene and gene-environment interactions) influencing SC. For example, gene-tobacco control policy interactions have already been suggested in tobacco use. The evolution of tobacco control policies moderates tobacco use by individual genotype [218]. This observation might be applied to SC in the future.

One important limitation of our research is that we restricted the search to prospective studies including 6-month follow-up. This criterion reduced the number of included publications on genomic studies because most original papers and most meta-analyses included retrospective and cross-sectional studies. The same applied for interventions at the society level. For example, even if experts believe that plain packaging will lead to a decline in smoking prevalence [219], currently no systematic review studied the impact of this on SC.

Implications for practice and research

This review presents various factors influencing SC and provides a framework to further analyse factors influencing SC. Future studies should analyse the interactions and the intensity of the relationship between the different variables of the working model. It will be necessary to validate the model and to assess its quality. Working models are dynamic and constantly changing by the emergence of new evidence. Therefore, the assessment of the quality of this model and the emergence of new developments (e. g. epigenetics, proteomics or vaccines) will lead to modification.

We believe that, in the future, the working model of SC may help to have a global view of factors influencing SC. This will be a key to target interventions on individual smokers and, consequently, improve SC success. The proposed model may also be helpful in the elaboration of future research, aiming to understand the different mechanisms linked to SC.

SUPPLEMENTARY MATERIAL – CHAPTER 3

*PubMed search***PubMed search: Factors influencing smoking cessation**

The research on Pubmed was realised using the following code:
(smoking cessation [mesh major topic])
Date 27th of September 2012 – N = 568

Filters

- Species: Human
- Languages: English
- Article types: Meta-analysis and Systematic review
- Date of publication: Since January 2000

PubMed search: Genomic factors influencing smoking cessation

The research on Pubmed was realised using the following code:
(smoking cessation[mesh major topic]) and ((genetic) OR (proteomic) OR (transcrip-
tomic) OR (genomic) OR (metabolomic) OR (methylome) OR (epigenome))
Date 27th of September 2012 – N = 176

Filters

- Species: Human
- Languages: English
- Article types: Original papers
- Date of publication: Since January 2000

Table 3.3: Description of the included studies for the genomic review

AUTHOR	SAMPLE SIZE	INTERVENTIONS	SNP	HWE+	REF.
Berrettini WH, 2007	N = 436	Bupropion vs Placebo	COMT rs165599	Yes	[176]
			COMT rs737865	Yes	[176]
			COMT Val108/158Met	0.001	[176]
Collila S, 2005	N = 178	NRT patch vs NRT spray	COMT Val108/158Met	Yes	[78]
Conti DV, 2008	N = 412	Bupropion vs placebo	CHRNA3 rs1051730	Yes	[80]
David SP, 2007	N = 741	NRT vs placebo	CHRNA3 rs1051730	Yes	[80]
David SP, 2007	N = 722	Bupropion vs placebo	CHRNA3 rs1051730	Not stated	[167]
David SP, 2007	N = 183	Bupropion vs placebo	CHRNA3 rs1051730	>0.46	[73]
			DRD2 TaqIA	Yes	[74]
			DRD2 TaqIA	Yes	[74]
			SLC6A4 VNTR	Yes	[74]
David SP, 2008	N = 792	UC + NRT vs ↑ counseling + NRT	CYP2B6 C1459T	Yes	[74]
			SLC6A4 5-HTTLPR	0.61	[168]
			TPH1 A779C	>0.1	[168]
			HTR1A C-1019G	>0.1	[168]
			DRD4 VNTR	0.66	[77]
David SP, 2008	N = 720	NRT vs placebo	DRD4 C-521T	0.45	[77]
Gold AB, 2012	N = 1,217	NRT patch vs NRT nasal spray vs bupropion vs placebo	GALR1 rs2717162	0.71	[178]
Johnstone EC, 2007	N = 724	NRT patch vs NRT spray	COMT Val108/158Met	0.86	[175]
Lee AM, 2007	N = 326	Bupropion vs placebo	CYP2B6*6	>0.53	[82]
Lerman C, 2002	N = 426	Bupropion and counseling vs placebo and counseling	CYP2B6 C1459T	Not stated	[70]
Lerman C, 2003	N = 418	Bupropion vs placebo	DRD2 TaqIA	0.60	[87]
			SLC6A3 VNTR	Yes	[87]
Lerman C, 2004	N = 320	NRT patch vs NRT spray	OPRM1 A118G	0.66	[71]
Lerman C, 2006	N = 414	Bupropion vs placebo	DRD2 -141C	0.03	[76]
			DRD2 C957T	0.6	[76]
Lerman C, 2006	N = 368	NRT patch vs NRT spray	DRD2 -141C	>0.8	[76]
			DRD2 C957T	>0.8	[76]
Leventhal AM, 2012	N = 331	Bupropion vs placebo	DRD4 VNTR	Yes	[173]
Munafò MR, 2006	N = 393	NRT patch vs NRT spray	SLC6A4 5-HTTLPR	>0.1	[169]
Munafò MR, 2007	N = 710	NRT vs placebo	COMT Val108/158Met	0.75	[72]
Munafò MR, 2008	N = 796	Low behavioral support + NRT vs High behavioral support + NRT	COMT Val108/158Met	0.46	[174]
Munafò MR, 2009	N = 878	UC + NRT vs weekly support + NRT	DRD2 TaqIA	<0.01	[170]
Munafò MR, 2011	N = 692	NRT patch vs Placebo	CHRNA3 rs1051730	Not Stated	[79]
	N = 817	Low behavioral support vs High behavioral support	CHRNA3 rs1051730	Not Stated	[79]
Perkins KA, 2009	N = 156	NRT vs placebo	CHRNA3 rs1051730	0.24	[81]
Quaak M, 2011	N = 214	Bupropion vs Nortriptyline vs placebo	CHRNA3 rs1051730	0.34	[83]
			SLC6A4 5-HTTLPR	0.99	[83]
			SLC6A4 rs25531	0.99	[83]
			SLC6A4 Stin2 (Intron 2 VNTR)	0.44	[83]

Continued on next page

AUTHOR	SAMPLE SIZE	INTERVENTIONS	SNP	HWE+	REF.
Ray R, 2007	N = 374	NRT patch vs NRT nasal spray	HINT1 rs3852209	Yes	[179]
			HINT1 rs2278060	Yes	[179]
			ARRB2 rs1045280	Yes	[179]
			ARRB2 rs2036657	Yes	[179]
			ARRB2 rs3786047	Yes	[179]
Spruell T, 2012	N = 835	Low behavioral support + NRT vs High behavioral support + NRT	CHRNA4 rs1044396	Yes	[177]
			CHRNA4 rs2273504	Yes	[177]
			CHRNA4 rs2236196	Yes	[177]
			CHRNA4 rs2273502	Yes	[177]
			CHRNA7 rs2133965	Yes	[177]
Styn MA, 2009	N = 881	Cohort study	CHRNA7 rs4779969	Yes	[177]
			CHRNA7 rs207660	Yes	[177]
			CHRNA4 rs207661	Yes	[177]
			DRD2 TaqIA	Yes	[75]
			DRD2 TaqIB	Yes	[75]
			DRD2 -141C	<0.01	[75]
			DRD2 C957T	Yes	[75]
			SLC6A3 VNTR	<0.01	[75]
			DRD2 TaqIA	0.37	[171]
			DRD2 TaqIA		
Swan GE, 2005	N = 1,524	Bupropion (150mg) and ↓ counseling vs Bupropion (150mg) and ↑ counseling vs Bupropion (300mg) and ↓ counseling vs Bupropion (300mg) and ↑ counseling	DRD2 TaqIA		
			DRD2 TaqIA		
			DRD2 TaqIA		
			DRD2 TaqIA		
Wilcox CS, 2011	N = 76	Rimonabant vs Placebo	DRD2 TaqIA	Not stated	[172]
			DRD2 TaqIA		

HWE Hardy Weinberg Equilibrium; EOT End of Treatment; NRT Nicotine Replacement Therapy; UC Usual care; SNP Single Nucleotide Polymorphism; Yes in HWE indicated that the SNP did not deviate from HWE; + p-value; ↑ increased; ↓ decreased

4

GENETIC SIMILARITIES BETWEEN COMORBIDITIES OF TOBACCO USE DISORDERS: AN EXPLORATORY STUDY

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Sander Ouburg

Submitted.

ABSTRACT

Background Tobacco use disorder (TUD), as defined by the tobacco use to the detriment of a person's health or social functioning, is associated with various disorders. We hypothesised that mutual variation in genes may partly explain this link.

Objectives The aims of this study were to make a non-exhaustive inventory of the disorders using (partially) the same genetic pathways as TUD, and to describe the genetic similarities between TUD and the selected disorders.

Methods We developed a 3 stage approach : (i) selection of genes influencing TUD using Gene2MeSH and Ingenuity Pathway Analysis (IPA), (ii) selection of disorders associated to the selected genes using IPA and (iii) genetic similarities between disorders associated to TUD using Jaccard distance and cluster analyses.

Results Fourteen disorders and thirty-two genes met our inclusion criteria. The Jaccard distance between pairs of disorders ranged from 0.00 (e.g. oesophageal cancer and malignant hypertension) to 0.45 (e.g. bladder cancer and addiction), a lower number Jaccard distance indicating higher similarities between two disorders. Two main clusters of genetically similar disorders were observed, one including coexisting disorders (e.g. addiction and alcoholism) and the other one with side-effects of smoking (e.g. gastric cancer and malignant hypertension).

Conclusions This exploratory study partly explains the potential genetic components linking TUD to other disorders. Two principle clusters of disorders were observed (i) coexisting disorders of TUD and (ii) side-effects of TUD disorders. Further deepening of this observation in a real life study should allow to strengthen this hypothesis.

INTRODUCTION

Tobacco use disorder (TUD) is the greatest cause of preventable death in developed countries and it is a well-known risk factor for many other disorders. As defined in the Medical Subject Heading (MeSH) index [220], TUD is the "*Tobacco used to the detriment of a person's health or social functioning. Tobacco dependence is included*".

TUD is influenced by multiple environmental as well as genetic factors. Environmental factors in genetic medicine encompass a broad range of factors (e.g. cultural, social, and/or economic factors). The genetic factors belong to two main groups: pathways related to nicotine metabolism and the cascade theory of reward. The most important genes influencing nicotine metabolism are cytochrome P450 *CYP2A6* and *CYP2B6*. Genes influencing the cascade theory of reward include the complex network of the serotonin, the opioid, the gamma-aminobutyric acid (GABA), and the dopamine pathways [221]. To assess these gene-environmental interactions is one of the tasks of public health genomics [6, 222].

Genes from these two different groups are also influencing other traits and disorders. For example, serotonin genes are associated to personality and psychiatric disorders such as depression [223, 224]. Furthermore, TUD is also related to many traits and disorders. For example, smoking increases the risk of several neoplasms [225] and a higher prevalence of smokers is observed in populations with, for example, schizophrenia [226]. The mechanisms accounting for comorbidity of smoking are, up to now, not well understood.

As proposed by Munafo *et al.* the relationship between, for example, smoking and depression may be either (i) depression causes people to smoke (through self-medication of the symptoms), (ii) smoking causes an increased risk of depression (through alterations of neurotransmitter following chronic exposure to tobacco), (iii) bidirectional (acute tobacco smoking reduces negative affect and chronic use increases it), (iv) caused by shared factors such as genetic factors, or (v) the relationship described in i-iii combined with iv. In the latter case the relationship is not causal but due to pleiotropy [227]. This raises questions about the relationship between TUD and disorders: Is it due to causality, pleiotropy, or common pathways in systems medicine? Pleiotropy occurs when a single gene variant influences multiple phenotypic traits. However, systems medicine is a field studying interactions. Thus, it is no more the influence of genetics but genomics such as epigenomics. Answering to that kind of questions is an important step to further improve the treatment and prevention in comorbidities of tobacco use disorder.

Given the high number of disorders associated with TUD, combined with the importance of genetic factors influencing TUD, this study aims to explore the genetic similarities between TUD and disorders genetically associated to TUD. Due to the high number of possible disorders, only an explorative study of disorders with the strongest association with the genes influencing TUD was developed. The aim of this study was (1) to make a non-exhaustive inventory of disorders using the same

genetic pathway as TUD, (2) to describe the genetic similarities between TUD and the selected disorders.

METHODS

Figure 4.1 presents the analyses flow of the exploratory study described below.

Candidate gene selection (Figure 4.1A)

To enhance the robustness of the candidate gene selection, two different tools (Gene2MeSH and Ingenuity Pathway Analysis) were used.

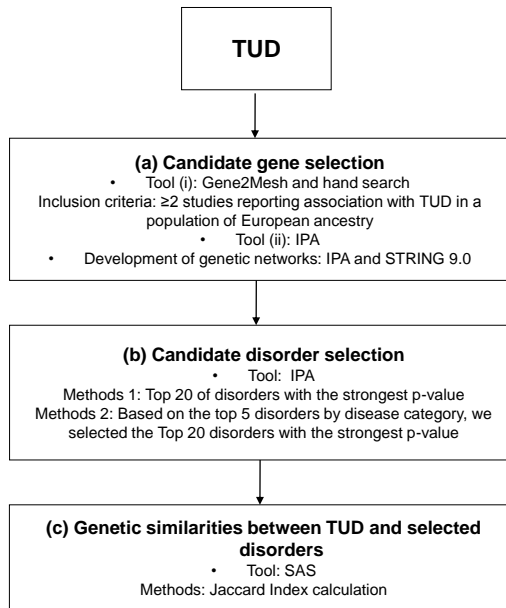
Gene2MeSH screens all publications on PubMed for genes and MeSH terms and calculates the over-representation of each gene for each specific MeSH term [228]. In June 2012, we searched for genes over-represented in the literature for the following MeSH terms '*tobacco use disorder*', '*nicotine*', '*smoking*' and '*smoking cessation*' in human studies of English language. Genes were selected if at least two independent studies reported a significant association with TUD in a European population. Publications were excluded if the entire population had a specific disorder or trait other than nicotine dependence (e. g. alcohol addiction, psychiatric disorder or pregnancy).

In Ingenuity Pathway Analysis (IPA, Ingenuity Systems; www.analysis.ingenuity.com), all genes reported in the search based on the term '*Tobacco use disorder*' were selected. IPA allows the development of gene and gene-disease networks through different sources and databases including major NCBI databases (EntrezGene, RefSeq, and OMIM disease associations), microRNA-mRNA target databases, GWAS databases, and Kyoto Encyclopedia of Genes and Genomes (KEGG).

To gain insights into the functional relationships between the selected genes, we developed a network analysis using IPA and STRING 9.0 (Search Tool for the Retrieval of Interacting Genes/Proteins) (Figure 4.2) [229]. Genes that were identified by IPA as being related to Tobacco use Disorder (Disease/function search) were selected for pathway analyses. Interactions between the genes were build using the 'Grow' and 'Path Explorer' options filtered for direct interaction, experimentally observed / highly predicted confidence levels, species *Homo sapiens*, and with the exclusion of chemicals and drugs. Interactions with only one supporting publication were manually excluded as "preliminary". STRING is a web-tool providing gene-gene and protein-protein association scores based on automatic literature-mining searches. We input our list of genes and set the minimum combined score to 0.900 (highest confidence). The model was built for *Homo sapiens*.

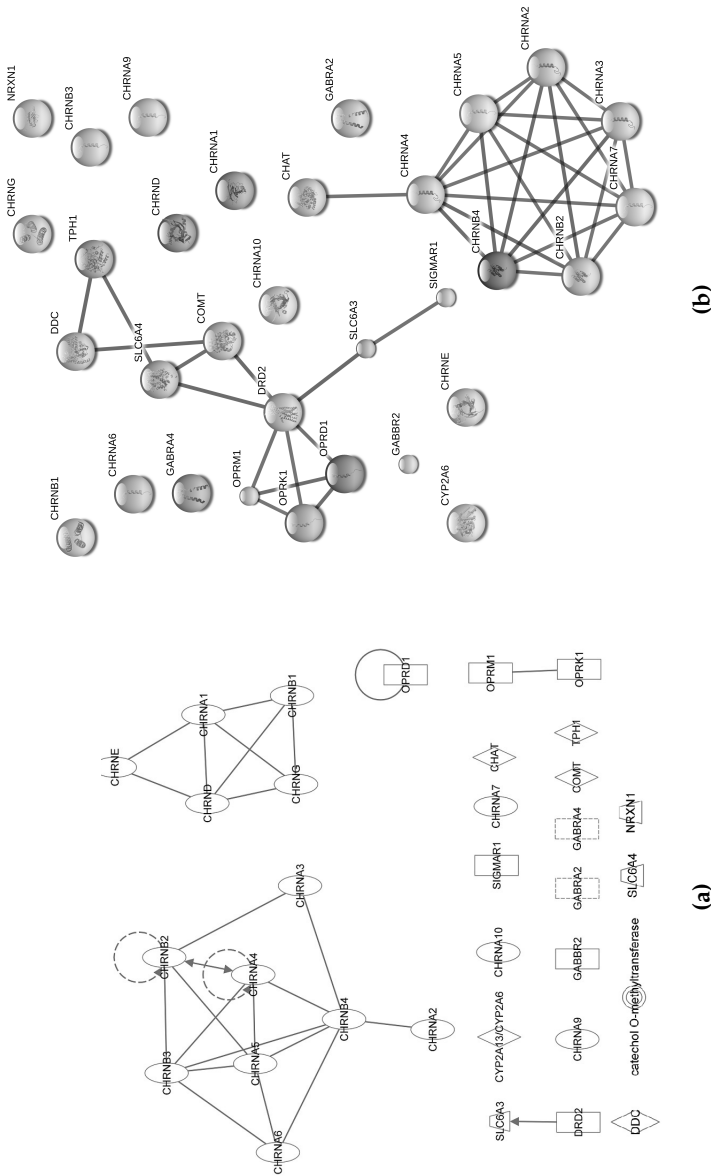
Candidate disorder selection (Figure 4.1B)

Disorders were selected based on their association to the previously selected genes using IPA. As number of associated disorders was expected to be high, we developed two methods of selection. Disorders retrieved from both methods were selected. The first methods included the 20 disorders with the strongest p-value indicating the relationship with the selected genes. In IPA, the p-value refer to a right-tailed Fisher's exact tests calculating the likelihood that a set of genes is associated with a specific disorder. The second methods was based on category of disorders and developed in two steps. The first step consisted in selecting the five disorders with the strongest p-value for each category. In the second steps, we limited our disorder selection to the 20 disorders with the strongest p-value. The combination of these two methods allowed the retrieval of broad categories of disorders having the strongest association to TUD.



Analysis proceeds from candidate gene selection, to candidate disorder selection, to genetic similarities between TUD and selected disorders. IPA, Ingenuity Pathway Analysis

Figure 4.1: Flow of the analyses



(a) Genetic network obtained from Ingenuity Pathway Analysis. The different shapes of nodes represent the functional class of the gene product. Edges with dashed lines show indirect interaction, while a continuous line represents direct interactions; (b) Genetic network obtained from STRING network. The STRING network incorporates the interactions of the selected genes with the highest confidence level (level of 0.900). Stronger associations are represented by thicker lines.

Figure 4.2: Genetic network analyses using Ingenuity Pathway Analysis and STRING

card distance of 0.00, four pairs of disorders were exactly similar from a genetic point of view. The dendrogram obtained from the cluster analysis in Figure 4.3 presented two main clusters of disorders. The first cluster contained disorders that are mostly side effects of smoking (e. g. vascular disorder, gastric cancer, and malignant hypertension) [231] and the second cluster disorders that are coexisting to smoking (e. g. addiction, alcoholism, and depressive disorders) [232].

Table 4.2: Disorders associated with genes influencing tobacco use disorder selected from methods 1 and 2

DISORDER	METHODS 1	METHODS 2
Addiction	X	X
Alcoholism	X	X
Bladder cancer		X
Cervical cancer		X
Coronary disease	X	X
Delirium	X	
Depressive disorder	X	X
Dyskinesia	X	
Gastric cancer	X	X
Gastrointestinal tract cancer		X
Hypertension		X
Insomnia	X	
Leukaemia		X
Liver cancer		X
Malignant hypertension	X	X
Mood disorders	X	
Movement disorders	X	
Motor dysfunction	X	X
Oesophageal cancer	X	X
Pancreatic cancer		X
Psychomotor agitation	X	X
Schizophrenia	X	X
Schizoaffective disorder	X	X
Stroke	X	X
Subarachnoid haemorrhage	X	
Vascular disorder	X	X

Methods 1, 20 disorders with the strongest p-value indicating the relationship with the selected genes using Ingenuity Pathway Analysis; Method 2, based on category of disorders and developed in two steps: Firstly selection of the five disorders with the strongest p-value for each category and secondly limitation to the 20 disorders with the strongest p-value; Final selected disorders are the one retrieved from both methods 1 and methods 2.

DISCUSSION

This exploratory study is a first step towards evaluating the genetic similarities between TUD and disorders genetically associated to TUD. Genes influencing TUD were associated with variety of other disorders. Cluster analyses reported two main clusters of disorders. The first cluster included disorders that are side effects of smoking (including e. g. vascular disorder, gastric cancer, and malignant hypertension) while the second cluster included coexisting disorders of smoking (including e. g. addiction, alcoholism, and depressive disorder).

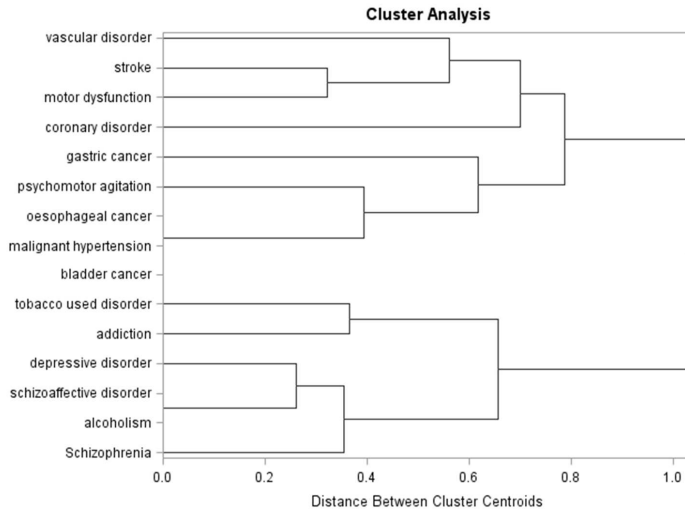


Figure 4.3: Dendrogram of disorders associated with the same genes as TUD resulting from centroid hierarchical cluster analysis, using the Jaccard distance obtained from 32 genes

To our knowledge, this study is the first to show that literature review combined with gene pathway analysis can provide relevant information in understanding the genetic basis for similarities between TUD and associated disorders; even if genes are not the only factors linking TUD to other disorders. Among other factors, environmental factors, treatments, and epigenetic modifications mediate the relation between TUD and other disorders.

The prevalence of coexisting disorders of smoking including mental health and addictive disorders appear to be 2 to 4 times higher in smokers than in the general population. Different theories were developed to explain this higher prevalence: (i) intrinsic factors such as genes that predispose people with mental and addictive disorders to smoke, (ii) self-treatment of mental and addictive disorders through TUD, (iii) common social and environmental determinants for TUD, and (iv) modulation of neurotransmitters involved in the development of mental health and addictive disorders due to TUD [233]. Shared genetic variation of *CHRNA7* is, for example, reported in TUD and schizophrenia [233]. Regarding disorders that are side-effects of smoking, the most plausible theory is epigenomic changes due to carcinogenic compounds of tobacco [104]. For example, it was reported that smoking induced a down-regulation of the interferon *IFIT1* involved in the progression and invasiveness of bladder cancer [30]. Therefore, genes are just one track to link TUD and related disorders.

Table 4-3: Jaccard distance between pairs of disorders associated with genes influencing tobacco use disorder

DISORDER	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)
(1) Addiction	0.138													
(2) Alcoholism	0.448	0.360												
(3) Bladder cancer	0.367	0.269	0.200											
(4) Coronary disorder	0.133	0.074	0.407	0.259										
(5) Depressive disorder	0.345	0.370	0.158	0.304	0.414									
(6) Gastric cancer	0.448	0.360	0.000	0.200	0.407	0.158								
(7) Malignant hypertension	0.310	0.269	0.200	0.261	0.321	0.227	0.200							
(8) Motor dysfunction	0.448	0.360	0.000	0.200	0.407	0.158	0.000	0.200						
(9) Oesophageal cancer	0.379	0.280	0.111	0.190	0.333	0.238	0.111	0.100	0.111					
(10) Psychomotor agitation	0.138	0.000	0.360	0.269	0.074	0.370	0.360	0.269	0.360	0.280				
(11) Schizoaffective disorder	0.161	0.107	0.429	0.286	0.103	0.433	0.429	0.345	0.429	0.357	0.107			
(12) Schizophrenia	0.241	0.192	0.273	0.174	0.250	0.292	0.273	0.091	0.272	0.182	0.192	0.276		
(13) Stroke	0.103	0.241	0.384	0.413	0.233	0.269	0.385	0.296	0.384	0.370	0.241	0.258	0.345	
(14) Tobacco use disorder	0.258	0.214	0.360	0.200	0.207	0.370	0.360	0.200	0.360	0.280	0.214	0.172	0.120	0.355
(15) Vascular disorder														

Colours representing the genetic similarities between disorders: Light gray = strong similarities (<0.15); Medium gray = middle similarities (0.15-0.35); Dark gray = low similarities (>0.35)

As hypothesised, the selected genes mainly influenced either the cascade theory of reward or the nicotine metabolism pathways. Most selected genes were nicotinic receptors (*CHAT*, *CHRNA1*, *CHRNA2*, *CHRNA3*, *CHRNA4*, *CHRNA5*, *CHRNA6*, *CHRNA7*, *CHRNA9*, *CHRNA10*, *CHRNB1*, *CHRNB2*, *CHRNB3*, *CHRNB4*, *CHRND*, *CHRNE*, and *CHRNG*). These receptors are activated by nicotine and a prolonged contact to nicotine will lead to receptor desensitisation [234]. Moreover, except *CHAT*, all nicotinic receptors influenced all selected disorders. There were only two genes that belong to none of these groups (*SIGMAR1* and *NRXN1*). *SIGMAR1* is a protein receptor involved in the modulation glutamatergic and dopaminergic neurotransmission [235]. *NRXN1* is a presynaptic neuronal adhesion molecule. However, its biological association with multiple disorders (e. g. autism and schizophrenia) is still unclear [236].

The reason why the networks developed in IPA and STRING (Figure 4.2) are different might be due to the selection criteria. Indeed, the options in IPA are very stringent, whereas STRING used a confidence level of 0.90. Besides that, differences in the text mining algorithms used and the databases accessed by IPA and STRING may also influence the outcome.

All expected categories of disorders associated with TUD were represented in our disease selection. Due to the limitation in the number of selected disorders, to make the analyses manageable, some specific disorders associated to TUD were not selected. This is, for example, the case for lung cancer [231], attention deficit disorder with hyperactivity (ADHD) [237], and bipolar disorder [238]. McEachin *et al.*, in their multi-gene network analysis, already reported an over-representation of genes associated to bipolar disorder and TUD. Their gene selection, developed in Gene2Mesh, included *COMT*, *SLC6A3*, and *SLC6A4* [238]. Those three genes also appeared in the gene selection of the present study.

Moreover, in the literature, not only links between (i) TUD and mental illness, (ii) TUD and cardiovascular disease, or (iii) TUD and cancer are observed. For example, depression has been reported to increase the risk of cardiovascular disease. The reason of this association may be the non-compliance to treatment, shared risk factors in the two disorders (e. g. smoking and hypertension), or physiologic factors (e. g. the activation of the hypothalamic-pituitary-adrenocortical axis and inflammation) [239].

Psychiatric disorders are influenced by multiple factors and it is reasonable to think that genes do not influence psychopathology but intermediate phenotypes, such as the inter-link between dorsolateral prefrontal cortex and hippocampus or striatum. This hypothesis is supported by the following example; *COMT* has been consistently associated with prefrontal regulation of dopamine, which indicates a risk of schizophrenia due to the reduced signal in the prefrontal cortex [240]. However, inconsistent results were obtained when studying the direct link between *COMT* and schizophrenia [240]. In TUD, intermediate phenotypes may also be used to better understand the link with other disorders. In disorders that are side effects of smoking, one plausible intermediate phenotype may be tobacco smoking.

Reward deficiency syndrome (RDS) is probably an important intermediate phenotype of coexisting disorders of smoking. RDS is a hypodopaminergic state including 4 main types of behavioural disorders: addictive behaviour (e. g. substance abuse or obesity), impulsive behaviour (e. g. attention deficit hyperactivity disorder or Tourette syndrome), compulsive behaviour (e. g. aberrant sexual behaviour or pathological gambling), and personality disorder (e. g. conduct disorder or aggressive disorder) [241]. Among others, the following variants influencing the dopamine pathway are suggested to induce RDS: *DRD2* TaqIA A1, *DRD2* 957T, *SLC6A3* VNTR 9R, and *COMT* Val^{108/158}Met ValVal [241, 242]. This enhances the need of individualised interventions in case of, for example, smoking cessation. Indeed, if a smoker with depressive disorder used cigarettes as a self-medication to enhance the release of dopamine, then, during smoking cessation the treatment of depression will need adaptation [237].

Previous publications such as Carlsten *et al.* already pointed out the benefit of personalised medicine in TUD [243]. Due to the strong evidence that genetic factors are involved in nicotine addiction and smoking cessation, interventions should be adapted in type of treatment, dose, and duration. For example, bupropion that modifies the activity of dopamine may have an impact on smoking relapse. This may partly explain why some individuals respond better to treatments than other one [244]. Therefore, as proposed by Walton *et al.*, there is a need to improve the 'understanding of the molecular mechanisms that underlie tobacco addiction' [244]. This understanding of the molecular mechanisms may also include those linking TUD to other disorders.

Limitations

Regarding the search strategy, the most important limitation was the low number of publications in European populations. Among other studies, there was a relatively high number of publications focusing on Asian population or on mixed ethnicities. Based on that observation, other genes may also be associated with TUD. However, the aim of the current study was not to be exhaustive in genes and disorders selection but explorative.

The use of Gene2MeSH allowed us to screen publications on PubMed in an easier way that may reduce our chance of missing publications. Looking to other databases may have increased the number of selected genes and disorders and enhanced the number of relations between selected genes and disorders. However, the addition of gene and disease selection in IPA enhanced our review as it includes text-mining research and various databases. Nevertheless, in IPA there is no possibility to limit our search based on our inclusion and exclusion criteria: focus on populations of European ancestries, and exclude studies with specific disorders or trait in the entire population. Therefore, some associations retrieved from IPA may not be specific to our criteria.

Networks based on literature-mining, as developed in IPA and STRING (Figure 4.2), may introduce false positivity because it does not take into account the true biological relation between the elements. Further studies might take epigenomics into account to gain insight from the dynamics of the genome-environmental interactions and comorbidities. Exposomes might be linked to health effects even if to date no direct association has been reported [245]. However, genetics, epigenomics, and exposome are just part of the whole pattern explaining the relation between TUD and other disorders. This explains the interindividual differences.

Implication for practice and future research

This exploratory study may partially explain the genetic similarities between TUD and disorders using the same genetic pathways. A better understanding of the disorders linked to the same genes as TUD may help in individualising and personalising care related to TUD. Indeed, global cares developed by taking into account all the different factors that may influence a trait or a disorder, are the best practice to improve health. The use of tobacco influences, for example, the metabolism of antidepressants treatments.

In future research, the type of analyses that we developed here might be extended to individual characteristics, effects of treatments, or severity of symptoms. Moreover, the mechanisms linking TUD to disorders might be assessed in twin or prospective studies. This may give insights into whether the relation is due to causality or pleiotropy. Finally, analysis of micro-array online database for the most significant diseases may give an idea whether the expression is similar or differs between disorders.

Part II

**ENHANCING THE COMMUNICATION OF
GENOMIC RISKS ABOUT SMOKING IN THE
GENERAL POPULATION**

IMPACT OF GENETIC NOTIFICATION ON SMOKING
CESSATION

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ABSTRACT

Objectives This study aimed to evaluate the impact of genetic notification of smoking related disease risk on smoking cessation in the general population. Secondary objectives were to assess the impact of genetic notification on intention-to-quit smoking and on emotional outcomes as well as on the understanding and the recall of this notification.

Methods A systematic review of articles from inception to August 2011 without language restriction was realised using PubMed, Embase, Scopus, Web of Science, PsycINFO, and Toxnet. Other publications were identified using hand search. The pooled-analysis included only randomised trials. Comparison groups were (i) high and low genetic risk versus control, and (ii) high versus low genetic risk. For the pooled-analysis random effect models were applied and sensitivity analyses were conducted.

Results Eight papers from seven different studies met the inclusion criteria of the review. High genetic risk notification was associated with short-term increased depression and anxiety. Four randomised studies were included in the pooled-analysis, which revealed a significant impact of genetic notification on smoking cessation in comparison to controls (clinical risk notification or no intervention) in short term follow-up less than 6 months (RR = 1.55, 95% CI 1.09 – 2.21).

Conclusions In short term follow-up, genetic notification increased smoking cessation in comparison to control interventions. However, there is no evidence of long term effect (up to 12 month) on smoking cessation. Further research is needed to assess more in depth how genetic notification of smoking related disease could contribute to smoking cessation.

INTRODUCTION

Smoking is a major public health problem worldwide and the most preventable cause of mortality and morbidity. It increases the risk of many diseases such as lung cancer, chronic obstructive pulmonary diseases and cardiovascular diseases [246], but smoking cessation highly contributes to the prevention of most of these harms. Every year, around 40% of smokers attempt to quit smoking for at least one day, but only few of them succeed: approximately 2% without any help and 20% with an adequate treatment [105, 106]. This highlights the importance of improving evidence-based interventions for smoking cessation, which could be enhanced by genetic notification of smoking related disease risk. The goal of genetic notification is to allow smokers to adapt their behaviour regarding their personal risks [247, 248].

Common diseases are highly dependent on multiple environmental and genomic factors. Both cigarette consumption and allele frequencies vary substantially between populations. Multiple single nucleotide polymorphisms (SNPs) are needed for the assessment of each specific smoking related disease risk. Generally speaking, testing multiple SNPs for diverse smoking related disease risks will identify smokers to be at higher risk of at least one disease. Different genes seem to be of interest in cancer risk prediction, among them: *GSTM1*, *GSTT1*, *CYP2D6*, *L-myc*, *NQO1*, and *CYP1A1* [249–253].

Risk communication and health literacy are complex issues dealing with the use, the understanding and the recalling of a notification by the patient [247, 254]. Combination of a numeric, verbal and pictorial approach maximises the understanding of the genetic risk [255]. Different models, such as the extended parallel process model [256], try to explain how people are managing information concerning their health. They highlighted that information influences emotional and cognitive representations, which could lead to an adaptive or a maladaptive change of behaviour. Genetic notification has an important psychological and emotional impact [49]. In the case of smoking, it could influence the motivation to quit smoking or lead to fear and depression symptoms that depend on the individual, the type of notification and the way it is done. Hence, being one of the core tasks of Public Health Genomics, genetic risk communication is challenging because an individual may interpret the risk as an absolute prediction. For example, he may believe that a high genetic risk of lung cancer will absolutely lead to cancer [257]. However, in general, benefits of genetic tests are more important than risks [247].

Studies reporting the impact of genetic notification on smoking cessation have been conflicting, which could, among other reasons, suggest that it is not a strong motivator of behavioural change.

The impact of genetic notification can be either explored in a real or a hypothetical situation. In hypothetical genetic testing, the anticipated reactions of smokers are assessed in view of a hypothetical genetic risk of smoking related disease. The outcome of interest is intention-to-quit smoking, which is an important precursor of

quit attempts that lead to smoking cessation [103]. Thus improvement in intention-to-quit (e. g. enhanced by genetic notification) could be associated with an increase smoking cessation rate.

The primary objective of this systematic review and pooled-analysis was to determine the impact of genetic notification on smoking cessation in the general population. We addressed this by the following questions:

- Is genetic notification of smoking related disease risk influencing smoking cessation success rate in comparison to clinical notification of smoking related disease risk (e. g. blood pressure and cardiovascular diseases) or no notification?
- Is high genetic risk notification of smoking related disease risk influencing smoking cessation success rate in comparison to low genetic risk notification?

The secondary objectives were to review the impact of genetic notification on intention-to-quit smoking and emotional outcome as well as to determine to which extend smokers really understand and recall their genetic notification.

METHODS

First, we conducted a systematic review. Then we carried out further quantitative assessment only on the primary outcome (smoking cessation) by a pooled analysis. For this systematic review and pooled-analysis, we followed the Quality of Reporting of Systematic reviews and meta-analyses (PRISMA) guidelines [258].

Eligibility criteria

Regarding the systematic review, we included studies incorporating smokers of any age receiving genetic notification of smoking related disease risk in prospective studies (randomised, not randomised trial or cohort studies). The only exclusion criterion was studies involving hypothetical genetic notification as intervention.

The intervention of interest was the genetic notification of smoking related disease risk. Notification based on one gene was stratified in high and low genetic risk based on dominant or recessive genetic model.

The primary outcome was smoking cessation. To assess the impact of genetic notification, we collected smoking cessation rates at each follow-up that was presented in the studies. Smoking cessation could be biochemically confirmed (salivary cotinine concentration less than 15 ng/ml) or self-reported. The outcomes in the selected studies included prolonged (continuous abstinence during a follow-up period) and point prevalence (1, 7 or 30-day) cessation rates. Only one study presented a sustained smoking cessation [48]. For the pooled-analysis, we focused on point prevalence smoking cessation, as this indicator was available for each study.

Velicer *et al.* demonstrated a high correlation between the different types of point prevalence (24-h, 7-day, 30-day) smoking cessation (r between 0.98 and 0.99) [259].

Secondary outcomes were: (a) intention-to-quit smoking; (b) emotional outcome (e. g. anxiety, depression or fear); (c) recall and understanding of the genetic notification.

Search strategy

We searched PubMed, Embase, Scopus, Web of Science, PsycINFO, and Toxnet for studies published until August 2011 without language restriction using the following terms: smoking cessation, genetic testing, and genetic predisposition to disease. The search strategy is available in the supporting information documents (Pubmed search in Supplementary material - Chapter 5). In addition, we manually reviewed the reference list of relevant articles and reviews.

Two authors (SDV and JVDH) independently screened for title and electronic abstract identified by the search for relevance to the inclusion criteria. Articles retrieved from this examination were full text screened by the same authors. Reasons for excluding studies were noted (Figure 5.1). Data were extracted by one author (SDV) and checked by the second one (JVDH). Disagreements were resolved by discussion.

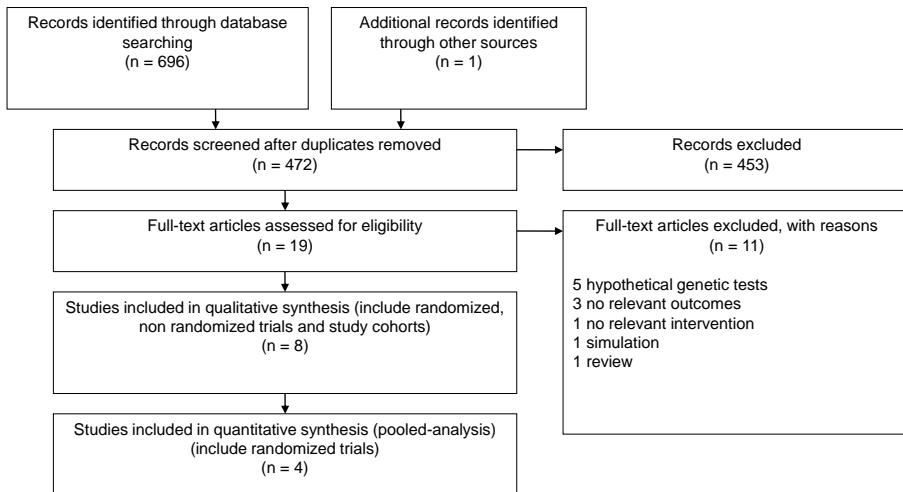


Figure 5.1: Flow chart of the study selection process

Data extraction and methodological quality assessment

From each eligible paper of the systematic review, we extracted information, where available, on first author, year of publication, country, study setting, study design, year of the recruitment, inclusion and exclusion criteria, sample size (total and by comparison groups), description of interventions, characteristics of participants (including age, gender, ethnicity, cigarettes per day, nicotine addiction and, age of initiation), outcomes (smoking cessation, intention-to-quit smoking, emotional effects, recall and understanding of genetic testing and assessment method of the outcomes), and length of follow-up.

Methodological quality and potential risk of bias were assessed using the following criteria: selection criteria clearly described, sample size calculation, adequate allocation concealment for randomised trials, comparability of groups at baseline, presentation of the Hardy-Weinberg Equilibrium (HWE, state that allele and genotype frequency remain constant within a population); intention-to-treat analysis, ascertainment of outcome, and control for confounding.

Statistical analyses

In the systematic review, we realised comparisons of sample sizes between studies, genetic risk and gene to understand the difference in the relative proportion of smoking cessation between studies. This was effectuated using Pearson's Chi-square test. Studies included in these analyses were randomised and non randomised trial [45, 46, 48, 260–262]. Sample size of high and low genetic risk was only available in four studies [45, 46, 48, 262].

Individual study risk ratios (RR) and binomial 95% confidence intervals were computed from event numbers extracted from each study.

For the pooled-analysis, we limited included studies to randomised trials for their ability to minimise likelihood of systematic error [263]. Analyses were carried out taking into account time to follow-up: (i) Short-term follow-up was lower or equal to 6 months. (ii) Last follow-up was the last follow-up presented in the study (from 2 to 12 months). We utilised the DerSimonian and Laird method to obtain summary RR and 95% confidence intervals, using random effect models for all analyses because of the important diversity between studies in the inclusion criteria or time of follow-up [264]. Statistical heterogeneity was assessed using the I^2 statistic, with a value of 50% or more indicating a substantial level of heterogeneity [265]. Potential publication bias was estimated by the Egger's test. Sensitivity analysis was realised to assess the effect of each single study on the overall results by dropping one study at a time [266].

In studies that had more than two arms, we collapsed arms to obtain one intervention and one control group (e.g. collapsing no intervention and clinical risk notification group). Tests were two-sided with a significance rate α of 0.05. All statis-

tical analyses were performed using STATA, version 10.1 (STATA Corporation Inc., College Station, TX, USA).

RESULTS

Description of studies

The selection of studies included in our review is summarised in Figure 5.1. The literature search identified 696 publications from the different databases and 1 from hand search [262]. The publication retrieved from hand search was in the reference list of Hishida *et al.* [45]. After removal of duplicate references, 472 were included. A total of 453 were discarded in the title and abstract screening because these papers did not meet the criteria. From the 19 studies included in full text review, 11 did not meet the inclusion criteria as described [50–52, 267–274]. Finally, 8 papers from 7 studies met the inclusion criteria (Table 5.1) [43, 45–48, 260–262]. The studies of Lerman *et al.* [261] and Audrain *et al.* [260] were based on the same population but presented the outcomes at two and twelve months of follow-up, respectively. Four studies had recruited their participants in 2000 and later [43, 45–47] and three studies recruited before 2000 [48, 260, 261]. In the last study, the recruitment period was not reported [24]. Studies took place in the UK [262], the US [48, 260, 261] and Japan [43, 45–47]. Study participants were recruited via newspapers advertisements [260, 261], university [41], annual check-up of employees [43, 45, 47], outpatients consulting general practitioners or specialists [46, 48], smoking clinic [261] or telephone quit smoking service [262]. The sample sizes ranged from 61 to 697 and the follow-up ranged from 2 to 12 months.

Participants were aged from 18 to 88 years old. The percentage of females was around 50% except in two studies where there were only 6.2% and 14.0% females [45, 47]. In general, participants had to smoke at least 1 cigarette per day (CPD) or 7 cigarettes per week to be recruited [46, 48, 262]. Four studies presented the mean CPD of their participants this ranged between 15.5 and 22.7 [45, 48, 261, 262]. Two studies enrolled patients that wanted to quit smoking [260, 261], whereas, in the other studies, participants were not necessarily trying to quit smoking [43, 45, 47, 48].

Table 5.1: Genetic notification and smoking cessation: Overview of included studies

STUDY, COUNTRY	STUDY CHARACTERISTICS	CRITERIA ON CPD	INTERVENTION/ CONTROL GROUP	GENETIC TEST	SAMPLE CHARACTERISTICS	OUTCOME CRITERIA (METHOD)
Audrain (1997) [260], USA	Recruitment: newspapers, advertisements and smoking clinic; Randomised trial; Last FU: 12 months	≥ 5 CPD	(a) Standard consultation + CO level + genetic risk; (b) Standard consultation; (c) Standard consultation + CO level	CYP2D6	N = 426; 62.8% female; age range 18 to 75; 83.9% white; FTND mean 5.4; Cont. N.R.	SR (30-day quit smoking)
Hamajima (2004) [43], Japan	Recruitment: Annual checkup; Study cohort; Last FU: 3 months	N.R.	Genetic risk	GSTM1; GSTT1; NQ01 C609T	N = 101; 31.7% female; age range 39 to 88; ethnicity N.R.; Add. N.R.; Cont. 89.1%	SR (current smoking status)
Hishida (2010) [45], Japan	Recruitment: Annual checkup at work place; Non randomised trial (Sequentially allocated); Last FU: 12 months	N.R.	(a) Genetic risk; (b) No intervention	L-myc	N = 562; 6.2% female; age 20 to > 60; ethnicity N.R.; Add. N.R.; Cont. 95.0%	SR (N.R.)
Ito (2006) [46], Japan	Recruitment: First visit outpatients in Cancer Center; Non randomised trial (Sequentially allocated); Last FU: 9 months (genetic notification: 3 month follow-up)	≥ 1 CPD	(a) Genetic risk; (b) No intervention	L-myc	N = 697; 40.5% female; age range 20 to 65; Ethnicity N.R.; 40.5% FTND from 6 to 10; Cont. 70.0%	SR (current smoking status)
Kano (2007) [47], Japan	Recruitment: Annual checkup in Municipal government; University (Employees and students); Study cohort; Last FU: 3 months	N.R.	Genetic risk	GSTM1; GSTT1; NQ01 C609T; CYP1A1 Ile/Val	N = 107; 14.0% female; age range 20 to 69; ethnicity N.R.; Add. N.R.; Cont. 68.2%	SR (current smoking status)
Lerman (1997) [261], USA	Recruitment: newspapers, advertisements and smoking clinic; Randomised trial; Last FU: 2 months	≥ 5 CPD	(a) Standard consultation + CO level + genetic risk; (b) Standard consultation; (c) Standard consultation + CO level	CYP2D6	N = 427; 61.4% female; age range 18 to 75; majority of white; CPD mean 22.7; Cont. 60%	SR (7 and 30-day quit smoking)
McBride (2002) [48], USA	Recruitment: Health clinic for low income residents (from the adult medicine, dental, urgent care, and specialty clinic); Randomised trial; Last FU: 12 months	≥ 1 CPD	(a) Genetic risk; (b) Standard consultation	GSTM1	N = 557; 60.0% female; age mean 44.5; 100% African American; CPD mean 15.5; Cont. 32%	SR (7-day quit smoking); CO level (Saltin vary sample)

Continued on next page

STUDY, COUNTRY	STUDY CHARACTERISTICS	CRITERIA ON CPD	INTERVENTION/ CONTROL GROUP	GENETIC TEST	SAMPLE CHARACTERISTICS	OUTCOME CRITERIA (METHOD)
Sanderson (2008) [262], UK	Recruitment: Call on the London Stop Smoking service the 4 previous years; Randomised trial; Last FU: 2 months	≥ 7 cig. in the past weeks	(a) Genetic risk; (b) No intervention	GSTM1	N = 61; 62% female; age range 26 to 79; 88% white; CPD mean 19; Cont. N.R.	SR (current smoking status)

CO level Carbon monoxide level; Cont. Pre-contemplator and contemplator from the stage of behavioural changes of Prochaska *et al.* [275]; CPD Cigarette per day; FTND Faggestrom Test of Nicotine Dependence; FU Follow-up; Add. Nicotine addiction; N.R. Not reported; SR Self-reported abstinence

Regarding the study design, four studies were randomised trials [48, 260–262], two studies did not randomise their interventions (sequential allocation) [45, 46], and the remaining two were cohort studies [43, 47]. Four studies compared groups that could receive genetic notification to control [45, 46, 48, 262]. The last two trials had three arms (i) standard quit smoking consultation (QSC) to (ii) clinical risk notification, which consisted of 10 minutes of motivational intervention including carbon monoxide (CO) level prior QSC, and (iii) genetic risk notification, which consisted in personalised feedback of genetic test, QSC and clinical risk notification [260, 261].

The disease of interest was always cancer. In six studies risk notification was based on a single-gene test (*GSTM1*, *L-myc* or *CYP2D6*) [45, 46, 48, 260–262]. In one study three genetic tests (*GSTM1*, *GSTT1* and *NQ01* C609T) [43] were involved. In the study of Kano *et al.* *CYP1A1* Ile/Val was added to the previous list [47].

Quality of studies and publication bias

A summary of the risks of bias for the included studies in Table 5.3 (Supplementary material - Chapter 5). One study reported allocation randomisation procedures in sufficient details (including the explanation of the procedure for the randomisation) [262], whereby intervention allocation were not known or predicted by the participants or the medical support teams before their assignments. The 3 other randomised studies did not mention the procedure of randomisation [48, 260, 261]. Studies in which interventions were randomised according to week or month of attendance [45, 46], were considered as non randomised studies in the analyses. Half of the studies reported the sample size calculation [46, 260–262] and one clearly reported the test of HWE [45]. Smoking cessation was sometimes defined as a continuous abstinence [46], 7-day abstinence [48, 261], 30-day abstinence [46, 260, 261], or 'current smoking status' [43, 45–47, 262]. Only one study tried to confirm biochemically the self-reported abstinence but the return rate of the samples was only 39%. Thus they decided not to use this outcome and to use only self-reported cessation [48]. Six studies controlled their results for confounding [45, 46, 48, 260–262].

Egger's two tailed p-value showed no significant publication biases for short follow-up as well as the last follow-up of main analyses (genetic notification versus control) (respectively, $P = 0.11$ and $P = 0.76$).

Primary outcome: Smoking cessation

The impact of genetic notification on smoking cessation was conflicting among randomised and non randomised studies [45, 46, 48, 260–262] although the results were not significant. Three studies displayed a higher smoking cessation rate in the genetic notification group than in the control group [48, 261, 262] and three other studies reported the opposite [45, 46, 260] (Table 5.2). Figure 5.2 indicated that, the distribution of high and low genetic risk was significantly different between genes

(*L-myc* and *GSTM1*; $P < 0.001$) and between the four different studies ($P < 0.001$) but not between authors within genes (*GSTM1* $P = 0.10$; *L-myc* $P = 0.79$). For *GSTM1*, more participants had a lower genetic risk and for *L-myc*, more participants had a higher genetic risk. However, distribution of high and low genetic risk notification were not available for two studies [260, 261].

Table 5.2: Risk ratios and 95% confidence intervals associated with smoking cessation following intervention (genetic notification versus control)

AUTHOR	GENE	RISK RATIO (CI 95%)
Audrain (1997)	<i>CYP2A6</i>	0.73 (0.41-1.28)
Hishida (2010)	<i>L-myc</i>	0.75 (0.40-1.41)
Ito (2006)	<i>L-myc</i>	0.90 (0.66-1.24)
McBride (2002)	<i>GSTM1</i>	1.47 (0.90-2.39)
Lerman (1997)	<i>CYP2D6</i>	1.44 (0.74-2.80)
Sanderson (2008)	<i>GSTM1</i>	0.92 (0.37-2.27)

Risk ratios higher than one mean a positive effect of genetic notification on smoking cessation.

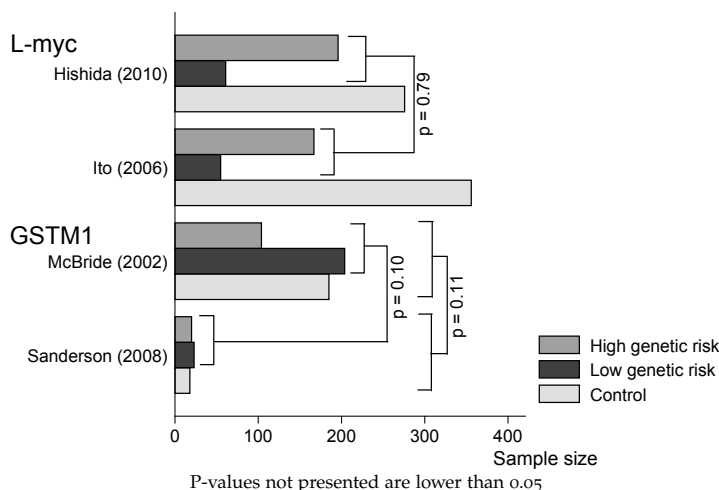
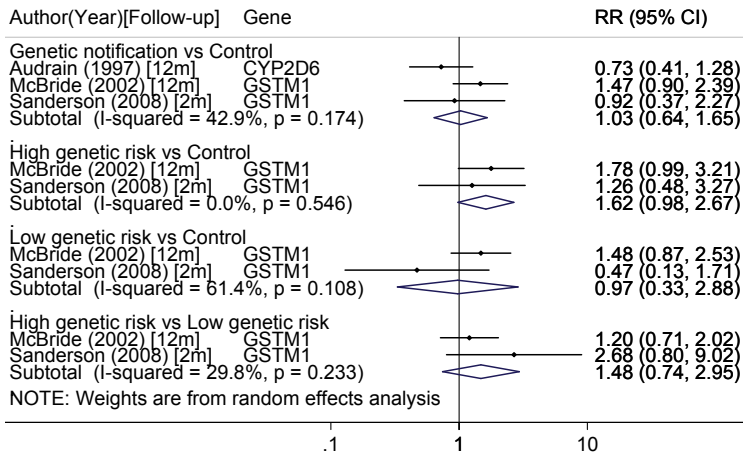


Figure 5.2: Comparison of the distributions (High, low genetic risk and/or control) between studies or genes

The pooled analysis indicated that, when considering the last follow-up, there were no significant differences in smoking cessation between the following sub-groups: genetic notification versus control, low genetic risk notification versus control, and high genetic risk notification versus low-genetic risk (respectively, RR (95% CI) 1.03(0.64 – 1.65); 0.97(0.33 – 2.88); 1.48(0.74 – 2.95)) (Figure 5.3). However, compared to the control group high genetic risk notification was borderline associated with an increased smoking cessation (RR = 1.62(0.98 – 2.67)). No heterogeneity was observed across studies in the different pooled-analyses (I^2 range from 0.0 to 42.9%,

P range from 0.17 to 0.54) except a substantial heterogeneity in the low genetic risk notification versus control group ($I^2 = 61.4\%$, $P = 0.11$).



Genetic notification group versus control; High genetic risk versus control; Low genetic risk versus control; High genetic risk versus low genetic risk. Risk ratios higher than one mean a positive effect of genetic notification on smoking cessation

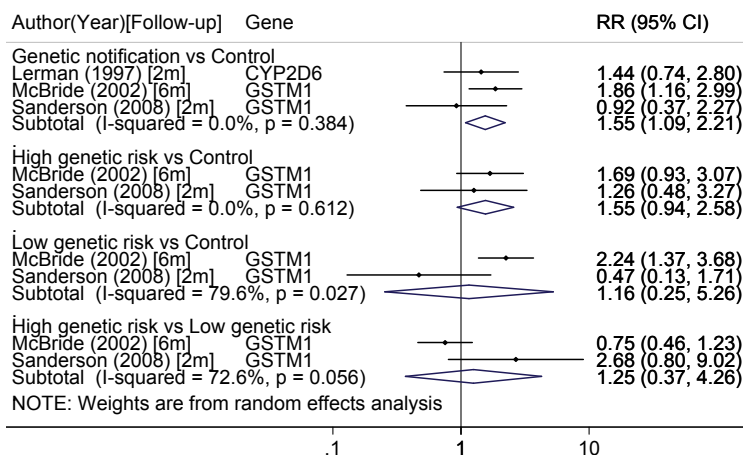
Figure 5.3: Pooled-analysis of smoking cessation associated with genetic notification in randomised trials for the last follow-up (2, 6 or 12 month)

When focusing only on short-term smoking cessation outcome (2 or 6 month), the borderline effect of high genetic risk versus control was still visible ($RR = 1.55(0.94 - 2.58)$). Moreover, genetic notification increased 1.55 times smoking cessation in comparison to control ($RR = 1.55(1.09 - 2.21)$) (Figure 5.4). These two analyses seemed fairly homogeneous ($I^2 = 0.0\%$ for the two analyses). Sensitivity analyses did not identify influential studies.

Secondary outcomes

Secondary outcomes were available for most of the studies but not all of them.

(a) Intention-to-quit. Six studies observed intention-to-quit smoking after a genetic notification of smoking related disease risk [43, 45–48, 262]. However, different notions were used: ‘wish to quit’ [43, 45, 47], ‘desire to quit’ [48] and ‘motivation to quit’ [46, 262]. Most studies just evaluated intention-to-quit smoking at baseline. Four studies presented multiple evaluations over time, such as at baseline, before genetic announcement and three months after announcement; or at baseline, and one week and two months after [43, 45, 47, 262]. Two studies indicated no difference in intention-to-quit at different time of follow-up [45, 262]. Although, one reported a significant difference in motivation to quit smoking at one week ($P = 0.003$) but no more at two months [262]. Nevertheless, Ito *et al.* reported no difference of motivation to quit smoking between high and low genetic risk of smoking related disease



Genetic notification group versus control; High genetic risk versus control; Low genetic risk versus control; High genetic risk versus low genetic risk. Risk ratios higher than one mean a positive effect of genetic notification on smoking cessation

Figure 5.4: Pooled-analysis of smoking cessation associated with genetic notification in randomised trials for follow-up ≤ 6 month (2 or 6 month)

($P = 0.18$) [46]. In the 6 studies assessing the stage of change, the majority of the population across 5 studies was pre-contemplator or contemplator (no concern or no intention-to-quit smoking): 89.1% [43], 95.0% [45], 68.2% [47], 60% [261], and 70% [46]. In only one study this percentage was low (32% [48]) (Table 5.1).

(b) Emotional outcome. Seven studies reported emotional outcome [43, 45–48, 261, 262]. Participants receiving genetic notification were more likely to report short-term depression, anxiety or fear arousal than others [45, 261, 262]. More specifically participants with high genetic risk reported increased fear arousal than those with low genetic risk ($P < 0.01$) [46]. This result was not observed in the study of McBride *et al.* [48] and was not significant anymore at 2 months follow-up in the study of Sanderson *et al.* [262]. Anxiety was not significantly different across comparison groups [262].

(c) Recall and understanding. Smokers seemed to reasonably understand the meaning of their genetic test results [262]. McBride *et al.* reported that half of their participants read the biomarker test result booklet and that an equal number of participants from the high genetic risk and low genetic risk groups interpreted accurately their results (respectively, 56 and 53%) [48].

DISCUSSION

Our systematic review indicated that few studies have assessed the impact of genetic notification on smoking cessation. Only 8 papers based on 7 different studies were available and just 4 of them were included in the pooled-analysis.

The pooled-analysis suggested a short-term increase of smoking cessation for participants receiving genetic notification in comparison to control group and a borderline increase of smoking cessation for high genetic risk smokers in comparison to control. No evidence of heterogeneity was observed for these results even if (i) characteristics of participants, (ii) inclusion criteria and (iii) study designs differed among studies. For example, (i) included participants were not necessarily interested in smoking cessation. Furthermore, participants were not necessarily from the same ethnicity, although mixing ethnicities in genetic studies could lead to population stratification. The majority of studies did not report HWE calculation. (ii) Inclusion criteria differed in number of CPD and none of the studies met the criterion of nicotine addiction, often defined as smoking more than 10 CPD for at least 12 months [71, 76, 80]. (iii) Control groups in the study design received either no intervention [48, 262] or clinical risk notification and no intervention [260, 261]. These factors may have affected our results. However, for example for the control groups, collapsing no intervention to clinical risk notification did not introduce a significant change in comparison to no interventions alone for both Audrain *et al.* [260] or Lerman *et al.* [261]. Moreover, this also did not influence significantly the results of the total pooled analysis.

The reason why some results of the pooled-analysis were significant and others were not remains open to interpretation. The impact of genetic notification is likely to vary with individual characteristics (e. g. willingness to quit smoking, socioeconomic status or health literacy), with the distribution of high and low genetic risk notification, with the way in which the genetic notification is done (e. g. counseling before genetic notification, only oral explanation or leaflet with graphical illustration), the intervention in the control group, and the length of the follow-up. Due to the low number of included studies, it was not possible to stratify the pooled-analyses by time of follow-up (2, 6 or 12 months). Stratification of the results before and after 6 months follow-up should be also of interest. However, after 6 months there were only 2 studies available for genetic notification versus control [48, 260] and only one for the stratified analyses (high genetic risk versus control; low genetic risk versus control; high versus low genetic risk) [48]. This enhances the need of increasing the follow-up of studies about the impact of genetic notification on smoking cessation. The inclusion of new studies in the pooled-analysis could improve the power of the analyses. This could either confirm our current results or in the opposite, present a significant impact of genetic notification in long-term follow-up. However, current results do not demonstrate any evidence of long term effect of genetic notification on smoking cessation. And in a population receiving high genetic risk notification, only one study reported a marginally non-significant long-term effect [48].

In a recent meta-analysis the same primary outcome was studied, but there were differences in the method that was used [155]. In our study, we decided to focus on randomised trials only for their ability to minimise the likelihood of systematic errors. Smerecnik *et al.* included both randomised [48, 260–262] and non randomised

trials [45, 46]. In order to avoid overestimation of a single study we considered one follow-up of each study in the pooled analysis (last follow-up or short-term smoking cessation), whereas this was not the case in the other study. We decided to use RR rather than OR for their easiness of interpretation and for their improved accuracy in prospective studies. In our study we also assessed secondary outcomes (intention-to-quit smoking, emotional outcome and recall and understanding of the genetic information). Despite the differences the main outcome of both studies is similar, which reinforces the validity of the results.

Genetic notification did not influence intention-to-quit smoking, except in one study reporting motivation to quit at one week follow-up [262]. In hypothetical genetic tests, higher anticipated intention-to-quit was reported in genetic notification in comparison to the control group [50] and in the high genetic risk group in comparison to the low genetic risk group [51, 267–269]. This discrepancy seemed to demonstrate that the anticipated reaction in hypothetical genetic tests did not represent reality. However, this could be due to divergence in the presentation and the understanding of genetic notification or differences in the characteristics of the population. The emotional outcome could also influence this result. In hypothetical genetic tests, smokers will probably be less influenced by depression, anxieties and fear arousal than in real genetic tests. Thus, how smokers recall and understand genetic notification as well as how they are influenced by emotional outcome could improve the use of this intervention in smoking cessation. In the pooled-analysis, most participants were in quite strong intention-to-quit at baseline [48, 262]. However, this variable was not assessed in the 2 last studies [260, 261].

Most studies were testing only one single gene to determine smoking related disease risk. This posed also ethical questions because of the uncertainty of disease risk, which is enhanced when using only single gene test in common diseases.

Genetic notification is one possible intervention among others. At the individual level, the most well-known one are the pharmaceutical interventions (nicotine replacement therapies, Bupropion or Varenicline). However, nicotine dependence is not only a physical dependence but also a behavioural and a psychological dependence. Consequently, interventions might take into account these three types of dependence (e. g. multidisciplinary follow-up including psychological counseling and pharmaceutical treatments). Other interventions are also available at the household level (e. g. smoke-free home and partner support) and the society level (e. g. mass media, package warning, and bans). As the evidence for benefit of these interventions is strong and well-established, it is incumbent upon genetics to demonstrate additional benefit [243].

Limitations of the review

Regarding the pooled-analysis, the most important limitation was the low number of included studies, which did not allow us to determine whether the risk varied with particular conditions (e. g. history of smoking related disease or stage of

behavioural change of Prochaska *et al.* [275]). This low number of included publications was even more present in the pooled-analysis. This is also explained by the fact that we would include only randomised trials that are known to be of higher quality [263]. Publication biases are in general the principal methodological limitation in meta-analyses. It is possible that we missed unpublished reports. The Egger statistical analysis, which is a test for publication biases, suggested that there were no small study effects (p-value comprised between 0.11 and 0.76). However, the sensitivity of this test is generally low in meta-analyses based on fewer than 20 studies [276]. Finally, we did not control our results for multiple testing.

Some limitations pertained to the studies themselves. The outcome measures differed across the studies (e.g. smoking cessation: prolonged abstinence or different point prevalence abstinence). Moreover, adjusted RRs were rarely presented in the included studies, which prevented control for confounding factors. Another limitation was that interventions in the control groups were not similar in the different studies included in the pooled-analysis: two studies had a control group without any intervention [48, 262] and the two others had two control groups (no intervention and clinical risk notification) [260, 261]. The latter have been collapsed in the pooled-analyses, which might dilute the effect of genetic notification on smoking cessation.

Finally, limitations are also due to the heterogeneity between the included studies. This is due to the diversity in the inclusion criteria. For example, the mean number of CPD ranged from 15.5 [48] to 22.7 [260, 261] depending on the study. Nevertheless, to take this problem into consideration we used random effect models in the pooled-analyses.

Implications for practice and research

The results from this study suggest that genetic notification of smoking related disease risk could have a positive impact on smoking cessation, particularly in short-term follow-up. To determine the possible implications for practice, further research of the impact of genetic notification on smoking cessation is needed. There is also need to investigate the cost-effectiveness of this intervention. Studies should (i) focus on smokers that want to quit smoking, (ii) focus on population of regular smokers by level of severity of nicotine addiction, (iii) use combination of genetic tests for a single or multiple smoking related diseases, (iv) standardise different concepts (e.g. smoker, addiction, intention-to-quit, and smoking cessation) to minimise the heterogeneity and risk of bias between studies.

SUPPLEMENTARY MATERIAL – CHAPTER 5

PubMed search

The research on Pubmed was realised using the following code:

((smoking cessation) AND ((genetic testing) OR genetic predisposition to disease)))

Quality assessment of studies included in the systematic review of genetic notification

Table 5.3: Quality assessment of studies included in the systematic review of genetic notification

	Selection criteria clearly described	Sample size calculation	Adequate allocation concealment	Comparability of groups at baseline	Presentation of the HWE	Intention-to-treat analysis	Ascertainment of outcome	Control for confounding
Studies included in the systematic review and pooled analysis								
Audrain 1997	+	+	± ¹	+	-	-	- ³	+
Lerman 1997	+	+	± ¹	+	-	-	- ³	+
McBride 2002	+	-	± ¹	± ²	-	+	+	+
Sanderson 2008	+	+	+	+	-	+	- ³	+
Studies just included in the systematic review								
Hamajima 2004	-	-	ø	ø	?	-	- ³	-
Hishida 2010	-	-	-	+	+	-	- ³	+
Ito 2006	±	+	-	+	-	+	- ³	+
Kano 2007	-	-	ø	ø	-	+	- ³	-

+ Yes; - No or not reported; ? unclear; ø Not applicable; ¹ No explanation on how the randomisation was processed; ² Significant difference in desire to quit at baseline (but not corrected for multiple testing); ³ Not even try to confirm the smoking status biochemically

COMMUNICATING GENETICS AND SMOKING THROUGH
SOCIAL MEDIA: ARE WE THERE YET?

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de Viron S, Suggs LS, Brand A, Van Oyen H (2013) Communicating genetics and smoking through social media: Are we there yet? *J. Med. Internet Res.* 15(9):e198.
DOI: 10.2196/jmir.2653.

ABSTRACT

Background Social media is a recent source of health information, which could disseminate new scientific research, such as genetics of smoking.

Objectives Therefore, the objectives were (1) to evaluate the availability of genetic information about smoking on different social media (YouTube, Facebook and Twitter) and (2) to assess the type and the content of the information displayed on the social media as well as the profile of people publishing this information.

Methods We screened the posts on YouTube, Facebook and Twitter with the following terms '*smoking*' and '*genetic*' in two time points (September 18, 2012 and May 7, 2013). The first 100 posts were reviewed for each media for the time points. Google was searched during Time 2 as an indicator of available information on the web and the other social media discussing genetics and smoking. The source of information, the country of the publisher, characteristics of the posts, and content of the posts were extracted.

Results In YouTube, Facebook and Twitter, respectively, 31, 0 and 84 posts were included. Posts were mostly based on addiction smoking related diseases, referring to scientific publications and the publisher was mostly from the US. In Google search, most results were scientific databases. Six scientific publications referred to within the Google search were also retrieved on either YouTube or Twitter.

Conclusions Despite the importance of public understanding of smoking and genetics and the high use of social media, little information is present on social media. Therefore, there is a need to monitor the information and to evaluate the understanding of the population about information related to genetics and smoking displayed on social media.

INTRODUCTION

Social media are increasingly recognised as important tools for information provision, gathering and transfer. Social media allow the spread of information to many people through different means [277]. For example, someone can publish a video on YouTube where anyone can view, listen, and even download the video. They can also create a group on Facebook to promote that video. In social media, every individual, regardless of credentials, is able to post and retrieve such information. Therefore, available information on social media is not exclusively based on expert's knowledge but both on experts' and laypersons' experiences [278].

Health consumers use social media for a variety of purposes. A recent consumer survey observed that 24% of consumers posted information about their health experiences on social media platforms. Sixteen percent of consumers posted reviews of medications, treatments, doctors or health insurers. Health symptoms or behaviour were traced and shared for 18% of the consumers. Health-related causes were joined by 20% of the consumers and supported by 28%. Further, 16% of consumers share health-related videos or images on social media. Consumer trust in information posted on social media varied by messenger source ranging from hospitals (55%), from others they know (46%), health insurance companies (42%), and from unknown patients (25%). Regarding their susceptibility to share their own health information on social media, 30% would share this information with other patients, 43% with hospitals, and 38% with health insurance companies [278, 279].

To date, most studies assessing the exposure to information about smoking on social media focused on pro- and anti-smoking information. Among adolescents, exposure to tobacco content appeared to be limited in volume with 43% of adolescents being exposed to a mean of 13 pages of pro-tobacco content during 1-month follow-up [280]. The rate was nearly similar for anti-tobacco content, with 45% of the adolescents exposed to a mean of 10 pages of anti-tobacco content [280]. Some studies focused on the content of posts on YouTube specifically, most of them being on tobacco control. But other topics were also developed: anti-smoking and quit smoking posts as well as smoking sexual fetish posts [278]. Facebook and Twitter are important ways to monitor the tobacco industry and to facilitate tobacco control [281]. As proposed by Hefler *et al.* social media strategies may be integrated into tobacco control organisations [281]. Moreover, social media, such as Facebook, already include information about many disorders and genetic syndromes [282].

Given the use of social media for health purposes and the increasing research, academic papers, and public and policy attention to genetic testing and genetic relationships with disease, it is expected that social media are likely to become an important source for obtaining and disseminating genome-based information [33].

Despite the vast amount of research and efforts to prevent smoking and support cessation, smoking is still a major public health problem worldwide. Factors influencing smoking behaviour are both non-genetic and genetic. Non-genetic factors included a broad range of aspects, such as social factors (e.g. smoking status of

peers), economic factors (e. g. level of income), or psychological factors (e. g. weight concerns). For genetic factors, the two main factors are the genes influencing the nicotine metabolism and genes influencing the cascade theory of reward [221].

Genetics and smoking are highly covered topics on different media. For example, a search for 'genetics' and 'smoking' on PubMed (including scientifically based content) resulted in 15,948 results. A search on Google (including both scientifically and non-scientifically based content) revealed 9,970,000 hits. On YouTube, 1,300,000 posts were obtained, on Facebook 472,000, and 8,020 on Twitter (using the searches, 'smoking + genetic + site: YouTube.com', 'smoking + genetic + site: facebook.com', and 'smoking + genetic + site: twitter.com'). We also conducted a search of a specialised social media platform, PatientsLikeMe, and found 167 hits. However, upon review of posts, only one publication about chronic obstructive pulmonary disease (COPD) and genetics was listed (and this publication was displayed multiple times). The high number of results in both scientific and non-scientific search sources suggests that such information could also be available in popular social media and could be found by lay public using typical simple search strategies.

Given the reach of social media and the growing reliance on it for health purposes, combined with the importance of genetics and smoking, this study aims to explore the availability of genome-based information about smoking on three popular social media platforms (YouTube, Facebook and Twitter). Questions examined include,

1. What type of information about genetics and smoking is displayed on social media?,
2. What is the source (scientific or non-scientific) of the posted information?,
3. What is the role of the publisher?, and
4. What countries is information being posted from?

We expected that the information would be posted primarily from scientific sources from research centers in the United States and Europe.

METHODS

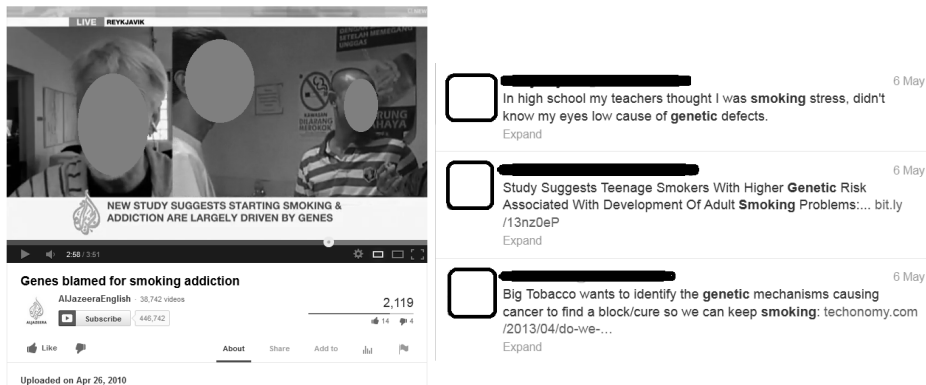
Sample

Posts from YouTube, Facebook and Twitter were included. YouTube (video sharing), Facebook (social networking) and Twitter (social networking and microblogging) are each ranked among the top 10 most popular websites [283], Facebook was positioned second place just after Google. YouTube and Twitter were respectively at positions 3 and 8. The other websites included in the top 10 were retail websites (e. g. Amazon. com) or Web-search engine (e. g. Google). Therefore, YouTube, Facebook and Twitter appeared to be the most relevant social media. The number of users on social media is growing daily, however Facebook is still the top used medium with

around 1.01 billion active users in 2012 [284]. Twitter counts roughly 500 million users and 200 million active users [285], and over 800 million unique users visit YouTube [286] each month.

Search strategy

The terms '*genetic*' and '*smoking*' were searched for on each of the three social media. These terms were selected because they were simple terms that the general population may use to get information on the topic. The search was performed using two time points, the first one on September 18, 2012, and the second on May 7, 2013. The first 100 posts available for each social media platform were examined. Posts on YouTube were searched with the 'relevance' option (the default option). On Facebook, posts were searched using both the total results and results by 'people', 'pages', 'groups', 'apps', 'events', 'music', 'public posts', and 'posts in groups'. On Twitter, only the posts of the previous days (approximately one week depending on the storage capacity of Twitter's database) were visible at Time 1. This changed at Time 2, when posts from the previous months were available. Posts were excluded if they did not express the link between genetics and smoking tobacco (including smoking initiation, addiction, cessation and smoking related diseases). Figure 6.1 shows an example of the posts retrieved on YouTube and Twitter.



(a) is the screenshot of YouTube (b) is the screenshot of Twitter.

Figure 6.1: Screenshots of YouTube and Twitter results

Moreover, the first 100 posts were searched on Google at Time 2 using the same search terms. The aim of searching posts on Google was twofold, firstly to indicate the type of information available on the Internet and secondly to determine if there were other social media that discussed genetics and smoking (e. g. health forums or blogs).

Data extraction

From the different posts, the date of the publication and the country of the publisher were extracted. To understand, at least partially, the credibility of the information provider, the role of the publisher was coded and classified as a research center, news, medical news, independent user (i.e. meaning that the person posting on the social media was acting as an individual citizen and not on behalf of a group of people or organisation or as a scientist) and other, if it belonged to none of the previous categories (e.g. foundation such as 'Arthritis Foundations' or companies such as '23andme'). The source of posted information was categorised as 'scientific publication', 'referring to a scientific publication' and 'non-referring to a scientific publication'. This allowed us to understand the differences in types of content posted on the three social media. The content of the posts was classified into smoking initiation, addiction, cessation, and smoking related diseases. At least a link between genetics and the specific category must have been mentioned to allow the classification. Moreover, one post may have been classified in more than one category. For smoking related diseases, we extracted the disease of interest. When available, we extracted the number of views and the opinion (like or dislike) of the post.

Statistical analyses

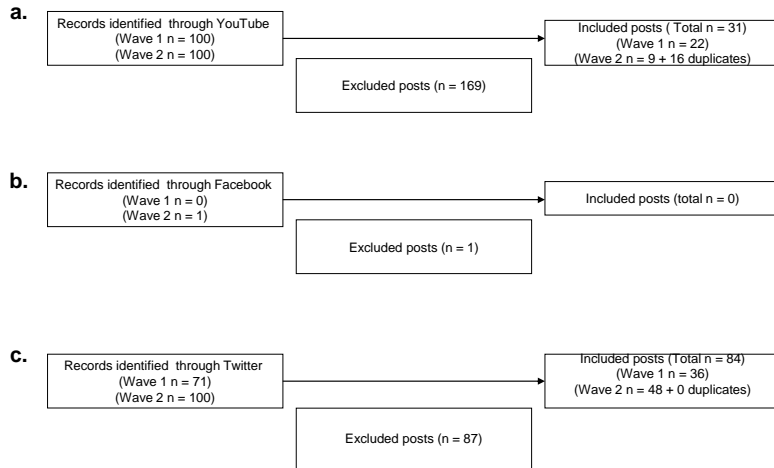
Univariate analyses were assessed by the Pearson's Chi square for categorical data and the Kruskal-Wallis one-way analysis of variance for continuous data (because the continuous variables were not normally distributed). Tests were two-sided with a significance rate α of 0.05. Tests were corrected for multiple testing through Bonferroni-Sidak. P-values lower than 0.001 remained significant after correction for multiple testing. All statistical analyses were performed using STATA, version 10.1 (STATA Corporation Inc., College Station, TX, USA).

To show the content of the posts on Twitter, the titles of the posts on YouTube, and the most frequent words found in the titles of the Google search, word clouds were used. Word clouds visually represent the frequency of the words used in the posts with larger size for more frequent words. Word clouds were created with the 'wordcloud' package using the R project for statistical computing (R version 2.14.1; <http://www.R-project.org>).

RESULTS

Characteristics of the three social media

Across both data collection points, YouTube, Facebook and Twitter retrieved, respectively, a total of 200, 0 and 171 posts among them 31, 0 and 84 discussed genetics of smoking. On YouTube 16 posts were retrieved both at Time 1 and 2. Moreover, from the 9 posts selected at Time 2, three were published after Time 1. By contrast, Time 1 (September 2012) and 2 (January to May 2013) did not overlap on Twitter. Therefore, no posts were found at both data collection points on Twitter (Figure 6.2). The number of included and excluded posts was significantly different between the three different social media ($P < 0.001$). Twitter obtained a higher proportion of posts discussing genetics and smoking (49.1% in comparison to 15.5% on YouTube).



(a) is the YouTube flow chart; (b) is the Facebook flow chart; (c) is the Twitter flow chart.

Figure 6.2: Flow Chart of the post selection

Table 6.1: Characteristics of included posts on YouTube and Twitter

VARIABLES	YOUTUBE (N=31)	TWITTER (N=84)	GOOGLE (N=86)	P-VALUE <i>youtube</i> <i>vs. twitter</i>	P-VALUE <i>youtube vs.</i> <i>twitter vs. google</i>
Source of information ^a				0.19 *	<0.001 *
Scientific publication	0 (0.0)	5 (6.0)	40 (46.5)		
Referring to a scientific publication	30 (96.8)	71 (84.5)	46 (53.5)		
Non-referring to a scientific publication	1 (3.2)	8 (9.5)	0 (0.0)		
Role of the publisher ^a				<0.001 *	<0.001 *
Research center	8 (25.8)	4 (4.7)	4 (4.7)		
News	11 (35.5)	7 (8.3)	16 (18.6)		
Medical news	10 (32.3)	17 (20.2)	19 (22.1)		
Independent user	1 (3.2)	38 (45.2)	0 (0.0)		
Scientific database	0 (0.0)	0 (0.0)	40 (46.5)		
Other	1 (3.2)	18 (21.4)	7 (29.9)		
Country of the publisher ^{a,c}				0.18	0.003
USA	21 (70.0)	42 (50.6)	61 (81.3)		
UK	2 (6.7)	1 (1.2)	7 (9.3)		
Canada	1 (3.3)	3 (3.6)	0 (0.0)		
Italy	0 (0.0)	3 (3.6)	1 (1.3)		
Other	2 (6.5)	14 (16.7)	15 (17.4)		
Characteristics of the post ^b				<0.001 *	<0.001 *
Total number of days available	876 [319; 1441]	12.5 [5; 39]	707 [230; 1951]		
Duration (min)	1.61 [1.43; 2.77]	n.a.	n.a.	n.a.	n.a.
Total number of viewership	232 [64; 1037]	n.a.	n.a.	n.a.	n.a.
Total number of likes for the post	1 [0; 2]	n.a.	n.a.	n.a.	n.a.
Total number of dislikes for the post	0 [0; 1]	n.a.	n.a.	n.a.	n.a.
Content of the post ^a				0.12	0.23
Smoking initiation	2 (6.5)	15 (18.1)	17 (19.8)		
Smoking addiction	14 (45.2)	53 (63.9)	62 (72.1)	0.07	0.03
Smoking cessation	8 (25.8)	23 (27.7)	32 (37.2)	0.84	0.31
Smoking related diseases	21 (67.7)	29 (34.5)	34 (39.5)	<0.001 *	0.005
Type of smoking related diseases ^{a,d}					

Continued on next page

VARIABLES	YOUTUBE (N=31)	TWITTER (N=84)	GOOGLE (N=86)	P-VALUE <i>youtube</i> <i>vs. twitter</i>	P-VALUE <i>youtube vs.</i> <i>twitter vs. google</i>
Lung disease	1 (4.8)	0 (0.0)	0 (0.0)	0.24	0.22
COPD	2 (9.5)	5 (17.2)	1 (3.0)	0.44	0.17
Lung cancer	12 (57.1)	16 (55.2)	21 (63.6)	0.89	0.78
Cancer in general	4 (19.1)	3 (10.3)	3 (9.1)	0.38	0.52
Cardiovascular disease	1 (4.8)	1 (3.5)	1 (3.0)	0.82	0.95
Multiple diseases	0 (0.0)	1 (3.5)	3 (9.1)	0.39	0.29

n.a. not applicable; ^a number (percent) and p-value from Pearson's Chi square; ^b Median [p25;p75] and p-value from Kruskal-Wallis one-way analysis of variance; ^c on YouTube, there were 5 missing values, 21 on Twitter, and 2 on Google search; ^d only posts referring to smoking related diseases were used; COPD Chronic obstructive pulmonary disease; **Bold** significant p-values; * Significant p-values after Bonferroni-Sidak correction for multiple testing.

When comparing included posts obtained from Twitter and YouTube (Table 6.1), no differences in the source of information or in the country of the publisher were observed. However, the role of the publisher was significantly different between the two media ($P < 0.001$). Most publishers were independent users on Twitter (45.2%) although it was the smallest role category (3.2%) on YouTube. On YouTube, most posts were published by news or medical news instead of independent users on Twitter. For the content of the posts, a higher number of YouTube posts reported an impact of genetics on smoking related disease than on Twitter ($P = 0.001$). The other contents (smoking initiation, addiction and cessation) obtained similar results on YouTube and Twitter. For smoking related diseases, no comparison of the different types of disorders led to differences between YouTube and Twitter.

Between the two time points for both YouTube and Twitter, posts did not differ in the source of information, role of the publisher, country of the publisher, and characteristics of the posts. On YouTube, the content of the posts were not different between the two time points. By contrast, on Twitter, the content differed for smoking initiation ($P < 0.001$), addiction ($P < 0.001$), cessation ($P < 0.001$), and related disease ($P < 0.001$) (Table 6.2). Moreover, on Twitter, there was a significant difference in the number of days the posts were available ($P < 0.001$).

Table 6.2: Comparison of the content of the posts between Time 1 and 2

	YOUTUBE			TWITTER		
	Time 1	Time 2	P-value	Time 1	Time 2	P-value
Smoking initiation	0 (0.0)	2 (22.2)	0.02	0 (0.0)	15 (31.9)	<0.001 *
Smoking addiction	8 (36.4)	6 (66.7)	0.12	13 (36.1)	40 (85.1)	<0.001 *
Smoking cessation	6 (27.3)	2 (22.2)	0.77	1 (2.8)	22 (46.8)	<0.001 *
Smoking related disease	17 (77.3)	4 (44.4)	0.08	22 (61.1)	7 (14.6)	<0.001 *

number (percent) and p-value from Pearson's Chi-square; **Bold** significant p-values; * Significant p-values after Bonferroni-Sidak correction for multiple testing.

Comparison between social media and Google search

Of the first 100 websites retrieved from the Google search, 86 were related to genetics and smoking. No new social media channels were revealed from this search. Websites retrieved from Google search were different from the posts on YouTube and Twitter, both in source of information and role of publisher. On Google, websites were more often scientific publications (46.5%) than on YouTube (0.0%) or Twitter (5.9%), explaining also the difference in the role of the publisher (scientific database, 46.5%) (Table 6.1).

Some scientific publications referred to on YouTube were also found on the Google search (e. g. Amos *et al.* [287] was listed five times on YouTube and once on Google) and the same for Twitter (e. g. Govidan *et al.* [288] appeared 12 times on Twitter and 1 time on Google, and Belsky *et al.* [289], 38 times on Twitter and 9 on Google). However, no scientific publication found on YouTube was also retrieved on Twitter.

ically as genetic testing and personalised medicine become more widely known. For YouTube and Twitter, most posts referred to scientific publications that were recently published.

The reason why no posts on genetics and smoking were retrieved using Facebook, versus the 472,000 posts obtained by using the search 'smoking + genetic + site:facebook.com', is that Facebook is not a search engine and by contrast to Google is. Interestingly, the same search strategy in another search engine resulted in a different number of retrieved posts (e.g. using Bing.com 37,000 posts were found). Nonetheless, social media do not allow for such advanced search strategies and users do not typically use such search strings. Our objective was to know what information lay people find on genetics and smoking when using social media, so we developed our search within the social media and used typical search strategies.

The reason for the highest number of posts coming from the United States in comparison to other countries may be explained by the size of the country and high Web adoption rate [290], rather than the importance of the topic in any country. For example, Facebook had the highest number of users in the United States (167,554,700 users). Brazil was second with only 60,665,740 users. In comparison, the United Kingdom had 33,227,180 users and was in sixth position [291]. Despite the European ITFoM project (IT Future of Medicine) [292], PHGEN project (Public Health Genomics European Network) [4], the activities of the EAPM (European Alliance for Personalised Medicine) [293], and the high policy attention of it in Europe, the mere size of the continents and way in which each respective public accesses science information, probably helps to explain why the posts from Europe were fewer than in the USA.

On Twitter, the period of availability of the posts changed between Time 1 and 2 (from approximately one week to several months). This may explain the highest number posts included in Time 2.

The contents of the posts mostly focused on genetics of addiction and smoking related diseases. This result is consistent with the higher number of scientific publications on both topics than on any other topic linking genetics and smoking. The smoking related disease of interest was mainly lung cancer; this is also in line with the knowledge of the general population. Simon *et al.* reported that smoking as a risk factor for lung cancer was recalled by 85% of the population and recognised in a list of factors by 94% of the population [294].

The opinion about the posts on YouTube (measured by the number of likes and dislikes, as reported on Table 6.1) should be viewed cautiously due to the small number of observations. The range of 'like' posts was between 0 and 16 and 'dislike' between 0 and 4 while the number of viewers ranged from 17 to 10,350. Moreover, for the posts that were retrieved in both time points, the number of likes and dislikes did not change significantly.

The difference between YouTube and Twitter for the number of days of a post's availability on the Web ($P < 0.001$) is explained by the fact that the Twitter search was performed by date and that posts on YouTube were classified by relevance. The

search by date for Twitter and relevance for YouTube were used because they were the default options and therefore, probably the most frequently used by the population. Nevertheless, no differences between YouTube and Twitter were reported in the source of information and the country of the publisher, making the information comparable.

When using Google search as an indicator of the information about genetics and smoking available on the Web, we first observed differences between the posts retrieved on social media. As expected, most websites were scientific publications per se (46.5%) or referred to scientific publications (53.5%). Six scientific publications were referred at least once on the Google search and either on YouTube or Twitter [68, 287–289, 295]. The second objective of searching Google was to discover any other social media that included discussions of genetics and smoking. Despite our expectations, no social media, such as health forums or blogs, were retrieved. This might be explained by the novelty of the topic.

Information on genetic testing and smoking is already on the Web with direct-to-consumer testing such as 23andMe where they look for the *CHRNA3* gene, more specifically the variant rs1051730. *CHRNA3* is a nicotinic receptor. Tests on smoking related disorders are also available on 23andMe for lung cancer. As proposed by Pray in 2008, *"imagine reading this warning on a cigarette package: Smokers with a particular mutation have a dramatically higher risk of developing lung cancer. Would you get tested for this mutation?"* [296]. In the future, this kind of message may also be displayed on social media.

The way that individuals understand the posts on YouTube and Twitter should be assessed in a further study. Indeed, it is becoming more common that people are looking to different social media to get information about their health [279]. As public health genomics, personalised medicine, and personalised health terms become more commonly known terms, the public, including the general population, patients, and health professionals, will certainly look to social media to learn more about them and discuss them. Hence, information must be translated and communicated in a way for the general public to understand, especially since genome-based information, which includes genetic information, is a complicated topic for the non-scientific population.

Providing health information via social media and developing methods to evaluate their impact may help in effectively increasing health literacy and risk awareness in an innovative way, with attention to avoiding the introduction or widening of health inequalities. However, to generate effective health information messages, different conditions may be needed depending, for example, on the topic, target group, or society, taking into account both environment (internal and external) and the process of information (automatic and rational) [39]. Therefore, there is a real need to develop efficient communication tools to improve the health and genetic literacy of the population. Moreover, any message should aim to be correct, clear and adapted to the target population to maximise understanding of the content. Also, any ethical and legal issues of displaying such messages should be considered. Achieving

these conditions is of critical importance to develop quality information that can be obtained and understood by those accessing it and those who need it.

Future research should examine the impact that information about genetics and smoking on popular social media has on target population literacy and behaviours. Exposure to genetic information about smoking in social media might be examined in various target populations (e.g. university students and pregnant women) in controlled settings where the target population is exposed to different genetic information about smoking during a certain period of time (e.g. one week). After the exposure step, the impact of the information and information channel on different outcomes (e.g. behaviour change, genetics and smoking knowledge) would be assessed. The exposure-outcome relationship might then be evaluated using advanced statistical methods, such as structural equation modeling. Finally, as with any communication channel, content spread through social media channels should be carefully scrutinised by the reader. All media have the potential to include biased and misleading information, but social media platforms can spread such information rapidly. At the same time, social media also allow for corrections and dialog about content to occur quickly and transparently. Moreover information may or may not be beneficial, but the ability to understand if the information is credible and ways in which to improve critical thinking and appraisal skills of social media users should be a priority of research and practice as well as codes of conduct for posting information.

Limitations

The most important limitation of our study is that we collected data from channels that change rapidly, at only two points in time. Consequently, the posts that were selected in our review may not be reflective of what is posted at another time. The collection of data at time points separated by 9 months, may give better insights of the evolution of posts over time. However, as the content posted on social media happens constantly, data collected over time points may yield different results. Particularly on Twitter, our results are likely to be different depending on the time of the search. For example, at Time 1, we observed that 35.2% of the posts were based on the lyrics of a song, which are likely to be ephemeral. At Time 2, only 16.0% of the posts referred to that song.

The search strategy may have resulted in posts being missed. We limited the search to two search terms ('genetic' and 'smoking') and the first hundred posts, which may not have captured all the relevant posts. However, the results obtained in our search provide a reasonable perspective of what someone interested in smoking and genetics would find on the topic on YouTube, Facebook and Twitter. Facebook, as a relatively closed system, did not allow an indepth overview look at the posts of users.

The limits on the three selected social media may influence the obtained results. Other social media such as health forums might lead to different results.

Implications for practice and research

This study focused on the availability of information on genetics and smoking and serves as a baseline measure from September 2012 and May 2013. Given the growing use of social media for health purposes, there is a need to monitor this situation over time to avoid the dispersion of false information. The topic of genetics and smoking is not currently widely discussed on the three social media platforms chosen. However, this is expected to change due to growing concerns about genetics in other media such as newspapers. This study did not provide any information on the profile of the viewers (e. g. smokers or non-smokers) or the use of that information (e. g. subsequent change in smoking behaviour). A future study assessing the habits and the characteristics of the population looking for health information (e. g. general population, patients, and health professionals) and more specifically information about genetics and smoking, will be needed. Moreover, a better overview of the users' understanding of the displayed information will be of high importance. Also, from the scientific point of view, the concept of 'genetic information' needs to be broadened towards 'genome-based information', taking into account emerging knowledge from the whole 'omics' field including epigenomics and the interaction of genomics and environment, such as in the case of smoking.

This study suggests that most of the information about genetics and smoking available on social media referred to scientific publications displayed by different kind of publishers (research center, news, and medical news). Increasing access to such information might improve the health and the genomic literacy of the population and, therefore, enhance smoking prevention and cessation.

7

WHICH INTERNET TOOLS ARE SEARCHED BY STUDENTS AT UNIVERSITY TO OBTAIN INFORMATION ABOUT HEALTH, SMOKING AND GENETICS? A PILOT STUDY

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ABSTRACT

Objectives The Internet is a new tool that provides health information and therefore may enhance the health literacy of the population. The study aims were twofold, to explore what Internet tools are used and what factors influence the search of information about health, smoking and genetics among Belgian university students on the Internet.

Methods In this pilot study, 9 out of 14 conveniently selected faculties of the Catholic University of Louvain in Belgium sent out a web-based questionnaire based on the Information seeking behaviour model to their students. The questionnaire was available from the 1st of March till the 31st of May 2013. Factors assessed were general demographics, smoking behaviour, and the use of social media to obtain information about health, smoking and genetics. Statistical analyses included Chi-square, t-test, Spearman correlations and multivariate logistics regressions.

Results Out of 2,171 students who answered the full questionnaire, 1,937 were searching for information about health, smoking and/or genetics on Internet tools. Students were mainly searching for information about health, smoking and/or genetics on web search engine (92.9%) and Forum (44.6%). Factors influencing the search of information about health were monthly budget, ethnicity, smoking status and the faculty of study ($P < 0.001$).

Conclusions University students are already used to searching for information about health, smoking and genetics on different Internet tools. Health topics are more frequently questioned than smoking and genetics. Therefore, monitoring and developing targeted messages on such media may improve the health and genetic literacy.

INTRODUCTION

With the growing access to the Internet and the ability to provide, gather and share information, Internet tools became a new source of health information. Indeed, the Internet is an easy tool allowing dissemination of health information to a large population in an inexpensive way [297]. Moreover, in comparison to other media such as television or newspaper, it allows the immediate information access [298]. Information may be gathered in an anonymous way and tailored for specific populations of interest (e. g. young adults and pregnant women) [299].

In 2010, about 80% of the American population connected to the Internet was searching for health information on the Internet [300]. The Internet is used for different purposes such as buying medicine and vitamins, communicating with physicians and participating in group discussion about medical conditions [301]. Genetics, as a field in huge expansion, represents new kinds of information available on the Internet. The use of genetic information leads to more personalized healthcare by, for example, communicating genetic risk of diseases or personalizing treatment based on genetic criteria. Direct-to-consumer genetic testing were read or heard by 29.2% of the population connected to the Internet in an American survey and around 8.1% bought the genetic test [301]. Despite the popularity of searching for health information on the Internet, people are still going to their physicians for confirmation or affirmation of what they searched [301, 302].

Research indicates that online communication is effective at improving health literacy of the population on specific health topics. Moreover, it appears to induce effective behaviour change that may have an impact on short and long-term follow-up. The use of theory (e. g. theory of planned behaviour), behaviour change techniques (e. g. emotional control setting) and methods of interaction with participants appear to improve the effectiveness of the online intervention [303].

The most important challenge facing the Internet tools, which serve as a source of health information, is to make Internet users access and return to a specific Internet page. To enhance this point, rapidly evolving and dynamic content might be adopted. Moreover, promoting active users is also a positive factor [299].

However, some concerns regarding the display of health information on the Internet are evidenced. They included questions about the quality of the information, the quantity of the information that may lead to confusion and reduced trust in physicians [39]. Moreover, a recent study assessed the availability of genetic information about smoking on three different social media (Twitter, Facebook and Twitter). The available information mostly referred to scientifically based publications [304]. Therefore, there is a need to assess the type of Internet tools used by the population, to develop new health information on Internet tools and to monitor the quality and the quantity of the information displayed. Indeed, improving health information on the Internet might enhance the health literacy of the population [254].

Given the importance of smoking as a major public health problem and the novelty of the genetics field, these two specific areas were used in combination with

health to have a broader idea of the state of the search on health information related to Internet tools. The aim of the study is twofold: to explore what Internet tools are used and what factors influence the search of information about health, smoking and genetics among Belgian university students on the Internet.

METHODS

Study design and study population

A cross-sectional study was conducted between the 1st of March and the 31st of May 2013 among students registered in 9 conveniently selected faculties out of the 14 faculties of the UCL. The 9 included Faculties were: law; polytechnic; political, economic and social science; pharmacy and biomedical science; philosophy, arts and letter; motor functions science; public health; architecture; psychology and education. The UCL is the largest French university in Belgium including more than 28,000 students. To get a higher visibility and therefore a potentially higher response rate, students got informed about the present study by a single email sent by the Dean of the Faculty. The Deans sent a single email to their students.

Questionnaire

A web-based questionnaire was formatted using LimeSurvey. LimeSurvey is an open source tool for online surveys that allows the storage of the answers on personal servers. The questionnaire was based on the conceptual frameworks of Johnson *et al.* [305] and Niedwiedzka *et al.* [306]. The questionnaire was developed in French and included 37 questions arranged in four groups: (i) socio-demographics, (ii) tobacco consumption, (iii) opinion and knowledge about tobacco and genetics, and (iv) the search of information about health smoking and genetics on Internet tools. Questions were either multiple choice, true-false or 5-point Likert scale questions. The questionnaire was pre-tested on a sample of 10 university students, allowing the adaptation of questions. The adapted questionnaire was used in the present study.

Data and measures

Only fully answered questionnaires were used in the calculations. However, as some questions were not mandatory or followed a filter the sample size may differ for some analyses.

Socio-demographic questions were used to control the statistical calculations. For ethnicity, three options were available: Belgian (coded as 0), European excluding Belgian (coded as 1) and non-European (coded as 2). Variables about education (bachelor, master and doctoral students) and the Faculty of study were extracted from one single open-question. The measure of monthly budget was an average of

the monthly net residual income including both pocket money and money earned by working and excluding the amount of money used to pay the housing. Seven options were proposed: less than 50 euros (coded as 1); between 50 and 99 euros (coded as 2); between 100 and 199 euros (coded as 3); between 200 and 399 euros (coded as 4); between 400 and 599 euros (coded as 5); between 600 and 899 euros (coded as 6); more than 899 euros (coded as 7).

The smoking status, as self-reported by students, was separated in the following categories: never smoker (coded as 0), former smoker (coded as 1), occasional smoker (not smoking every day) (coded as 2) and current smoker (smoking every day) (coded as 3). The score of genetic knowledge, ranging from 0 to 3, was calculated based on the three following true/false questions: Each individual, carrier of a genetic disorder whichever it is, will develop the symptoms of the disorder (False); Most human characteristics are controlled by a single gene (False); A cell from a nail contains all genetic information necessary to create a human (True). Each right answer increased the score by one.

Internet tools used by students were assessed for the three topics (health, smoking and genetics) using the following options: no tool; web-search engine (e. g. Google); Forum (e. g. Doctissimo); Facebook; Twitter; YouTube. Moreover, students had the opportunity to report other Internet tools. The frequency in the use of social media was evaluated with the following options: never (coded as 0), less than once a year (coded as 1), more than once a year (coded as 2); more than once a month (coded as 3), more than once a week (coded as 4), and more than once a day (coded as 5).

Outcome variables

The three different outcomes variables were searching for information about health, smoking and genetics using Internet tools. The outcomes were dichotomous (Yes or No, respectively coded as 1 and 0).

Statistical analyses

Univariate analyses were assessed by the Pearson's Chi square for categorical data and the t-test for continuous data. Spearman correlations were developed using Bonferroni correction for multiple testing.

Stepwise logistic regression models were used to determine explanatory variables of searching for information about health, smoking and genetics on different types of Internet tools. For each of the model, a forward and a backward selection were conducted, using a significance level of, respectively, 0.05 and 0.10. Independent variables were selected if the correlation with the outcome was higher than 0.05. This method was used due to the low current knowledge of factors influencing the search of information about health, smoking and genetics on Internet tools. Moreover, interactions between reasons to quit smoking and other variables were examined.

Analyses were two-sided with a significance rate α of 0.05. All statistical analyses were performed using STATA, version 10.1 (STATA Corporation Inc., College Station, TX, USA).

RESULTS

Initially 2,574 students answered the questionnaire, 403 answers were removed due to (i) incomplete questionnaire, (ii) inconsistent answers and (iii) not being a student at the UCL or from one of the nine selected Faculties. The final sample included 2,171 participants (Figure 7.1), which represents about 10% response rate of the 9 included Faculties (the same response rate was observed in each Faculty separately). As in the total population of students from the UCL, the mean age was about 22 years and women were more represented (63.9%). Most students were actually doing their bachelor studies (55.2%) and living in student housing (49.4%). About 12.8% of students were currently smoking and 11.4% occasional smokers. Moreover, most students had the maximum score of genetic knowledge (59.9%). Additionally, students mostly used social media more than once a day (79.2%) (Table 7.1).

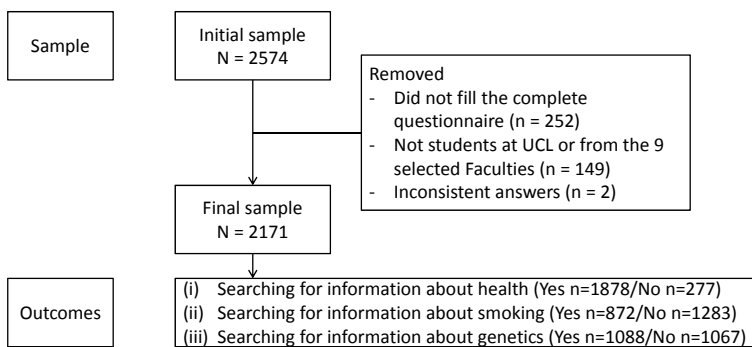


Figure 7.1: Flow diagram of data of the study exploring the Internet tools used by students at the Catholic University of Louvain to search for information about health, smoking and genetics

Most students were searching for information about at least health, smoking or genetics on Internet tools (89.2%). Those students searching for information on Internet tools were mostly women ($P < 0.001$), living in student housing ($P = 0.003$) and using social media more than once a day ($P < 0.001$) (Table 7.1).

Among different Internet tools, students were mainly searching for information about health on web-search engine (78.7%); this result was observed in a lower case for tobacco (34.4%) and genetics (45.0%). Web-search engine was followed by, respectively, Forum, YouTube, Facebook and Twitter. Moreover, students were more frequently using no tools to search for information about smoking (59.5%) or genetics (49.5%) than health (12.9%) (Table 7.2).

Table 7.1: General characteristics of the student's population by searching or not for information about at least health, smoking or genetics in Internet tools

	SEARCHING FOR INFORMATION (n = 1932)	NOT SEARCHING FOR INFORMATION (n = 239)	TOTAL (N = 2171)	P-VALUE
Male gender ^a	658 (34.1)	126 (52.7)	784 (36.1)	<0.001
Age ^b	21.8 ± 3.8	21.8 ± 4.6	21.8 ± 3.9	0.95
Ethnicity ^a				0.37
	Belgian	1687 (87.3)	209 (87.5)	1896 (87.3)
	European	190 (9.8)	25 (10.5)	215 (9.9)
	Non-European	49 (2.5)	3 (1.3)	52 (2.4)
Monthly budget ^a				0.40
	Less than 50 euros	186 (9.8)	30 (13.2)	216 (10.2)
	Between 50 and 99 euros	333 (17.6)	48 (21.1)	381 (18.0)
	Between 100 and 199 euros	522 (27.6)	56 (24.6)	578 (27.3)
	Between 200 and 399 euros	561 (29.7)	58 (25.4)	619 (29.2)
	Between 400 and 599 euros	141 (7.5)	21 (9.2)	162 (7.7)
	Between 600 and 899 euros	34 (1.8)	3 (1.3)	37 (1.8)
	More than 899 euros	87 (4.6)	8 (3.5)	95 (4.5)
Education ^a				0.76
	Bachelor students	1026 (55.0)	131 (57.5)	1157 (55.2)
	Master students	766 (41.0)	90 (39.5)	856 (40.9)
	Doctoral students	19 (1.0)	1 (0.4)	20 (1.0)
Faculty ^a				0.14
	Law	246 (12.7)	29 (12.1)	275 (12.7)
	Polytechnic	223 (11.5)	39 (16.3)	262 (12.1)
	Political, economic, and social science	692 (35.8)	93 (38.9)	785 (36.2)
	Pharmacy and biomedical science	104 (5.4)	9 (3.8)	113 (5.2)
	Philosophy, arts and letter	280 (14.5)	30 (12.6)	310 (14.2)
	Motor functions science	120 (6.2)	11 (4.6)	131 (6.0)
	Public health	56 (2.9)	3 (1.3)	59 (2.7)
	Architecture	96 (5.0)	16 (6.7)	112 (5.2)
	Psychology and education	115 (6.0)	9 (3.8)	124 (5.7)
Smoking status ^a				0.06
	Never smoker	1366 (70.7)	154 (64.4)	1520 (70.0)
	Former smoker	110 (5.7)	16 (6.7)	126 (5.8)
	Occasional smoker	222 (11.5)	26 (10.9)	248 (11.4)
	Current smoker	234 (12.1)	43 (18.0)	277 (12.8)
Use of social media ^a				<0.001
	Never	10 (0.5)	16 (6.7)	26 (1.2)
	< 1 time per year	7 (0.4)	1 (0.4)	8 (0.4)
	> 1 time per year	22 (1.1)	2 (0.8)	24 (1.1)
	> 1 time per month	34 (1.8)	5 (2.1)	38 (1.8)
	> 1 time per week	299 (15.5)	55 (23.0)	354 (16.3)
	> 1 time per day	1560 (80.8)	160 (67.0)	1720 (79.2)
Genetic knowledge score ^a				0.39
	0	3 (0.2)	1 (0.7)	4 (0.3)
	1	97 (7.3)	15 (9.7)	112 (7.5)
	2	426 (32.0)	52 (34.8)	480 (32.3)
	3	804 (60.5)	84 (54.8)	889 (59.9)

^a number (percent) and p-value from Pearson's Chi-square; ^b mean ± standard deviation and p-value from t-test; **Bold** significant p-values

Multivariate models of explanatory variables of the search for information about health, smoking and genetics are reported in Table 7.3. The two Internet tools included and combined in the model were web-search engine and Forum. Predictors of searching for information about health were monthly budget, ethnicity, faculty of study and smoking status. Those predictors explained 77.2% of the variability of searching for information about health ($LR\ Chi^2 = 1195.1, P < 0.001$). In smoking, 75.1% of the variability of searching for information about smoking was explained by budget and the Faculty of study. Web-search engine and Forum, as Internet tool, were included in the model ($LR\ Chi^2 = 1,669.8, P < 0.001$). The last model assessing the search of information about genetics included budget and web-search engine as Internet tool ($LR\ Chi^2 = 885.7, P < 0.001$).

Table 7.2: Types of internet-based tools used to obtain information about health, smoking and genetics

	HEALTH	SMOKING	GENETICS
No tool	277 (12.9)	1283 (59.5)	1067 (49.5)
Web-search engine	1696 (78.7)	741 (34.4)	970 (45.0)
Forum	837 (38.8)	192 (8.9)	190 (8.8)
Facebook	32 (1.5)	14 (0.7)	9 (0.4)
Twitter	7 (0.3)	3 (0.1)	3 (0.1)
YouTube	72 (3.4)	40 (1.9)	51 (2.4)

number (percent)

Table 7.3: Multivariate logistic regressions about the use of Internet tool to search for information about health, smoking and genetics

VARIABLES	HEALTH (n = 2012)	SMOKING (n = 1660)	GENETICS (n = 908)
Monthly budget ^a	1.38 (1.13-1.68)	1.31 (1.13-1.53)	1.31 (1.04-1.64)
Ethnicity ^a	1.93 (0.99-3.75)		
Faculty ^a	1.13 (1.00-1.29)	1.11 (1.00-1.22)	
Smoking status ^a	0.79 (0.61-1.01)		
Searching for information on web-search engine ^{a,b}	827.16 (358.20-1910.07)	1300.62 (550.93-3070.54)	706.42 (294.36-1695.32)
on Forums ^{a,b}	266.54 (78.94-899.92)	122.24 (34.57-432.22)	
<i>LR Chi²</i>	1195.1	1669.8	885.7
<i>P-value</i>	<0.001	<0.001	<0.001
<i>Pseudo R²</i>	77.2%	75.1%	70.6%

^a Odds ratio (95% confidence interval); ^b Search for information about health in the health model, smoking in the smoking model and genetics in the genetic model.

DISCUSSION

This is, to our knowledge, the first study that explored the types of Internet tools and different factors influencing the search of information about health, smoking and genetics on the Internet.

Results indicated that Internet tools were mainly used to search for information about health and in a lower case about smoking and genetics. A previous study reported that around 60% of the population searched for health information at least once a month. The topic of health information search was mostly symptoms, treatment and diseases/conditions [302, 307]. Moreover, people were searching for health information for themselves (37%), for someone else (49%) and both (8%) [307].

Regarding the Internet tools used, the dominance of web-search engine to search for information about health, smoking and genetics is in line with results reported by Elkin *et al.* [302]. Web-search engine gained the trust of a large audience. Moreover, they reported an emergence of search on social media including e. g. Wikipedia, Facebook or YouTube [302]. In the present study, the emergence of search on social media was mainly observed in Forum followed by YouTube, Facebook and lastly Twitter.

Factors explaining the search for information about health, smoking and genetics on Internet tools were gender, smoking status and the use of social media in univariate analyses and monthly budget, ethnicity, Faculty, and smoking status in multivariate analyses. These results are in line with those find in the literature [298, 302, 307, 308]. Women were already reported to have an increased use of Internet tools to search health information in comparison to men [302]. Cotten *et al.* reported that age, education and income appeared to influence the search of health information on the Internet. Internet seekers were younger, with a higher degree of education and with higher incomes than non-seekers [298]. Additionally, Chou *et al.* reported that education, race and healthcare access did not have an impact on social media use in the context of health [308]. It is why, the current study targeted a population of university students inducing a more homoogeneous population in age but also education and income.

The reason why the smoking status variable was not included in the multivariate model of searching for information about smoking and the score of genetic knowledge variable in the multivariate model of searching for information about genetics remains open to interpretation. Either these two variables are truly not influencing the outcomes or they might be avoided due to power issues.

In the future, a better monitoring of the information about health, smoking, genetics and all other health topics displayed on Internet tools might be developed. Moreover, methods to improve translation from evidence-based health information including or not genetic information is of high importance to improve the health [307] and the genetic literacy of the population [254]. To develop such methods, first questionnaires assessing the types of preferred Internet tools (e. g. Forum or YouTube), the types of relied publisher (e. g. scientific publisher or peer), the types of preferred message (e. g. paternalistic or autonomy) and disorders of interest might be sent to targeted populations. Moreover, to improve the content of the message, questions might measure the knowledge, the understanding and the attention of the population to that type of message. Thereafter, the effectiveness of the developed

messages might be evaluated in real life. The assessment of the effectiveness will be an important challenge due to the fact that there is no control on who actually search for the information.

Limitations

The present study, as a pilot study, did not aim to be representative of the total population of university students. Other studies will be needed in different universities to be able to generalise the results. However, even if the study was a pilot, a relatively high response rate was obtained (10%) when knowing that students received only one email presenting the study. This response rate was comparable with studies assessing the effect of invitation on response rates, e. g. Kaplowitz *et al.* reported a response rate of 15% when sending two emails to the target population [309].

In multivariate analyses, the wide confidence intervals of Internet tools (web-search engine and Forum) to search for information about health, smoking and genetics (Table 7.3) indicated a limited precision of the odds ratios, likely due to the small sample size or residual confounding by unmeasured factors. Indeed the addition of interaction factors did not improve the confidence interval width.

Due to the cross-sectional design of our study, there might be recall biases. This might have an impact on the estimation. Nevertheless, the use of Internet tools to search for information about health is already suggested in different studies [298, 300, 302]. Future prospective studies should be able to control for the recall bias.

Implications for practice and research

Internet tools, as new sources for health communication, might be used in public health and health promotion to improve the health and the genetic literacy of the population. This kind of tools for health information should help, in a further step, in enhancing behaviour change. Due to the important search of health information on Internet tools and more specifically on web-search engine and forum, future research might monitor and develop adapted health messages for the population. To obtain faster translation from the scientific background to the population, methods of translation should be developed. Moreover, the effectiveness of such message must be further assessed in real life.

Public Health Genomics (PHG), defined as '*the responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health*' [1, 2], is the field of translational research from basic sciences into healthcare systems, which give new insights in the prevention and the treatment of complex disorders and traits such as smoking.

Despite the widespread knowledge of consequences of smoking on health, smoking still remains a major public health problem worldwide. Indeed, tobacco killed around 6 million people worldwide from direct use or second-hand smoking in 2011 [19]. Moreover, it is an important risk factor for the four leading non-communicable diseases (cardiovascular diseases, diabetes, cancers, and chronic respiratory disorders) [19].

Like all complex disorders and behaviours, smoking is a multifactorial trait including both non-genomic and genomic factors. Genomic factors seem to be an important part of the causal mechanisms leading to smoking addiction and influencing smoking cessation. This is why, by improving the translation from bench to bedside and beyond to healthcare, PHG highly contributes to all health interventions tackling smoking.

Therefore, approaches and methods are needed to enhance the translation from bench to bedside and even beyond healthcare. Multiple approaches and methods are already developed such as the PHG enterprise (Figure 1.1) [1, 2], which is a tool that represents a way of approaching problems. It includes multiple factors necessary in the translation to the healthcare system, such as the role of genome-based science and technology and knowledge integration. Moreover, the wheel of public health (Figure 1.2) [10] is also an effective tool including different dimensions: assessment, policy development and assurance. Lal *et al.* [16] proposed a model to enhance translation using both technology transfer activity and public health assessment technologies in relationship to public-private partnerships. Khoury *et al.* [3] proposed a framework of translation aiming to move promising genomic applications to clinical and public health practice by using four different phases (from gene discovery to population health impact). Compared to LAL model, the Khoury framework does not include the technology transfer. These approaches and methods might be applied to all types of disorders and traits to enhance the translation of genomic research that is most often slow. For example, currently in smoking, no genomic applications are already in use in the daily clinical practice. However, in the near future, we could imagine to personalise treatment (in the type of drugs, dose, and duration) of smokers attempting to quit depending on their genes.

In the present thesis, we investigated innovative tools to enhance the translation of smoking from basic sciences into healthcare systems. For this, we explored and developed new tools to improve healthcare for smokers by taking both genomic and non-genomic factors into account. Furthermore, we investigated original ways to communicate genome-based information about smoking through genetic risk notification, the use of social media, and other Internet tools. Indeed, the Internet is an innovative medium for health information provision, gathering and transfer.

This final chapter gives an overview of the main findings, the limitations, and implications for public health practice and future research for each of the two parts of the thesis (i) improving healthcare for smokers, and (ii) enhancing the communication of genomic risks about smoking in the general population. Thereafter, a final conclusion is formulated.

IMPROVING HEALTHCARE FOR SMOKERS

Overview of the main findings

In order to improve the health for smokers and healthcare interventions related to smoking, we first reviewed genetic predictors for smoking initiation and cessation (**Chapter 2**). Two main pathways of interest were associated with smoking initiation and cessation: (i) the cascade theory of reward (influencing the pharmacodynamics of nicotine), and (ii) the nicotine metabolism (influencing the pharmacokinetics of nicotine). The cascade theory of reward includes four main neurotransmitters: serotonin, opioid receptors, gamma-aminobutyric acid (GABA), and dopamine. Serotonergic neurons release serotonin (5-HT). This activates opioidergic neurons that, at the same time, release endogenous opioid. The opioid inhibits the release of GABA, and finally this inhibition increases the release of dopamine in the nucleus accumbens in the brain [26]. Genes influencing nicotine metabolism mostly include cytochrome P450 genes (e.g. *CYP2B6*). Moreover, nicotinic acetylcholine receptors are also of high importance in predicting smoking initiation and cessation. It includes two kinds of subunits: alpha (α_1 - α_{10}) and beta (β_2 - β_4). Genetic predictors of smoking cessation were found to interact with interventions used in smoking cessation (e.g. *DRD2* Taq1A and bupropion) [73–75] and with other genes (*DRD2*-141C with *FREQ* rs1054879 and *SLC6A3* with *DRD2* Taq1A) [86, 87].

In **Chapter 3**, a systematic review of reviews of environmental factors, genomic factors and interventions influencing smoking cessation in the general population was carried out. This review reported eight categories of factors influencing smoking cessation: smoking behaviour (e.g. past quit attempts), demography (e.g. gender), socioeconomic status (e.g. income), social (e.g. marital status), health (e.g. health status), biology (e.g. menstrual phase), psychology (e.g. self-efficacy), and genomics (e.g. reward cascade). No factor presented a predominant effect on smoking cessation in previous meta-analyses. Relative risk ratios and odds ratios reported in meta-analyses ranged from 1.26 to 2.56. These factors were dynamically linked to interventions, as presented by three target levels (individual, neighbourhood and society), in order to lead to smoking cessation as presented in the developed working model of smoking cessation (Figure 3.2). Factors included in the working model of smoking cessation were quite similar to the ones used in the integrative model of tobacco use and dependence developed by Swan *et al.* in 2002 [112], except intervention factors in the latter model.

Based on a literature review and data-mining analyses, 32 genes influencing tobacco use disorder (TUD) were selected in **Chapter 4**. TUD, as defined by the Medical Subject Heading (MeSH) index, is the *'Tobacco used to the detriment of a person's health or social functioning. Tobacco dependence is included'*. Most selected genes were nicotinic receptors. However, the cascade theory of reward and nicotine metabolism were well represented. Disorders associated with these genes were selected through data-mining and represented all expected disease categories (addiction, mental disorders, cardiovascular disorders, and cancer). When observing genetic similarities between selected disorders, two main clusters of disorders were observed: the first one including coexisting disorders of smoking (e. g. alcoholism and depressive disorder) and the second one, disorders that are side-effects of smoking (e. g. stroke and oesophageal cancer). This raises the question about the relationship between TUD and disorders. The relationship may either be due to causality, common pathways in systems medicine, or pleiotropy. The field of systems medicine takes into account multiple interactions, such as those retrieved in epigenomics. However, pleiotropy occurs when a single gene variant influences multiple phenotypic traits [310]. Nevertheless, genetics is only one part of the mechanism explaining the association between TUD and other disorders. Among other environmental and genomic factors, epigenomics and exposomics are plausibly influencing the association between TUD and other disorders.

Limitations

In both systematic reviews of **Chapter 2 and 3**, inclusion criteria might have introduced limitations in our results. We focused on prospective studies (except for the systematic review on smoking initiation) to reduce recall bias and for their better accuracy in giving information about causality. Nevertheless, this might have narrowed our obtained results due to the lack of publications. In **Chapter 3**, restriction on prospective studies including at least 6-month follow-up even increased this limitation. However, most smoking relapses take place during the first six months after quitting [311]. Therefore, factors influencing smoking cessation might differ depending on the time to follow-up after quitting [311]. For example, self-efficacy and frequency of urges to smoke were related to smoking relapse only during the first month of cessation [311].

In **Chapter 4**, the search strategy to collect both genes and disorders associated to TUD might induce limitations in the study. Indeed, the search on Gene2MeSH, limited the review to publications available on PubMed and Ingenuity Pathway Analysis (IPA) uses data-mining as sources of information. It includes various source of information such as text-mining research and multiple databases. However, data-mining may introduce false positivity because it does not take into account the true biological relation between elements. Moreover, genetics is only one part of the mechanism leading to both coexisting disorders of smoking and disorders that are side-effects of smoking. Therefore, further studies will have to include epigenomic

factors to improve the understanding of the mechanisms linking TUD to other disorders.

Implications for clinical practice and future research

In order to improve healthcare for smokers, different strategies were proposed in **Chapter 2, 3, 4**. Understanding smoking in a holistic way including both environmental and genomic factors is essential to enhance smoking prevention and smoking cessation. Moreover, personalised interventions through, for example, individualised interventions for addicted smokers using pharmacogenetic tests to target the most effective and efficient drug, dose and duration based on multiple genetic variants are major approaches to improve healthcare for smokers.

In direct link to the work developed in the present thesis, a statistical validation of the working model of smoking cessation developed in **Chapter 3** is needed. This validation should assess the interactions between the different factors and the effect size of each factor. A way to validate this model would be to develop a prospective cohort of smokers that are willing to quit smoking and to follow them for at least 6 months after quitting. The statistical technique to deal with this is structural equation modelling, in which the number of observations is based on the number of variables. In the proposed working model, around 40 variables are included, which implies that the minimum number of observations should be 820. The strength of that kind of model would be that it allows to evaluate the effect of each single factor and consequently, to quantify the effect of the components [108]. Model testing through simulations under different conditions will also help in understanding complex systems behaving in an unexpected fashion [107].

In the future, nicotine might not be the only target for therapeutic interventions, but researcher will have to include multiple other chemicals (xenobiotica) contained in the cigarette. Deeper evaluation of epigenetic factors leading to behaviour change and how to communicate them to the general population are needed. Future research is required to better understand the biological mechanisms leading to smoking addiction and smoking related disorder. This better understanding will help in developing prediction models of smoking initiation, addiction, cessation or smoking related disease risks.

Moreover, the analyses developed in **Chapter 4** might be extended to individual characteristics, effects of treatment, or severity of treatment. Analyses of the most significant disorders associated to TUD in micro-array online databases may highlight whether the expression of the genes are similar or different between disorders. Furthermore, experiments should be developed to highlight the mechanisms leading to the association between TUD and other disorders. This might be developed in either twin studies or prospective studies. In those studies, not only genetic factors might be analysed but also environmental and genomic factors.

Finally, in the present thesis, the target population was the general population. Therefore, applications of the research developed on **Chapter 2, 3 and 4** on specific

populations (e. g. pregnant women, multi-addict population, or population with a cardiovascular disease) might provide additional knowledge.

ENHANCING THE COMMUNICATION OF GENOMIC RISKS ABOUT SMOKING IN THE GENERAL POPULATION

Overview of the main findings

From the systematic review and the pooled analysis, developed in **Chapter 5**, genetic notification of smoking related disorders was suggested to improve smoking cessation in comparison to control at short-term follow-up, less than 6 months (relative risk ratio = 1.55, 95% confidence interval 1.09-2.21). A recent meta-analysis reported the same primary outcome [155]. However, differences were observed in the methods used. In our study, we decided to focus on randomised controlled trials for their ability to minimise the likelihood of systematic errors. Smerecnik *et al.* [155] included both randomised and non-randomised trials. In order to avoid overestimation of a single study, we considered one follow-up of each study in the pooled analysis (last follow-up or short-term smoking cessation), whereas this was not the case in the other study. We decided to use relative risk ratios (RR) rather than odds ratios (OR) for their easiness of interpretation and for their improved accuracy in prospective studies. In our study we also assessed secondary outcomes (intention-to-quit smoking, emotional outcome and recall and understanding of the genomic information). Despite these differences the main outcome of both studies is similar, which reinforces the validity of the results.

In **Chapter 6**, a review of posts discussing genetics and smoking was conducted on YouTube, Facebook and Twitter using two different time points (September 18, 2012 and May 7, 2013). Little information about genetics and smoking was reported in these three social media and even none in Facebook. However, this is expected to change in the near future due to the growing interest in genetic research in the general population. Google search was used as an indicator of the information available on the Internet and a source of other social media than YouTube, Facebook or Twitter. Websites retrieved through the Google search were more often scientific publications per se (46.5%) or referring to scientific publications (53.5%) than on YouTube or Twitter. Moreover, no social media such as blogs or Forum were identified in the Google search.

A survey in university students assessing the search of information about health, smoking and genetics was described in **Chapter 7**. Results indicated that Internet tools were mainly used to search for information about health and in much less case to search about smoking and genetics. Web-search engine and Forum were the two mostly used Internet tools followed by, respectively, YouTube, Facebook and Twitter. Moreover, factors explaining the search for information about health, smoking and genetics on Internet tools were gender, smoking status and the use of social media

in univariate analyses and monthly budget, ethnicity, faculty, and smoking status in multivariate analyses.

Limitations

In **Chapter 5**, the main limitation of the pooled-analysis about the impact of genetic notification on smoking cessation was the low number of included studies inducing lower sensitivity in the test. Moreover, the outcome measures differed across studies (e.g. prolonged or point-prevalence smoking cessation) being one factor inducing heterogeneity between the included studies.

Social media, due to their easiness to create new information, are rapidly changing channels as reported in **Chapter 6**. Consequently, the posts selected in our review may not be reflective of what is posted at another time. Therefore, two different time points separated at 9 months in the time were used to collect information. Moreover, the search strategy using only two terms 'smoking' and 'genetic' and the first hundred posts may appear to be limited. However, the results obtained in our search provide a reasonable perspective of what someone interest in smoking and genetics would find on the topic on YouTube, Facebook and Twitter.

In **Chapter 7**, the sample of students having answered to the web-questionnaire might not be representative of the total population of university students. Indeed, 9 faculties were conveniently selected over the 14. Moreover, students only received one email inviting them to answer to the web-questionnaire. However, around 10% of students answered to the questionnaire, which is comparable to other studies [309]. Furthermore, the cross-sectional design used in the study might have induced recall biases. Therefore, future prospective studies will be needed to confirm our results even if Internet tool were already reported to be used to search for information about health [298, 300, 302].

Implications for clinical practice and future research

Genetic notification mostly focused on one single variant in the literature. However, many variants are suggested to be associated with smoking initiation, addiction, cessation and smoking related disorders. Therefore, future study assessing the impact of genetic notification should include multiple variants. Genetic notification appeared to enhance smoking cessation only at short-term follow-up. It may suggest that reminders of the results might be necessary at longer term follow-up. In the future, genetic notification may also apply to epigenomics. By using epigenomic factors, the notification may evolve during time depending, for example, on the actual smoking status of the smoker. Indeed, methylations are found to be rapidly reversible and, therefore, remethylations are suggested after smoking cessation [31]. Consequently, impact on longer follow-up are plausible due to the constant and dynamic change in the test results over time.

As reported in **Chapter 7**, students are often searching for information about health, smoking and genetics on Internet tools. Consequently, Internet tools might be used in public health to enhance the health and the genetic literacy of the population and thus to induce behaviour changes. As the population is more and more searching for information about health, smoking and genetics on the Internet and on social media, doctors and clinical researchers have to be part of the information displayed on the Internet. Moreover, they have to be ready to answer questions of the population based on what people might have read on the web.

As Internet tools and social media allow everybody to create new information, there is a need to monitor health information displayed over time to avoid the dispersion of false or misleading information and to manage the quantity of the information. Moreover, to enhance and develop faster translation of genome-based information from bench to bedside and even beyond to healthcare, methods may be developed. These methods might assess the type of Internet tools preferred to obtain health information (e. g. YouTube or Forum), the type of believed publisher (e. g. scientific or peers), and the preferred message content (e. g. paternalistic versus autonomy or positive-framed versus negative-framed messages). A web-questionnaire sent to one or different target populations (e. g. pregnant women or university students) may help in developing methods. Indeed, most likely the type of preferred Internet tools, the type of believed publisher and the preferred message content will differ from one target population to another one. Finally, the effectiveness of displaying such health messages on Internet tools might be assessed in real life. However, the control of people searching for such information remains challenging due to the anonymous access of information on the Internet.

CONCLUSION

Based on the results of the thesis, conclusions can be drawn with regard to the two main parts of the thesis: improving healthcare for smokers and enhancing the communication of genomic risks about smoking in the general population.

Improving healthcare for smokers

The use of genome-based information, in combination with a better overview of environmental factors influencing smoking, may improve the prevention of smoking initiation and addiction, as well as the treatment of smoking cessation. For example, in smoking cessation, genome-based information might be used to personalise and individualise interventions based on the choice of the drug, dose and duration. Improving healthcare for smokers is not only limited to research on smoking initiation, addiction and cessation but also on smoking related disorders like cancer or cardiovascular diseases as we observed genetic similarities between TUD and other disorders.

Enhancing communication of genomic risks about smoking in the general population

The communication of genome-based information about smoking is of main importance to improve the health and the genomic literacy of the population. Multiple variants and epigenomic markers might be used to be closer to the reality and to enhance long-term impact of the notification. Both personalised (based on the genetic susceptibility of the individual) and generalised (based on the genetic risk associated to smoking or smoking related disorders) information to the population may be helpful. Therefore, developing reliable information through highly used media such as the Internet and social media is needed. Health information displayed on such media might be monitored and methods should be developed to increase the translation of scientific results for the general population.

SUMMARY

INTRODUCTION

Public Health Genomics (PHG) is the field of translating genome-based information and technologies into policies and healthcare. Among its many tasks, PHG provides also new insights in the prevention and the treatment of complex disorders and traits such as smoking. Despite the widespread knowledge of consequences of smoking, smoking still remains a major public health problem worldwide. Genomic factors and their interactions with environmental factors seem to be part of the causal mechanisms leading to smoking addiction and influencing smoking cessation. This is why, by improving the translation from bench to bedside and even beyond healthcare, PHG is a very innovative approach for tackling smoking in a most holistic way leading to targeted and personalised interventions.

Two broad groups of genes influence smoking initiation, addiction, cessation, and smoking related disorders. The first one includes genes influencing nicotine metabolism, such as *CYP2A6*. Those genes are enzymes responsible for the metabolism of nicotine into cotinine. The second group of genes consists of four different neurotransmitters (serotonin, mu-opioid, gamma-aminobutyric acid, and dopamine) influencing the reward.

The main objective of the present thesis is to demonstrate that the use of genome-based information, which goes beyond the influence of single or combined genes, is essential for further improvement in preventing and treating smoking. This thesis meets the challenge to use genome-based information arising from basic science in order to improve public health. The first aim of the present thesis was to provide research on how to improve healthcare for smokers (**Chapter 2**, **Chapter 3** and **Chapter 4**). The second aim was to enhance the communication on the evidence of genomic risks about smoking to the population (**Chapter 5**, **Chapter 6** and **Chapter 7**).

IMPROVING HEALTHCARE FOR SMOKERS

Chapter 2 provides a literature review of the genetic predictors for smoking initiation and smoking cessation. Two main classes of genes influence smoking initiation and cessation (i) genes influencing the cascade theory of reward and (ii) genes influencing nicotine metabolism. Those genes were also reported to interact with intervention during smoking cessation. Moreover, 'omics' factors are also suggested to influence smoking initiation and cessation even if to date, few studies did such research.

The environmental and genomic factors as well as interventions influencing smoking cessation were reviewed and visually displayed through the development of a working model described in **Chapter 3**. Smoking cessation was dynamically influenced by a broad range of factors and interventions. This includes genomic, smoking behaviour, demographic, socioeconomic status, health, psychological, biological, and social factors. Interventions were classified in three levels of target being individual, neighbourhood and society level.

The genetic similarities between disorders associated with tobacco use disorder are reported in **Chapter 4**. Based on a literature review and data-mining, 32 genes and 14 disorders met our inclusion criteria. Disorders included an extensive range of categories such as addictions, mental disorders, cardiovascular disorders, and cancer. Genetic similarities were observed between two main clusters of disorders. The first one included mostly disorders that are side effects of smoking (e. g. vascular disorder and oesophageal cancer). The second one targeted coexisting disorders of smoking (e. g. alcoholism and depressive disorder).

ENHANCING THE COMMUNICATION OF GENOMIC RISKS ABOUT SMOKING IN THE GENERAL POPULATION

Chapter 5 provides a systematic review and a meta-analysis describing the impact of genetic notification on smoking cessation. Eight papers, assessing the impact of cancer genetic risk communication, were included in the review. In short-term follow-up (less than 6 months), the pooled-analysis suggested an improvement of smoking cessation in people receiving genetic notification in comparison to controls (relative risk ratio = 1.55, 95% confidence interval 1.09-2.21).

Chapter 6 describes the availability of genetic information about smoking in three different social media (YouTube, Facebook, and Twitter). Over 31, 0 and 84 posts were retrieved from, respectively, YouTube, Facebook and Twitter. Most posts referred to scientific publications and focused on smoking addiction and smoking related disorders. Improving access to such information might improve the health and the genomic literacy of the population and, therefore enhance smoking prevention and cessation.

Chapter 7 reports the Internet tools used and the factors explaining the search of information about health, smoking and genetics on the Internet. Out of the 2,171 students that answered the full questionnaire, 1,937 searched for information about at least health, smoking or genetics on Internet tools. The two mostly used Internet tools were web-search engine and Forum. The other factors explaining the search of information about health, smoking or genetics were gender, student's housing, smoking status and the use of social media in univariate analyses; and monthly budget, nationality and the faculty of study in multivariate analyses. Due to the important search of such information on Internet tools, further research should assess and monitor the quality of the information displayed.

CONCLUSIONS AND PERSPECTIVES

Chapter 8 summarises the main findings and the implications for public health practice and future research of the present thesis for the two main parts of the study (i) improving healthcare for smokers and (ii) enhancing the communication of genomic risks about smoking in the general population. Results of our research indicated an important need (a) to include both environmental and genomic factors associated to smoking, (b) to better understand the biological mechanisms leading to smoking and smoking related disorders to improve healthcare for smokers by targeted interventions, and (c) to develop methods and communication strategies that may enhance the translation of genome-based information on smoking to the general population. Two different types of communication were developed, the use of genetic notification to boost smoking cessation and the use of Internet tools and social media to improve the genomic literacy of the population. Genetic notification is, to date, mainly studied with one single gene variant. In the future, multiple genetic variants and most importantly epigenomic markers and exposomics might be used to be closer to the reality and to enhance long-term impact of the notification. The Internet and social media, as tools for information displaying, sharing and gathering, will become an increasingly important place to improve the health and the genomic literacy of the population. Therefore, there is a need to monitor the displayed health information and to develop methods that may increase the translation of results from basic science to the general population.

SAMENVATTING

INTRODUCTIE

'Public Health Genomics' (PHG) is de manier om genomische informatie en technologieën in het beleid en de gezondheidszorg te vertalen. Onder haar vele taken biedt PHG ook nieuwe inzichten in de preventie en behandeling van complexe aandoeningen en verslavingen zoals roken. Ondanks de wijdverspreide kennis van de gevolgen van roken blijft roken een belangrijk probleem voor de wereldwijde volksgezondheid. Genomische factoren en hun interacties met omgevingsfactoren lijken een deel te zijn van de causale mechanismen die tot een rookverslaving leiden en die de efficiëntie van het stoppen met roken beïnvloeden. Dit is de reden waarom - met een verbeterde toepassing van praktische en theoretische concepten bij patiënten en zelfs buiten gezondheidszorg - PHG een zeer innovatieve benadering is voor de aanpak van roken op een zeer holistische wijze die tot gerichte en gepersonaliseerde interventies kan leiden.

Twee grote groepen van genen beïnvloeden het starten met roken, de verslaving, het stoppen en aan roken gerelateerde aandoeningen. De eerste groep bevat genen die het metabolisme van de nicotine beïnvloeden zoals *CYP2A6*. Deze genen zijn enzymen die verantwoordelijk zijn voor het metabolisme van de nicotine in cotinine. De tweede groep genen bestaat uit vier verschillende neurotransmitters (serotonine, mu-opioid, gamma-aminoboterzuur en dopamine) die de 'beloning' van het roken beïnvloeden.

Deze thesis stelt tot doel de op de genoom-gebaseerde informatie uit de fundamentele wetenschap te gebruiken ter verbetering van de volksgezondheid. De eerste doelstelling van dit proefschrift was het genomische onderzoek te gebruiken om te bezien hoe de gezondheidszorg voor rokers verbeterd kan worden (**Hoofdstuk 2**, **Hoofdstuk 3** en **Hoofdstuk 4**). De tweede doelstelling was de communicatie met de bevolking over het bewijs van genomische risico's bij roken te verbeteren (**Hoofdstuk 5**, **Hoofdstuk 6** en **Hoofdstuk 7**).

IMPROVING HEALTHCARE FOR SMOKERS

Hoofdstuk 2 betreft een literatuuroverzicht van de genetische voorspellers die een rol bij het starten en stoppen met roken spelen. Twee belangrijke klassen van genen beïnvloeden het starten en stoppen met roken: (i) genen die de cascade van de beloning beïnvloeden en (ii) genen die betrokken zijn bij het nicotinemetabolisme. Deze genen werden ook gerapporteerd als betrokken zijnde bij de interacties die het stoppen met roken beïnvloeden. Bovendien worden 'omics'-factoren er ook van

verdacht het starten en het stoppen met roken te beïnvloeden, hoewel tot nog toe weinig studies een dergelijk onderzoek uitvoerden.

De milieu- en genomische factoren evenals de interventies die het stoppen met roken beïnvloeden werden beoordeeld en visueel weergegeven in een werkmodel. Dit wordt in **Hoofdstuk 3** beschreven. Stoppen met roken is via een breed scala aan factoren en interventies dynamisch te beïnvloeden. Deze omvatten genomica, rookgedrag, demografie, sociaaleconomische status, gezondheid en psychologische-, biologische - en sociale factoren. De interventies werden in drie doelgroepen ingedeeld: het individuele-, het buurt- en het maatschappelijke niveau.

De genetische overeenkomsten tussen de verschillende aandoeningen die met tabaksmisbruik worden geassocieerd worden in **Hoofdstuk 4** beschreven. Op basis van een literatuurstudie en data-extractie voldeden 32 genen en 14 aandoeningen aan onze inclusiecriteria. De betreffende aandoeningen omvatten een breed scala aan categorieën zoals verslaving, psychische stoornissen, hart- en vaatziekten en kanker. Genetische overeenkomsten werden bij twee belangrijke clusters van aandoeningen gevonden. De eerste cluster betrof voornamelijk aandoeningen die een bijwerking van roken zijn (bv. vasculaire aandoeningen en slokdarmkanker). De tweede cluster was op de coëxisterende aandoeningen van roken gericht (bv. alcoholisme en depressieve stoornis).

VERBETERING VAN DE COMMUNICATIE OVER GENOMISCHE RISICO'S VAN ROKEN IN DE ALGEMENE BEVOLKING

Hoofdstuk 5 betreft een systematisch overzicht en een meta-analyse die de invloed van genetische kennisgeving op het stoppen met roken beschrijven. In het overzicht werden acht artikelen over de impact van communicatie over het genetische risico op kanker opgenomen. In een korte termijn follow-up (minder dan zes maanden) constateerde de pool-analyse een verbeterd resultaat ten aanzien van het stoppen met roken bij de mensen met een genetische kennisgeving in vergelijking tot de controlegroep (relatieve risico ratio = 1,55, 95% betrouwbaarheidsinterval 1,09-2,21).

Hoofdstuk 6 beschrijft de beschikbaarheid van genetische informatie over roken in drie verschillende sociale media (YouTube, Facebook en Twitter). Bovendien 31, 0 en 84 berichten werden respectievelijk uit YouTube, Facebook en Twitter opgehaald. De meeste berichten refereerden aan wetenschappelijke publicaties en waren op rookverslaving en aan roken gerelateerde aandoeningen gericht. Een verbeterde toegankelijkheid tot dergelijke informatie kan de gezondheid en de 'genomische' geletterdheid van de bevolking verbeteren. Dit kan rookpreventie bevorderen en de resultaten bij het stoppen met roken verbeteren.

Hoofdstuk 7 beschrijft de middelen die via het Internet gebruikt zijn en de verklarende factoren voor het zoeken van informatie over gezondheid, roken en genetica op het Internet. Van de 2.171 studenten die de volledige vragenlijst beantwoord hebben zochten ten minste 1.937 studenten naar informatie over gezondheid, roken of genetica op het Internet. De twee meest gebruikte Internet tools waren

web-zoekmachines en Fora. De andere factoren die het zoeken naar informatie over gezondheid, roken of genetica verklaarden waren het geslacht, de huisvesting van de student, de rookstatus en het gebruik van sociale media in de univariate analyses en het maandelijkse budget, de nationaliteit en de studiefaculteit in de multivariate analyses. Vanwege het belang van de zoektocht naar dergelijke informatie op Internet zou verder onderzoek deze informatie moeten beoordelen en de kwaliteit van de getoonde informatie moeten bewaken.

CONCLUSIONS AND PERSPECTIVES

Hoofdstuk 8 is een samenvatting van de belangrijkste bevindingen, de implicaties voor de volksgezondheidspraktijk en het gewenste vervolgonderzoek voor de twee belangrijkste onderdelen van het onderzoek: (i) de verbetering van de gezondheidszorg voor rokers en (ii) het verbeteren van de communicatie over genomische risico's van roken in de algemene populatie. De resultaten van ons onderzoek wezen op een belangrijke behoefte (a) om zowel milieu- als genomische factoren die met roken verband houden te betrekken, (b) een beter inzicht te hebben in de biologische mechanismen die leiden tot roken en aan roken gerelateerde aandoeningen om de gezondheidszorg voor rokers door gerichte interventies te verbeteren en (c) om methoden en communicatiestrategieën te ontwikkelen die de genoom-gebaseerde informatie over roken naar de algemene bevolking kunnen vertalen. Twee verschillende vormen van communicatie werden ontwikkeld; het gebruik van genomische kennisgeving bij het stoppen met roken en het gebruik van Internet tools en sociale media om de genomische geletterdheid van de bevolking stimuleren. Genetische kennisgeving is tot op heden vooral bij een enkel gen variant bestudeerd. In de toekomst zouden verschillende genetische varianten alsook epigenomische markers en exposomics kunnen worden bestudeerd om een completer beeld te krijgen en om de langetermijneffecten van roken op een zo efficiënt mogelijk manier te verminderen. Het Internet en de sociale media als instrumenten voor het weergeven, delen en verzamelen van informatie zullen steeds belangrijker worden om de gezondheid en de genomische geletterdheid van de bevolking te verbeteren. Daarom bestaat de behoefte om de weergegeven informatie over gezondheid te monitoren en methoden te ontwikkelen die resulteren in een heldere en begrijpelijke vertaling van fundamentele wetenschappelijke resultaten naar de algemene bevolking

RÉSUMÉ

INTRODUCTION

La Santé Publique Génomique (PHG) a pour objectif de traduire les informations et technologies basées sur la génomique en pratique clinique et politiques de santé. Parmi ses multiples tâches, la PHG propose un nouveau regard sur la prévention et le traitement de maladies complexes telles que l'addiction au tabac. Malgré l'importante connaissance des conséquences du tabac sur la santé, l'addiction au tabac reste un problème majeur de santé publique. Les facteurs génomiques ainsi que les interactions avec les facteurs environnementaux semblent faire partie du mécanisme causal menant à l'addiction au tabac et influençant l'arrêt du tabac. C'est pourquoi, en améliorant la traduction de la recherche, du laboratoire au chevet du patient et même au-delà de la pratique clinique, la PHG aborde le problème de la consommation de tabac de manière innovante et holistique menant à des interventions plus ciblées et personnalisées.

Deux grands groupes de gènes influencent l'initiation, l'addiction, l'arrêt du tabac ainsi que les maladies liées au tabac. Le premier groupe inclut les gènes influençant le métabolisme de la nicotine tels que *CYP2A6*. Ces gènes sont des enzymes responsables de la métabolisation de la nicotine en cotinine. Le second groupe de gènes contient quatre neurotransmetteurs (la sérotonine, les mu-opioid, les acides gamma-aminobutyriques et la dopamine) influençant le sentiment de récompense.

L'objectif principal de cette thèse est de démontrer que l'utilisation d'informations basées sur la génomique, allant au-delà de l'influence d'un seul ou d'une combinaison de gènes, est essentiel afin d'améliorer la prévention ainsi que l'arrêt du tabac. Cette thèse rencontre donc un défi, celui d'utiliser les informations basées sur la génomique résultant de la recherche scientifique de base afin d'améliorer la santé publique. Le premier objectif de cette thèse est, dans ce cadre, d'améliorer les soins de santé des fumeurs (**Chapitre 2, Chapitre 3 et Chapitre 4**). Le second objectif est d'accroître la communication à propos de l'évidence des risques génomiques concernant le tabac (**Chapitre 5, Chapitre 6 et Chapitre 7**).

AMÉLIORER LES SOINS DE SANTÉ DES FUMEURS

Le **Chapitre 2** décrit, sur base d'une revue de la littérature, les prédicteurs génétiques de l'initiation et l'arrêt du tabac. Deux classes de gènes influencent principalement l'initiation et l'arrêt du tabac (i) les gènes influençant le sentiment de récompense et (ii) les gènes influençant le métabolisme de la nicotine. Ces gènes ont aussi présenté des interactions avec différentes interventions lors de l'arrêt du tabac. De plus, une influence des facteurs '-omique' est aussi suggérée lors de l'initiation

et l'arrêt du tabac même si, actuellement, peu d'études se sont penchées sur la question.

Les facteurs génomiques et environnementaux ainsi que les interventions influençant l'arrêt du tabac ont été examinés via une revue systématique de la littérature et présentés visuellement à l'aide d'un modèle de travail décrit au **Chapitre 3**. L'arrêt du tabac est dynamiquement influencé par une large gamme de facteurs et d'interventions. Ceci inclut les facteurs génomiques, démographiques, socio-économiques, psychologiques, biologiques, sociaux et de santé ainsi que les facteurs déterminant le comportement tabagique. Les interventions ont été classifiées en trois niveaux de cibles: le niveau individuel, du voisinage et de la société.

Les similarités génétiques entre les maladies associées à l'utilisation du tabac sont rapportées au **Chapitre 4**. Sur base d'une revue de la littérature et de data-mining, 32 gènes et 14 maladies ont rencontré nos critères d'inclusion. Les maladies se rapportent à une gamme étendue de catégories telles que les addictions, les maladies mentales, les maladies cardiovasculaires et le cancer. Principalement deux clusters de maladies présentent des similarités génétiques. Le premier inclut des maladies se présentant comme des effets secondaires de la consommation de tabac (p. ex. les maladies vasculaires et le cancer de l'oesophage). Le deuxième cible des maladies coexistantes au tabac (p. ex. l'alcoolisme et les maladies dépressives).

ACCROÎTRE LA COMMUNICATION À PROPOS DE L'ÉVIDENCE DES RISQUES GÉNOMIQUES CONCERNANT LE TABAC DANS LA POPULATION GÉNÉRALE

Le **Chapitre 5** présente une revue systématique de la littérature et une méta-analyse décrivant l'impact de la notification génétique sur l'arrêt du tabac. Huit publications évaluant l'impact de la communication de risques génétiques ont été incluses dans notre revue. La méta-analyse suggère une amélioration de l'arrêt du tabac à court terme (moins de 6 mois) chez les personnes recevant une information génétique en comparaison des contrôles (risque relatif = 1.55, Intervalle de confiance à 95% 1.09-2.21).

Le **Chapitre 6** décrit les informations disponibles à propos de la génétiques et du tabac dans trois média sociaux (YouTube, Facebook et Twitter). YouTube, Facebook et Twitter ont permis de sélectionner, respectivement, 31, 0 and 84 postes. La plupart des postes font référence à des publications scientifiques et se concentrent sur l'addiction au tabac et les maladies liées au tabac. Améliorer l'accès à de telles informations devrait permettre d'améliorer la santé ainsi que la connaissance en génomique de la population et, par conséquent, accroître la prévention ainsi que l'arrêt du tabac.

Le **Chapitre 7** présente les outils Internet et les facteurs expliquant la recherche d'informations sur la santé, le tabac et la génétique sur Internet. Parmi les 2.171 étudiants qui ont répondu entièrement au questionnaire, 1.937 ont, par le passé, cherché de l'information sur la santé, le tabac ou sur la génétique via des outils Internet. Les deux outils Internet les plus utilisés sont les moteurs de recherche et

les Forum. Les autres facteurs expliquant la recherche d'information sur la santé, le tabac ou la génétique sont le sexe, le type d'habitation, le statut tabagique et l'utilisation des média sociaux en analyses univariées; ainsi que le budget mensuel, la nationalité ainsi que la faculté d'étude en analyses multivariées. Compte tenue de l'importance de la recherche d'informations sur les outils Internet, davantage de recherches devraient évaluer et monitorer la qualité des informations disponibles.

CONCLUSIONS ET PERSPECTIVES

Le **Chapitre 8** résume les principaux résultats de cette thèse ainsi que les implications pour la pratique en santé publique et les futures recherches concernant les deux parties principales de cette étude (i) améliorer les soins de santé des fumeurs et (ii) accroître la communication à propos de l'évidence des risques génomiques concernant le tabac dans la population générale. Les résultats de notre recherche indiquent un important besoin (a) d'inclure à la fois les facteurs environnementaux et les facteurs génomiques associés à la consommation de tabac, (b) d'améliorer la compréhension des mécanismes biologiques menant à la consommation de tabac et aux maladies liées au tabac afin d'améliorer les soins de santé des fumeurs à l'aide d'interventions ciblées et (c) de développer des méthodes ainsi que des stratégies de communication afin d'accroître la traduction des informations génomiques à propos du tabac dans la population générale. Deux différents types de communications ont été développés dans cette thèse, l'utilisation de notification génétique afin d'améliorer l'arrêt du tabac et l'utilisation d'outils Internet et de média sociaux pour accroître la connaissance en génomique de la population. La notification génétique est, actuellement, principalement étudiée à l'aide d'un seul variant génétique. Dans le futur, de multiples variants génétiques ainsi que des marqueurs épigénomiques et exposomiques devraient être utilisés afin d'être au plus proche de la réalité et donc d'améliorer l'impact à long terme de la notification. Internet et les media sociaux, en tant qu'outils d'information permettant de développer, partager et rassembler de l'information, représentent un espace important afin d'améliorer la santé et les connaissances en génétique de la population. Par conséquent, il y a un besoin de monitorer les informations de santé disponibles et de développer des méthodes permettant d'augmenter la traduction des résultats de la recherche scientifique de base pour la population générale.

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CURRICULUM VITAE

Sylviane de Viron was born in Brussels, Belgium, on the 11th of July 1986. In 2004, she acquired her secondary school diploma at the Institut Saint André (Brussels). In September of the same year, she started a bachelor in Nursing followed by a specialization in Paediatrics in Brussels. In September 2008, she started a master of Public Health at the Catholic University of Louvain (UCL), Brussels. As part of this master, she followed several elective courses and more particularly a specialization on genetic epidemiology at the Ludwig Maximilians University (LMU), Munich. During her master, she assessed the genetic and clinical determinants of pulse wave velocity in renal transplant patients. She obtained her degree in September 2010. After her master, she worked as teaching and research assistant at the public health faculty of the UCL.

In January 2011, Sylviane started working as scientific researcher within the Scientific Institute of Public Health (WIV-ISP), Brussels, and as PhD candidate within the Institute for Public Health Genomics (IPHG) at Maastricht University on the project described in this dissertation. The project was granted by the Belgian Federal Science Policy Office. During her PhD, she presented orally the results of her research to different national and international congresses such as the World Cancer Congress 2012 and the European Public Health Conference 2012. She also took part in the group of Public Health Genomics within the Belgian Health Council and the Public Health Genomics European Network coordinated by Prof. Dr. Angela Brand.

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