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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Key Words

Environment · Genomics · Intervention · Public health · Public health genomics · Smoking cessation · Systematic review · Working model

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:** Describing the environmental and genomic factors as well as the interventions influencing smoking cessation (SC) and developing a working model incorporating the different factors influencing SC were our main objectives. **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 an iterative process of discussion and re-examination by the authors. **Results:** We confirmed the importance of the 4 main factors influencing SC: (1) en-

vironmental factors, (2) genomic factors, (3) gene-environment interactions, and (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.

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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 [1]. Successful smoking cessation (SC) reduces the incidence of comorbidities as well as mortality among smokers [2–4].

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 60–70% of the variance of nicotine dependence is explained by inherited factors [5, 6]. Genomic factors are explored in 3 types of studies: candidate asso-

ciation 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, 2 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 4 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 [7]. 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 [8]. SC is reported to be influenced by sociodemographic characteristics, psychological factors and policy decisions [9, 10].

Epigenetic mechanisms, such as methylation, histone modification, miRNAs, and chromatin remodelling are induced by tobacco components. Up to now, epigenetic studies have mostly focussed on the development of smoking-related disorders, such as lung cancer, chronic obstructive pulmonary disease and cardiovascular disease [11]. However, some methylations appear to be correlated with smoking status and increase with smoking intensity (e.g. *RARB* and *FHIT*) [11].

Every year, around 40% of smokers try to quit smoking for at least one day. Unfortunately, most of them relapse due to nicotine dependence [12, 13]. 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 [14]. 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 [15].

The models on SC that have been developed up until now had 4 different focuses: (1) application of a general model of behavioural changes on SC [16]; (2) impact of tobacco policies [9]; (3) social classes [17], and (4) environmental factors and interventions [10, 18]. These models mostly targeted specific populations (e.g. women, adolescents) and environmental factors. Only one model considered genomic factors focussing mainly on pharmacogenetics [18]. However, the conceptual model assessing tobacco use and dependence includes both non-genomic and genomic factors [19]. 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 (1) to review the environmental and the genomic factors as well as the interventions influencing SC reported in the recent literature, and (2) 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.

Fig. 1. Flow chart of the study selection process. **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.

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 [20].

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 hospitalized patients and pregnant women.

Search Strategy (fig. 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’ (online suppl. table 1; for all supplementary material, see www.karger.com/doi/10.1159/000351453). 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’ (online suppl. table 1). In addition, we searched for ‘smoking cessation’ in HuGENet, and we manually reviewed the reference lists of relevant articles and reviews.

One author (S.D.V.) 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 [9, 10, 16–18]: smoking behaviour, demographic factors, social factors, socioeconomic status (SES), psychological factors, biological factors, health factors, genomic factors, and interventions.

For the interventions, we distinguished 3 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 a level of heterogeneity) were extracted (table 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.

Table 1. Overall results of the selected meta-analyses

Variable	RR ^a /OR ^b	95% CI	Follow-up	Ref.
<i>Environmental factor (individual level)</i>				
Gender (male versus female)	1.33 ^b	0.91–1.95	≥6 m	[21]
Low income (female)	1.28 ^a	0.96–1.72	≥6 m	[28]
Low income (male)	1.58 ^a	0.79–3.14	≥6 m	[28]
Higher cotinine level	0.80 ^b	0.63–0.92	≥6 m	[21]
Smoking within 30 min after waking	0.40 ^b	0.25–0.62	≥6 m	[21]
Not having other smokers in the household	1.43 ^b	1.25–1.65	≥6 m	[21]
Longest previous quit attempt (female)	1.23 ^b	1.11–1.39	≥6 m	[21]
Longest previous quit attempt (male)	1.09 ^b	0.68–1.02	≥6 m	[21]
Male initiating smoking before the age of 16 (vs. later age)	2.10 ^b	1.40–3.00	≥6 m	[21]
Smoking reduction before cessation	2.06 ^a	1.34–3.15	≥6 m	[25]
<i>Pharmacotherapy (individual level)</i>				
NRT	1.56 ^b	1.16–2.11	3–6 m	[68]
	1.94 ^b	1.70–2.20	6 m	[65]
	1.72 ^b	1.61–1.84	6 m	[69]
	2.06 ^{a,*}	1.34–3.15	≥6 m	[66]
	1.58 ^a	1.50–1.66	≥6 m	[64]
NRT over-the-counter	2.5 ^b	1.8–3.6	2.5–6 m	[138]
NRT (female)	1.61 ^b	1.29–2.00	6 m	[139]
	1.76 ^b	1.48–2.10	6 m	[65]
NRT (male)	2.20 ^b	1.75–2.76	6 m	[139]
	2.16 ^b	1.80–2.59	6 m	[65]
NRT gum	1.71 ^b	1.35–2.21	6–12 m	[67]
	1.66 ^b	1.52–1.81	6–12 m	[69]
	1.43 ^a	1.33–1.53	≥6 m	[64]
NRT inhaler	2.08 ^b	1.43–3.04	6–12 m	[69]
	1.90 ^a	1.36–2.67	≥6 m	[64]
NRT intranasal spray	2.27 ^b	1.61–3.20	6–12 m	[69]
	2.02 ^a	1.49–3.73	≥6 m	[64]
NRT patch	1.74 ^b	1.57–1.93	6–12 m	[69]
	1.66 ^a	1.53–1.81	≥6 m	[64]
	1.95 ^b	1.65–2.34	6–12 m	[67]
NRT tablet	1.73 ^b	1.07–2.80	6–12 m	[69]
	2.00 ^a	1.63–2.45	≥6 m	[64]
NRT preloading	2.17 ^b	1.46–3.22	6 m	[140]
	1.16 ^a	0.97–1.38	6–12 m	[141]
Bupropion	2.07 ^b	1.73–2.55	6–12 m	[67]
	1.69 ^a	1.53–1.85	6–12 m	[70]
Nortriptyline	2.03 ^a	1.48–2.78	≥6 m	[70]
Varenicline	2.41 ^b	1.91–3.12	≥6 m	[67]
	2.27 ^a	2.02–2.55	6–12 m	[142]
Cytisine	1.83 ^b	1.12–2.99	3–6 m	[77]
	3.98 ^a	2.01–7.87	≥6 m	[142]
Naltrexone	1.26 ^b	0.80–2.01	≥6 m	[79]
Clonidine	1.89 ^b	1.30–2.74	≥3 m	[71]
Combined pharmacotherapy	2.14 ^b	1.28–3.60	6–12 m	[117]
	2.19 ^b	1.7–2.8	6–12 m	[119]
	1.54 ^a	1.19–2.00	6 m	[118]
<i>Counselling (individual level)</i>				
Individual counselling	1.39 ^a	1.24–1.57	≥5 m	[81]
	1.20 ^{b,*}	0.72–2.00	6–9 m	[68]
	1.49 ^b	1.08–2.07	6–12 m	[82]
Group counselling	1.98 ^a	1.60–2.46	≥6 m	[83]
	1.76 ^b	1.11–2.93	6–12 m	[82]

Table 1 (continued)

Variable	RR ^a /OR ^b	95% CI	Follow-up	Ref.
Telephone counselling	1.37 ^{a,*}	1.26–1.50	≥6 m	[88]
	1.58 ^b	1.15–2.29	6–12 m	[82]
Call-back counselling	1.41 ^{b,*}	1.27–1.57	6–12 m	[89]
Motivational interviewing	1.35 ^b	1.02–1.78	≥6 m	[92]
	1.45 ^b	1.14–1.83	1–12 m	[93]
	1.70 ^{a,*}	1.32–2.21	≥5 m	[94]
Brief advice	1.74 ^{a,*}	1.37–2.22	≥5 m	[94]
	1.47 ^a	1.24–1.75	≤12 m	[143]
Intermediate advice	1.71 ^{a,*}	1.39–2.09	≥5 m	[94]
Intensive advice	1.60 ^{a,*}	1.13–2.27	≥5 m	[94]
<i>Counselling by provider (individual level)</i>				
Counsellor	1.82 ^a	0.84–3.96	≥6 m	[99]
Trained health professional	1.60 ^b	1.26–2.03	≥6 m	[116]
Physician	1.76 ^a	1.58–1.95	≥6 m	[112]
	1.87 ^a	1.42–2.45	≥5 m	[99]
Nurse	1.28 ^{a,*}	1.18–1.38	≥6 m	[115]
	1.45 ^{b,*}	1.17–1.80	≥6 m	[114]
	1.76 ^a	1.21–2.57	≥5 m	[99]
Nurse – high intensity	1.28 ^{a,*}	1.18–1.39	≥6 m	[115]
	1.46 ^{b,*}	1.12–1.89	≥6 m	[114]
Nurse – low intensity	1.27 ^a	0.99–1.62	≥6 m	[115]
	1.43 ^b	0.96–2.14	≥6 m	[114]
Psychologist	1.94 ^a	1.04–3.62	≥5 m	[99]
<i>Other intervention (individual level)</i>				
Biomedical risk assessment (CO measure + spirometry)	2.45 ^b	0.73–8.25	≥6 m	[101]
CO measure	1.07 ^b	0.83–1.39	≥6 m	[101]
	1.06 ^a	0.85–1.32	6–12 m	[100]
Aversive therapy	1.98 ^b	1.36–2.90	≥6 m	[111]
	4.26 ^b	1.26–14.38	6–12 m	[107]
Acupuncture	3.53 ^{b,*}	1.03–12.07	6–12 m	[107]
	1.79 ^a	0.98–3.28	6–12 m	[108]
Hypnotherapy	4.55 ^b	0.98–21.01	6–12 m	[107]
Web-based intervention	1.93 ^a	1.44–2.60	6 m	[144]
	1.44 ^{a,*}	1.27–1.64	3–12 m	[84]
Minimal clinical intervention	1.50 ^b	0.84–2.78	6–12 m	[82]
Self-help intervention	1.28 ^a	0.89–1.82	≥5 m	[99]
	1.08 ^a	0.99–1.17	6–12 m	[98]
Written self-help material	1.59 ^{a,*}	1.22–2.07	≥5 m	[94]
Genetic notification	1.55 ^a	1.06–2.21	≤6 m	[96]
	1.87 ^b	1.20–2.92	≤6 m	[97]
	0.68 ^b	0.57–1.30	≥6 m	[97]
	1.03 ^a	0.64–1.65	≤12 m	[96]
<i>Intervention (neighbourhood level)</i>				
Partner support	0.99 ^a	0.84–1.15	6–9 m	[122]
	1.08 ^b	0.81–1.44	6–9 m	[121]
Incentive in workplace	1.44 ^b	1.01–2.01	6 m	[103]
Workplace interventions	2.03 ^b	1.42–2.90	6 m	[145]

Reference group for the risk ratios and odds ratios were placebo/no intervention. RR = Risk ratio; OR = odds ratio; m = months; NRT = nicotine replacement therapy.

* Heterogeneity in the analyses ($I^2 \geq 50\%$).

Fig. 2. Conceptual model of SC. 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 so-

ciety level), and (3) SC (the actual outcome). Interventions are always part of the success of SC. At least unconsciously, interventions at the societal 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). NRT = Nicotine replacement therapy.

Model Formulation

Building upon the classification of factors extracted from the literature review, we developed the working model of SC (fig. 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.

Results

Literature Reviews

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 (fig. 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 CI) of the meta-analyses for the different categories of factors are presented in table 1.

Regarding the systematic review of genomic factors influencing SC, out of 293 publications, 34 studies met our inclusion criteria (fig. 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.

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) [21–23]. Higher nicotine dependence, indicated for example in those who start smoking within 30 min after waking up, reduces SC success [21–24]. Moreover, a longer duration or a higher number of past cessation attempts is positively associated with SC [21, 24]. Compared to abrupt cessation, smoking reduction doubles the probability of SC [23, 25]. A positive association with SC is reported for intention-to-quit smoking and the confidence level in quitting [22, 24, 26, 27]. Negative beliefs about smoking and health benefit expectancy increase cessation [22–24]. By contrast, a negative impact on SC is reported when enjoying smoking [24] and having easy access to cigarettes [22, 23].

Environmental Factor 2 – Demographic Factors

Gender does not influence SC (OR = 1.33, CI = 0.91–1.95) [21], despite hypotheses that women might have lower SC rates due to, for example, more weight concerns or emotional sensitivity [21, 22, 24]. Regarding age, although in the review of Vangeli et al. [24] 5 studies did not yield significant results, 2 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, couples living together [21, 22, 24] or having children at home [22–24] has no impact on SC. However, living with both biological parents is suggested to enhance SC [22]. Not having friends who smoke and the absence of other smokers in the household are positively associated with SC [21–23].

Environmental Factor 4 – Socioeconomic Status

SES is mainly assessed through education, employment (e.g. employed vs. unemployed, blue vs. 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 [10]. However, the relation between SC and the 3 aforementioned socioeconomic factors does not prove to be statistically significant in most studies [23, 24]. 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) [28].

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 [21]. By contrast, both self-efficacy and intrinsic motivation to quit smoking improve SC [21, 24, 29]. Therefore, mood and stress management programmes are thought to improve SC [30].

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 [30]. Weight concern is linked to psychological and biological factors. A low physical activity is also negatively associated with SC [23].

For women, choosing the target quit day in relation to the menstrual phase, more specifically during the follicular phase, improves SC [30].

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 [21, 23]. A better perceived mental and physical health status enhances SC [22, 23]. However, in most studies there is no significant relation with improved knowledge of health risks associated with smoking [23, 24].

Genomic Factors (table 2 and online suppl. table 2)

Regarding the cascade theory of reward, no study reports a significant impact of serotonin and GABA on SC [31–34]. In opioids, contradictory results are obtained concerning the *OPRM1* A118G variant. One study reports that the G-allele improved SC [35]; another confirms this in women but reports an increased SC in men with AA-genotype [36]. Dopamine influences SC through some variants, but some results could not be replicated in different studies [37–47]. The A1-allele of *DRD2* Taq1A [38] and the long-allele of *DRD4* VNTR [48] appear to reduce SC. By contrast, the *Del*-allele of *DRD2*-141C [41], the TT-genotype of *DRD2* C957T [41], the 9-repeats of *SLC6A3* VNTR [40], and the Met-Met-genotype of *COMT* Val^{108/158}Met [49, 50] improve SC. Gene-gene interactions are reported between *DRD2* Taq1A-*SLC6A3* VNTR [40] and *DRD2* Taq1A-*CYP2B6* C1459T [47]. The variant *CHRNA2* rs2072661, which encodes for a nicotinic receptor is associated with SC [51, 52]. However, this finding is not replicated in the study of Spruell et al. [53].

Regarding the nicotine metabolism, only one study reports a significant association with *CYP2B6**6 in a population of European ancestry [54].

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 [55] and the T-allele of *HINT1* (rs3852209) increases SC at 6-month follow-up [56].

In none of the GWAS [57–60] a significant association was found (level of significance in GWAS is $\alpha = 5 \times 10^{-8}$). Also in 3 (non-GWAS) studies that included many different SNPs, no significant result was found after correction for multiple testing [61–63].

Table 2. Genes influencing SC and reported interactions with interventions

Gene	Genetic variant	Effect on cessation	References
Serotonin			
<i>SLC6A4</i>	5-HTTLPR	No effect	[31–34]
		Interaction with bupropion	[34]
	rs25531	No effect	[34]
	Stin2 (Intron 2 VNTR)	No effect	[34]
<i>TPH1</i>	A779C	No effect	[32]
<i>HTR1A</i>	C–1019G	No effect	[32]
Opioids			
<i>OPRM1</i>	A118G	G-allele: ↑ cessation (NRT patch)	[35]
		G-allele (women): ↑ cessation (EOT of NRT)	[36]
		AA genotype (men): ↑ cessation	[36]
		Interaction with NRT patch	[36]
Dopamine			
<i>DRD2</i>	TaqIA	A1-allele: ↓ cessation	[38]
		A2A2-genotype: ↓ cessation (among <i>CYP2B6</i> 1459 CC carriers)	[47]
		No effect	[37, 39, 40, 42, 44, 47]
		Interaction with bupropion and rimonabant	[42, 44, 47]
	TaqIB	No effect	[38]
	–141C	Del-Allele: ↑ cessation (EOT)	[41]
		No effect	[38, 41]
		Interaction with bupropion	[41]
	C957T	TT-genotype: ↑ cessation	[41]
		No effect	[38, 41]
<i>DRD4</i>	VNTR	Long-allele: ↓ cessation	[48]
		No effect	[45]
		Interaction with NRT and bupropion	[45, 48]
	C–521T	No effect	[48]
<i>SLC6A3</i>	VNTR	9/9 and 9/10-genotype: ↑ cessation (EOT) (among <i>DRD2</i> TaqI A2/A2 carriers)	[40]
		No effect	[47]
<i>COMT</i>	Val ^{108/158} Met	MetMet-genotype: ↑ cessation	[49, 50]
		No effect	[43, 46]
		Interaction with NRT	[43]
	rs165599	No effect	[46]
	rs737865	No effect	[46]
Nicotinic receptor			
<i>CHRNA3</i>	rs1051730	No effect	[146]
<i>CHRNA4</i>	rs1044396	No effect	[53]
	rs2273504	No effect	[53]
	rs2236196	No effect	[53]
	rs2273502	No effect	[53]
<i>CHRNA7</i>	rs2133965	No effect	[53]
	rs4779969	No effect	[53]
<i>CHRNA2</i>	rs2072661	A-allele: ↓ cessation	[51]
		GG-genotype: ↑ cessation	[52]
		No effect	[53]
	rs2072660	No effect	[53]
Nicotine metabolism			
<i>CYP2B6</i>	*6	No effect	[120]
		Interaction with bupropion	[120]
	C1459T	T-allele: ↓ cessation (EOT)	[54]
		No effect	[47]

Table 2 (continued)

Gene	Genetic variant	Effect on cessation	References
Other			
<i>GALR1</i>	rs2717162	C-allele: ↓ cessation Interaction with treatment (NRT, bupropion)	[55]
<i>HINT1</i>	rs3852209	T-allele: ↑ cessation	[56]
	rs2278060	No effect	[56]
<i>ARRB2</i>	rs1045280	No effect	[56]
	rs2036657	No effect	[56]
	rs3786047	No effect	[56]

EOT = End of treatment; NRT = nicotine replacement therapy; ↑ = increased; ↓ = decreased.

Interventions

Individual Level

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

Meta-analyses (table 1) indicate that various pharmacological treatments improve SC: nicotine replacement therapy, substitutes of nicotine [64–69], bupropion and nortriptyline (antidepressants) [67, 70–74], and varenicline, cytisine and mecamylamine (agonists of the nicotine acetylcholine receptors) [67, 75–78]. Naltrexone, an opioid antagonist, has no significant impact on SC [79]. 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 [80].

Different types of nonpharmacological interventions indicate a substantial improvement in SC: individual counselling (although in contrast with 2 other meta-analyses, Coleman et al. [68] did not report any benefit of individual counselling, $I^2 = 68\%$) [68, 81, 82], group counselling [82, 83], web-based interventions [84–87], telephone counselling (with pro-active telephone counselling being even more effective than simple telephone counselling) [82, 88–91], motivational interviewing [92–95], and genetic notification of smoking-related disease risk [96, 97]. Other interventions described in the meta-analyses do not demonstrate statistical significant differences. It concerns: self-help material [98, 99], biomedical risk assessment (e.g. CO or spirometry measurement) [100–102], incentive-based interventions [85, 103, 104], and hypnosis (even if men were more likely to respond than women) [105–107]. Positive associations are observed for acupuncture [107, 108], increased physical activity [23, 30, 109, 110] and aversive therapy [107, 111], but the results are not significant. Improvement of SC is also re-

lated with the type of provider; e.g. physicians nearly doubled SC in comparison to control [99, 112, 113], and this is also the case for nurses [99, 114, 115], psychologists [99] and trained health professionals [116].

Combining pharmacological and/or nonpharmacological interventions appears to improve SC in comparison to no intervention [117–119] or to monotherapy (RR = 1.54, CI = 1.19–2.00) [118].

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 nicotine replacement therapy are observed for *OPRM1* A118G [36], *DRD4* VNTR [48], *COMT* Val^{108/158}Met [43], *CHRNA2* rs2072661 [52], and *GALR1* rs2717162 [55]. Bupropion interacts with *SLC6A4* 5-HTTLPR [34], *DRD2* TaqIA [42, 47], *DRD2*-141C [41], *DRD4* VNTR [45], *CYP2B6**6 [120], and *GALR1* rs2717162 [55]. Finally, rimonabant interacts with *DRD2* Taq1A [44] (table 2).

Neighbourhood Level

At the neighbourhood level, only nonpharmacological interventions are available. Enhancing partner support does not demonstrate any efficacy in improving SC [121, 122]. 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 [123]. Home smoking restrictions have a positive impact on SC [24]. At workplace, no conclusion can be drawn regarding the efficacy of the interventions, due to their heterogeneity of the interventions [124].

Society Level

Policy-makers launch different actions to reduce smoking prevalence at the society level. Increased taxa-

tion [23, 125] and mass media campaigns [23, 125–127] appear to improve SC. However, in lower socioeconomic groups, mass media are more effective when also other interventions are included such as free nicotine replacement therapy and telephone counselling or there is a policy to change the social and structural context of cigarette use [127]. Other interventions such as bans (e.g. banning advertising and sponsorship or smoking in public places) [125, 128] and health warnings [125] could help to modify SC through health belief modification.

SC Working Model

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

(1) Factors influencing SC – 8 dimensions are included: smoking behaviour, demography, SES, psychology, social situation, health, biology, and genomics. The 8 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 [129].

(2) Interventions – 3 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 focussing on specific factors such as environmental factors [10] or policy [9], 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 focussed 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. [19] in 2003. In that model, 7 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 Fagerström 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 7 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 2 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 [15]. 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 [15]. Model testing through simulations under different conditions will also help in understanding complex system behaviour in an unexpected fashion [14].

We observe in table 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 [130]. However, the interpretation of probabilities often reflects our ignorance about the causal mechanism of a disorder or a trait [130].

Regarding the selection of genomic studies, we focussed 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 [131]. Environmental factors are also modified by ethnicity; this is, e.g. the case for tobacco use, perception of health risk, or social unacceptability [132]. 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 2 different loci (*F2RL3* and *GPR15*), even though no epigenetic study re-

ported an effect on SC. Methylations are found to be rapidly reversible, and therefore, remethylations are suggested after SC [133]. 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 disorders in later life [134]. 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. [135] reported in their meta-analysis that: (1) a genetic variant of the serotonin (*5-HTTLPR*) was associated with avoidance and aggression traits; (2) 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 [136]. 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 [137], no systematic review exists that 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 interac-

tions 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.

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