

## The nocebo effect and tobacco control—First, do no harm?

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### ARTICLE INFO

#### Keywords:

Tobacco control  
Nocebo effect  
Fear appeal  
Health communication  
Preventive medicine

### ABSTRACT

Since tobacco remains a leading cause of global morbidity and mortality, emphasis needs to be given to preventive approaches to tobacco consumption. Environmental and policy strategies with fear appeals are important contributors to reductions in smoking prevalence. Fear appeals are persuasive messages—often using graphic and emotionally evocative imagery and language—that attempt to scare their audiences into tobacco cessation. While the intentions of fear appeals are benign, their effects are not necessarily so; here, we argue that some fear appeals carry a significant risk of backfiring by eliciting nocebo effects among its viewers. In this context, it is important to recognize that there is currently no justification for disregarding potential nocebo effects. Therefore, we should improve our understanding of nocebo effects in the field of preventive medicine, as well as the impact of strategies aimed at mitigating their negative health effects.

### Introduction

One-hundred eighteen countries or jurisdictions currently mandate the inclusion of pictorial warnings of tobacco-related harms on tobacco and related products, which are often accompanied by equally strong text warnings [1]. Studies indicate that these emotionally evocative anti-tobacco campaigns constitute among the most cost-effective tools for motivating the audience toward tobacco cessation [2]. Not surprisingly, these “fear appeals” have become a central theme of many tobacco-control campaigns and other persuasive communications; they are found just about everywhere we look—from tobacco packages to the television screens in our homes. Following the advent of these fear appeals, tobacco consumers are now more adequately informed of the health risks they face, including heart disease, stroke, erectile dysfunction, and lung cancer [3]. We propose, however, that environmental and policy strategies using fear appeals, regrettably, compromise full compliance with the principle of nonmaleficence (i.e., “do no harm”) by disregarding potential nocebo effects completely without justification.

### Do some anti-tobacco strategies backfire?

Nocebo responses and subsequent effects are noxious changes in individuals’ physiological conditions that are attributable to the overall context surrounding any intervention (either active or inert), rather than to the specific action of that intervention [4–6]. They are triggered or exacerbated by both conscious and nonconscious mechanisms such as outcome expectancies, associative learning processes, past experiences, explicit emotions, and social cues [4–6]. Although most health-care providers now recognize that nocebo effects contribute to perceived side effects, poor medication adherence, and a diminished sense of well-being in clinical practice [6,7], few would consider the possibility of nocebo effects adversely influencing the effectiveness of environmental and policy strategies with fear appeals for preventive purposes. However, we argue that these well-intended interventions may create—or at least reinforce—negative outcome expectancies through insistent connection of tobacco consumption with its related harms, which are somewhat fatalistic in nature and often lacking nuance, strong emotional arousal elicited by graphic images and language, negative framing of prevalence data causing overestimation of the risk by the viewer, and conditioned associations (Fig. 1). It is critical to note, however, that we do not intend to question or seek to

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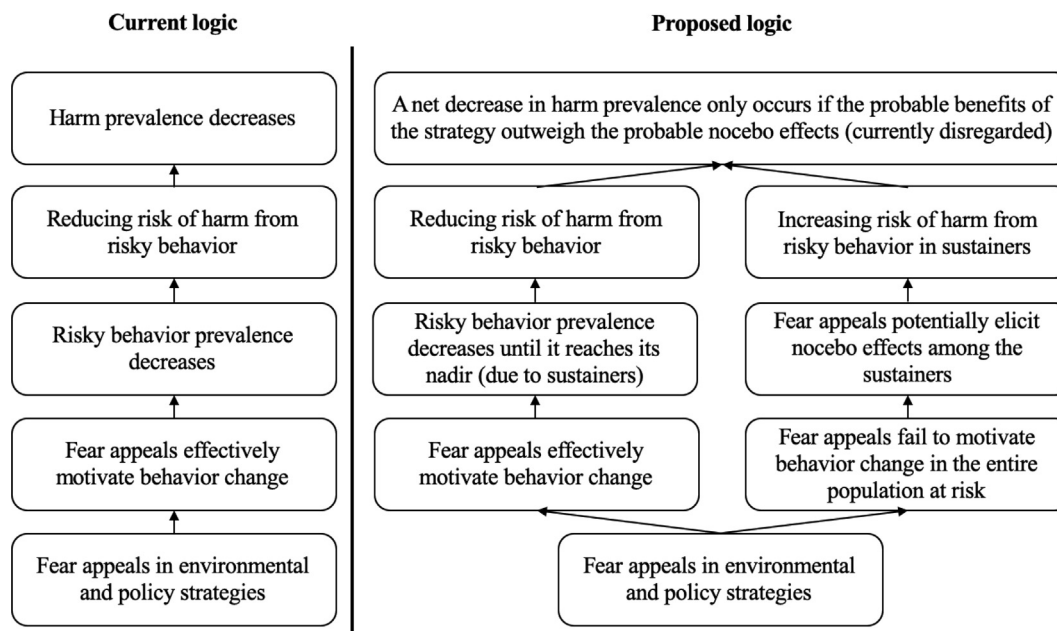


Fig. 1. Logic Flow Diagram.

undermine the importance and consequences of tobacco cessation. Let us be clear—tobacco consumption can and does cause harm [8–10]; however, the message should not be delivered via nocebogenic fear appeals.

#### Are some tobacco-related harms more nocebo-prone than others?

Presumably, our proposition is more likely to be considered for “non-specific” tobacco-related harms with fluctuating courses than for “somatic” harms (e.g., erectile dysfunction vs lung cancer). Indeed, a series of studies has provided evidence on the relationship between disclosure of medication side effects and the incidence of erectile dysfunction. In one study, blinded administration of finasteride was associated with a significantly higher overall incidence of erectile dysfunction in men with benign prostatic hyperplasia ( $N = 107$ ) who were informed about the potential sexual side effects (“...it may cause erectile dysfunction, decrease libido, problems of ejaculation; but, it is uncommon”), as compared to those who were omitted from disclosure (30.9% vs 9.6%, respectively;  $p = .02$ ) [11]. In another study, 96 men were prescribed beta-blocker therapy (atenolol) and randomized into three groups with distinct degrees of information disclosure. The first group that was not told what drug they were taking reported a 3.1% incidence of erectile dysfunction, whereas the groups knowing that they were receiving a beta-blocker reported a 31.2% and 15.6% ( $p < .01$ ) incidence of erectile dysfunction, depending on the fact if they were or were not informed on the potential side effect of erectile dysfunction, respectively (“... it may cause erectile dysfunction; but, it is uncommon”) [12]. These findings were confirmed in an independent study with similar design involving the use of metoprolol [13].

Much can be learned from these three elegant and innovative reports; they demonstrate that information disclosure about the risk of erectile dysfunction is not merely an abstract speculative warning; rather, it can independently be self-fulfilling. There is little reason to believe that the legally obligated image of a deeply worried man and the statement, “Smoking increases the risk of impotence” on European tobacco products, for example, does not elicit a similar nocebo effect among the about 55 million male smokers in the European Union. Given that similar emotionally evocative health warnings about impotence are in place in many other countries around the world, including Brazil, Canada, Egypt, the Russian Federation, and Thailand

[14], nocebogenic fear appeals pose a global problem.

One might be more reluctant, however, to consider this postulate for “somatic” tobacco-related harms, even though placebo—nocebo’s benevolent twin—was shown to improve treadmill-induced ST-segment depression [15], motor function in Parkinson’s Disease [16–19], and various other clinical outcomes beyond subjective perceptions of quality [17]. That aside, one might argue that lung cancer, for instance, differs from subjective responses. It has to do with the growth of cancer cells initiated by mutations and epigenetic changes that activate oncogenic drivers. There cannot be a nocebo effect in lung cancer development, can there? Though many, if not most, would dismiss this apparent paradox of increased lung cancer risk as mere philosophical speculation, proponents would note that it might not be completely impossible, since nocebos and oncogenesis involve common biochemical pathways. In defense of the latter, it should be noted that behavioral conditioning of the neuroendocrine and immune system (e.g., cortisol, IL-2, IFN- $\gamma$ , and lymphocytes) has been repeatedly demonstrated since its first report in 1886 [17,20–24]. Perhaps such tumor environmental changes would suffice for shifting the delicate (immunoediting) equilibrium from cancer cell elimination to escape [25]? Further, the repeated admonitions that smoking is self-destructive could increase psychological stress levels in continuing smokers [26]. From both animal and clinical studies, there are extensive data concerning the contributions of stressors to diverse (objective) pathophysiological processes, including cancer development and progression, altered DNA repair, angiogenesis, immune tolerance, and metastasis [27,28].

#### Experimental considerations

Assessing the impact of nocebo effects on rates of tobacco-related harms is not an easy undertaking and may require different study designs depending on the harm being studied. Some understanding could be gained by analyzing longitudinal data from large cohorts, using well-defined diagnostic criteria and confounding adjustment. Using a time-dependent approach, hazard ratios for harm incidence can be calculated and compared. An onset of increasing hazard beginning soon after implementation of the fear appeal, would lend support to our hypothesis. Unfortunately, such adequate high-quality data are rare and/or costly to obtain.

The currently accepted assumption that changes in cigarette design (e.g., the addition of filters) are responsible for the increased lung cancer risk in smokers over the past decades is actually based on this type of evidence, complemented by some toxicology data [29]. Interestingly—and provocatively, changes in cigarette design were implemented synchronously with the first health warnings on cigarette packages (1966 in the USA) [30]. It is tempting to question whether this observed increased risk can be explained by a nocebo effect due to environmental and policy strategies using fear appeals (even if to a—very—discrete extent). In our opinion, there is no definite answer to that question, at least not without more research addressing this specific question. Perhaps not; however, is it not plausible enough to consider?

Experimentally, one could design a trial in which clusters of smokers (e.g., cigarette shops) are randomized to exposure to either erectile dysfunction or non-erectile dysfunction fear appeals only, in which baseline and post-exposure erectile dysfunction prevalence are compared. However, in addition to being ethically fraught, such trial might be confounded by (nocebo) information input from other sources (e.g., internet).

A note of caution is in place here, as the nocebo effect size may not only be dependent on the way the environmental or policy strategy is communicated (e.g., strongly emotionally evocative fear appeals vs. emotionally neutral strategies) or the harm in question (e.g., erectile dysfunction vs. lung cancer), but also on the characteristics of the viewer. In fact, as is often the case, the most vulnerable may be among those who disproportionately have to bear the unintended adverse consequences of policy initiatives [31,32]. First, the literature pertaining to risk factors that contribute to nocebo effects have identified several nocebo-prone personality traits, including type A personality, lower positive affect, pessimism, neuroticism, and somatization [33]; of these, some might, in turn, be associated with higher smoking prevalence [34,35]. Second, at an international level, although many low- to middle-income countries are currently implementing tobacco health warnings with fear appeals [1,14], they are encountering a relatively steady increase, rather than a decrease, in tobacco consumption prevalence which in turn increases the population at risk [36]. Together, these findings suggest that the nocebo burden of environmental and policy strategies with fear appeals is theoretically much greater in vulnerable populations. This should be a matter of high priority in future research.

## Conclusion and recommendations

The moral of this *Article* is not just that the nocebo effect is inescapably real, but that it has significant public health ramifications, which have never been properly considered within the field of tobacco control. Thus, the question arises: how should this *Article* influence clinical practice? Given that fear appeals are increasingly used to motivate tobacco cessation globally and based on the findings concerning information disclosure about the risk of erectile dysfunction, we would strongly urge our respective governments and public health bodies to take robust action against fear appeals stating that smoking causes impotence, in effort to reverse the deleterious impact on millions of male smokers worldwide due to a nocebo effect. For other tobacco-related harms (e.g., cancer, heart disease, stroke, etc.), however, the available evidence is more circumstantial, and simply omitting environmental and policy strategies with fear appeals altogether could potentially undermine some advantageous public health missions (Fig. 2). Regardless, even in this context, we urge extreme caution in the use of fear appeals—will we continue to violate the precautionary principle by potentially exposing remaining smokers to further liability?

What else should be done to reduce unnecessary suffering and avoid potentially harmful preventive interventions? Various strategies may mitigate the potential threat of a nocebo effect posed by environmental

and policy strategies with fear appeals. First, alternative approaches that are scientifically established as being (highly) effective but less morally conflicted, such as increased tobacco taxation and smoking bans in public spaces [37], should be preferred over fear appeals as it is in the mutual interest of society and the individuals concerned. Second, acknowledging that fear appeals are a potential nocebo gives policy-makers the additional responsibility of actively considering if the probable benefits of the fear appeal outweigh infringed ethical norms, such as the precautionary and nonmaleficence principles and any probable nocebo effects (Fig. 2). Third and finally, longitudinal data with a sufficient sample size, preferably involving well-defined diagnostic criteria and reasonable confounding adjustment, are warranted to verify the conclusions presented here (as discussed above), with the eventual aim to develop and adopt, at the national and international level, comprehensive evidence-based tobacco control strategies that consider the nocebo effect. Lessons from the past can be applied to motivate such future research. The once widespread perceptions—often based on unblinded clinical experience—that arthroscopic debridement of the knee, vertebroplasty, and percutaneous coronary intervention unquestionably improve osteoarthritis [38], vertebral fracture [39], and angina [40], respectively, were all demonstrated not to correspond to reality. Double-blind sham-controlled trials revealed that the observed differences are attributable to a placebo effect whereas the interventions themselves are lacking true efficacy. Creative (perhaps unusual) thinking and audacious experimental research was what was needed to expose the placebo effect and prove conventional wisdom wrong.

Although our *Article* focused on fear appeals, and more specifically on tobacco control, similar findings may be present with fear appeals targeting other risky behaviors (such as alcohol and marijuana consumption), as well as other preventive health communications without fear appeals. Because the way information is communicated to individuals has the potential to change reality, as has been suggested by many and neglected by more [41], it is vital to take great care in how information is disclosed in all areas of clinical practice as well as in policy setting.

In conclusion, we argue that since nocebo responses and subsequent effects to environmental and policy strategies with fear appeals are plausible, we should improve our understanding of nocebo effects in the context of preventive medicine, as well as the impact of strategies aimed at mitigating the negative health effects connected with fear appeals. The message we deliver and the way we deliver it should have the least potential to cause harm and the greatest potential to successfully motivate behavior change.

## Contributor's statement

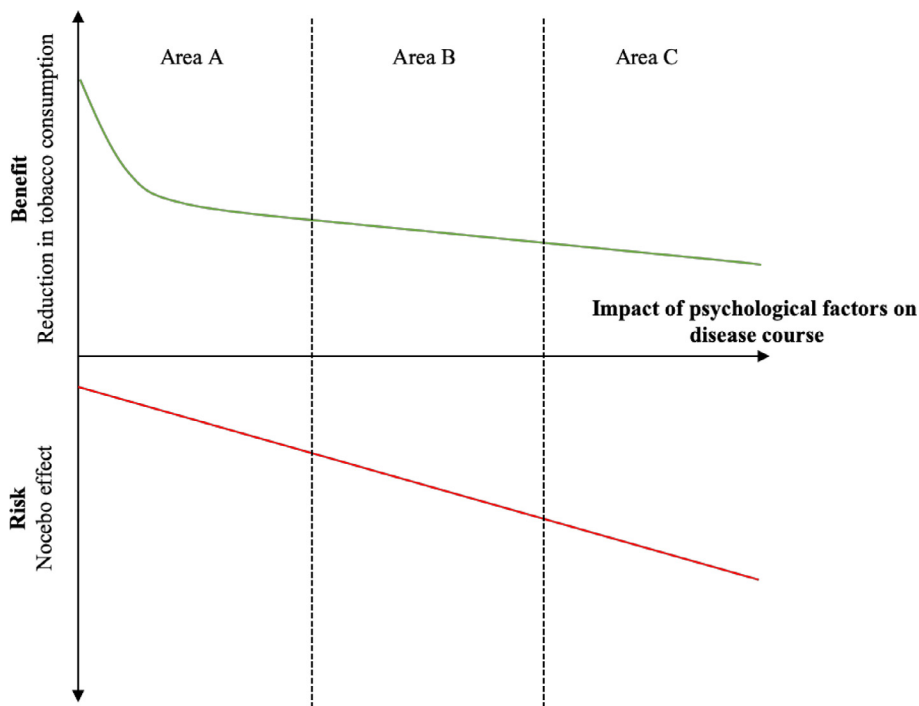
All authors contributed substantially to the conception and design of the Comment. E.A.D. drafted the manuscript and all authors contributed to its final revision. H.G.D. supervised the project and was in charge of overall direction and planning. All authors approved the final version of the manuscript for publication.

## Acknowledgement

E.A.D. is an “*Aspirant*” (Ph.D. Fellow) of the Research Foundation-Flanders (FWO) (Grant Number: 1195919N).

## Declaration of Competing Interest

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have nothing to disclose.



**Fig. 2.** Benefit-Risk Ratio of Fear Appeals. It has been consistently noted that the amount of fear (i.e., high depicted disease severity) in the message's content is positively correlated with motivation for behavior change. Generally speaking, the more severe a disease, the less impact of psychological factors on its course, and, the more it will scare individuals (e.g., lung cancer). Taken together, we hypothesize that the benefit-risk ratio of fear appeals is modulated by the impact of psychological factors on disease course, encompassing a spectrum. For tobacco-related harms at one end of the spectrum (area A), characterized by a low impact of psychological factors (e.g., lung cancer; "somatic harms"), fear appeals could be indicated because they probably have an advantageous benefit-risk ratio. For tobacco-related harms at the other end of the spectrum (area C), characterized by a high impact of psychological factors (e.g., erectile dysfunction; "non-specific harms"), fear appeals should be omitted since they could do more harm than benefit. It is critical to note that although some fear appeals might very well be beneficial to the society as a whole (because they effectively motivate behavior change; e.g., lung cancer fear appeals), for the individuals that continue smoking despite the many efforts of public health bodies, only the nocebo effect will remain—without benefit, by definition.

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