ABSTRACT

Introduction: Tobacco control researchers have recently become more interested in systems science methods and mathematical modelling techniques as a means to understand how complex inter-relationships among various factors translate into population-level summaries of tobacco use prevalence and its associated medical and social costs. However, there is currently no resource that provides an overview of how mathematical modelling has been used in tobacco control research. This review will provide a summary of studies that employ modelling techniques to predict tobacco-related outcomes. It will also propose a conceptual framework for grouping existing modelling studies by their objectives.

Methods and analysis: We will conduct a systematic review that is informed by Cochrane procedures, as well as guidelines developed for reviews that are specifically intended to inform policy and programme decision-making. We will search 5 electronic databases to identify studies that use a mathematical model to project a tobacco-related outcome. An online data extraction form will be developed based on the ISPOR-SMDM Modeling Good Research Practices. We will perform a qualitative synthesis of included studies. Ethics and dissemination: Ethical approval is not required for this study. An initial paper, published in a peer-reviewed journal, will provide an overview of our findings. Subsequent papers will provide greater detail on results within each study objective category and an assessment of the risk of bias of these grouped studies.

INTRODUCTION

In its early years, the field of tobacco control benefited from studies examining the aetiology of tobacco-related disease. Today, the research paradigm in the field relies on a broader perspective that takes into account the complete system within which tobacco use and tobacco control interventions operate.1 2 Acknowledging the complex drivers of tobacco use and related diseases, tobacco control researchers have become increasingly interested in systems science methods.3 4

One approach used in systems science research is mathematical modelling which, broadly conceived, illustrates and attempts to quantify how a system’s components are inter-related and how outcomes of interest might be affected when a system undergoes change.3 In tobacco control research, such models have been used to understand the future scope of disease burden,5 6 the potential effects of policies and regulations,7 8 9 and the economic consequences of interventions.10 11 12 However, there is currently no resource that provides an overview or synthesis of how these modelling techniques have been developed and used in tobacco control. This gap limits the ability of researchers to learn from and improve on existing models. Moreover, modelling approaches have been heterogeneous in their methods and even though they attempt to predict similar types of outcomes (eg, lung cancer, quality-adjusted life years), results have not been adequately synthesised, weakening their ability to contribute to the evidence base for regulatory policy decisions. This review will address this gap by providing a summary of

Strengths and limitations of this study

- To the best of our knowledge, this is the first review to systematically synthesise studies that have employed mathematical models to predict tobacco-related outcomes.
- This study will produce a conceptual framework for grouping existing modelling studies, which will serve as the foundation for future analyses of these data.
- The results of this study may inform future mathematical models in the field of tobacco control.
- This review will be limited to English language and peer-reviewed articles.

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modelling techniques that have been used in tobacco control research to predict tobacco-related outcomes. It will also propose a conceptual framework for grouping existing modelling studies by their objectives, which will serve as the foundation for future analyses of these data. This effort is intended to inform regulatory decision-making. The Center for Tobacco Products at the US Food and Drug Administration has expressed an interest in modelling the impact of its policies.14 The results of this review will help decision-makers at the national, state and local levels to gain a better understanding of the scope, content and quality of existing modelling studies.

METHODS AND ANALYSIS

The Cochrane Collaboration provides rigorous guidelines for conducting systematic reviews.15 However, these guidelines were developed to inform systematic reviews that investigate the effectiveness of healthcare interventions.16 Thus, while the Cochrane approach to conducting systematic reviews will inform the methodology of this review,15 we will also draw on guidelines from reviews that are specifically intended to inform policy and programme decision-making.17 This protocol reports on recommended items to address in a systematic review protocol, in compliance with the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P).18

Eligibility criteria

Eligible studies must use a mathematical model to project a tobacco-related outcome. ‘Projection’ is defined as the use of data—real or hypothetical—to estimate an outcome prospectively beyond the date from when the data were collected. Mathematical models with differing structures, purposes and outcomes will be eligible for this review, including system dynamics models,19 dynamic simulations,20 state-transition models,21 decision trees,22 microsimulations23 and economic models.24

Outcomes must estimate the prevalence of tobacco use (including changes in initiation or cessation), tobacco-related health outcomes, and/or tobacco-related costs. Tobacco-related health outcomes are broadly defined to include any outcome that has evidence of a relationship with tobacco use, including outcomes for which the Surgeon General finds inadequate evidence to conclude that a causal relationship is present.25-26 Eligible models may include any analytic time horizon. Models with lifetime horizons will be included, even if the authors do not report outcomes to a specific date. Studies assessing nontobacco related outcomes, such as alcohol use or obesity prevalence, will be included if a tobacco-related outcome is also examined. Real and hypothetical populations contributing data for these modelling studies may be of any age, gender, race/ethnicity, and from any geographic location. Only peer-reviewed, published literature will be eligible for inclusion.

Models that project only retrospectively, such as those that analyse the historical burden of disease, will be excluded from this review, as will studies that model individual smoker trajectories that do not also project population-level outcomes. Additionally, animal studies, human genetics studies, and posters and abstracts without full-text records will be excluded from this review. This review will be limited to English language studies.

Search methods for identification of studies

A comprehensive search strategy, developed in consultation with a university librarian and group of tobacco control experts, will be used to identify eligible papers (see table 1). We developed the search strategy by identifying medical subject headings for recent tobacco simulation model publications.8 27-29 A search strategy was developed to address the unique features and indexing of each of the five electronic databases: PubMed, Embase, EconLit, CINAHL and PsychInfo. These databases were selected based on recommendations from the university librarian, and these will be searched with no date restrictions. We will use EndNote X6 to manage records throughout this review.

Data collection and analysis

Selection of studies

Eligibility criteria will be piloted by multiple reviewers prior to the title and abstract review, and refined to ensure consistency across reviewers. In the first stage of study selection, coders will independently review the title and abstract of each included record. In order to be selected for the full-text review, titles and abstracts must refer to any type of tobacco product or tobacco use, and indicate that the study projected a tobacco-related outcome, as defined above. After the double review, each record will be categorised using the following criteria: (1) both authors agree on inclusion; (2) one author recommends inclusion; (3) both authors are unsure; (4) one author recommends exclusion and the other is unsure or (5) both authors agree on exclusion. Full-text articles for abstracts classified as 1 or 2 will be retrieved. Records classified as 3 or 4 will be discussed further by two reviewers and if needed, a third reviewer will be consulted to determine whether the record should be included in the full-text review. Records classified as 5 will not be considered for full-text review.

Using the same pilot testing, double review and categorisation process, two coders will review the full texts of selected articles. After independent review of the articles, the coders will meet to categorise each article using the criteria listed above; again, records classified as 1 or 2 will be considered as included studies. At this time, the coders will resolve discrepancies and record the reasons for record exclusions in a log. If an article is excluded for multiple reasons, only the primary reason for exclusion will be noted. The hierarchy for identifying
| Concept 1: modelling | Concept 2: tobacco | Restrictions |
|---------------------|-------------------|--------------|
| PubMed              | ‘Smoking’[Mesh] OR ‘Smoking Cessation’[Mesh] OR ‘Tobacco Use Cessation Products’[Mesh] OR ‘Tobacco’[Mesh] OR ‘Tobacco Products’[Mesh] OR ‘Tobacco, Smokeless’[Mesh] OR ‘Smoking’[TI] OR ‘Tobacco’[TI] OR ‘Smoker’[TI] OR ‘Smokers’[TI] OR ‘Cigar’[TI] OR ‘Smokeless’[TIAB] OR ‘E-cigarette’[TIAB] OR ‘Electronic cigarette’[TIAB] OR ‘Snus’[TIAB] OR ‘Nicotine’[TIAB] AND English[lang] | NOT ‘gene’[TIAB] Filter: English |
| Embase              | ‘smoking’[mj] OR ‘cigarette smoke’[mj] OR ‘bidi smoking’[mj] OR ‘smoking regulation’ OR ‘smoking cessation’[exp] OR ‘tobacco’[exp] OR ‘smokeless tobacco’[exp] OR ‘electronic cigarette’:ab,ti OR ‘e-cigarette’:ab,ti OR ‘snus’:ab,ti OR ‘nicotine’:ab,ti NOT ‘cannabis smoking’[exp] NOT ‘cigarette smoke condensate’[mj] | NOT ‘gene’[exp] OR ‘genetic’[exp] AND [english]/lim AND [humans]/lim |
| EconLit             | KW ‘Smoking’ OR ‘tobacco’ OR TX ‘smokeless’ OR ‘Smoking’ OR ‘Tobacco’ OR ‘Smoker’ OR ‘Smokers’ OR ‘Cigar’ OR ‘Smokeless’ OR ‘E-cigarette’ OR ‘Electronic cigarette’ OR ‘Snus’ OR ‘Nicotine’ OR ‘smoking-attributable deaths’ OR ‘smoking attributable deaths’ | No English Language Limiting Option |

Continued...
| Concept 1: modelling                                                                 | Concept 2: tobacco                                                                     | Restrictions                          |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------|
| ‘cost-effectiveness analyses’ OR ‘cost-benefit analysis’ OR ‘cost-benefit analyses’ OR ‘microsimulation’ OR ‘micro simulation’ OR ‘monte carlo’ OR ‘life year’ OR ‘life years’ OR ‘deterministic’ OR ‘probabilistic’ OR ‘stochastic’ OR ‘dynamic transmission model’ OR ‘state-transition’ OR ‘state transition’ OR ‘discrete event’ OR ‘continuous event’ OR ‘analytic horizon’ OR ‘cohort simulation’ OR ‘second-order simulation’ OR ‘first-order simulation’ OR ‘threshold analysis’ OR ‘years of healthy life’ OR ‘decision problem’ OR ‘transition probabilities’ OR ‘discount rate’ | MJ Tobacco OR Smoking OR Smoking Cessation OR Smoking—Trends OR Smoking Cessation OR TX smokeless OR ‘Smoking’ OR ‘Tobacco’ OR ‘Smoker’ or ‘Smokers’ OR Cigar* OR ‘Smokeless’ OR E-cigarette* OR Electronic cigarette* OR ‘Snus’ OR ‘Nicotine’ OR ‘smoking-attributable deaths’ OR ‘smoking attributable deaths’ | Only English Language |
| MJ Computer Simulation OR Models, Statistical OR Forecasting OR Cost Benefit Analysis OR Quality-Adjusted Life Years OR TX ‘system dynamics’ OR ‘agent-based model’ OR ‘agent-based models’ OR ‘agent-based modelling’ OR ‘agent-based modelling’ OR ‘simulation model’ OR ‘decision analysis’ OR ‘decision framework’ OR ‘markov’ OR ‘cost-utility analysis’ OR ‘cost-utility analyses’ OR ‘cost-effectiveness analysis’ OR ‘cost-effectiveness analyses’ OR ‘cost-benefit analysis’ OR ‘cost-benefit analyses’ OR ‘microsimulation’ OR ‘micro simulation’ OR ‘monte carlo’ OR ‘life year’ OR ‘life years’ OR ‘deterministic’ OR ‘probabilistic’ OR ‘stochastic’ OR ‘dynamic transmission model’ OR ‘state-transition’ OR ‘state transition’ OR ‘discrete event’ OR ‘continuous event’ OR ‘analytic horizon’ OR ‘cohort simulation’ OR ‘second-order simulation’ OR ‘first-order simulation’ OR ‘threshold analysis’ OR ‘years of healthy life’ OR ‘decision problem’ OR ‘transition probabilities’ OR ‘discount rate’ | PsychInfo                                                                                     |                          |
| KW cost effectiveness OR economic analysis OR smoking-attributable deaths OR quality adjusted life expectancy OR economic impact OR SU ‘Costs and Cost Analysis’ OR Health Care Policy OR Simulation OR Decision Making OR Life Expectancy OR TX ‘system dynamics’ OR ‘agent-based model’ OR ‘agent-based models’ OR ‘agent-based modelling’ OR ‘agent-based modelling’ OR ‘simulation model’ OR ‘decision analysis’ OR ‘decision framework’ OR ‘markov’ OR ‘cost-utility analysis’ OR ‘cost-utility analyses’ OR ‘cost-effectiveness analysis’ OR ‘cost-effectiveness analyses’ OR ‘cost-benefit analysis’ OR ‘cost-benefit analyses’ OR ‘microsimulation’ OR ‘micro simulation’ OR ‘monte carlo’ OR ‘life year’ OR ‘life years’ OR ‘deterministic’ OR ‘probabilistic’ OR ‘stochastic’ OR ‘dynamic transmission model’ OR ‘state-transition’ OR ‘state transition’ OR ‘discrete event’ OR ‘continuous event’ OR ‘analytic horizon’ OR ‘cohort simulation’ OR ‘second-order simulation’ OR ‘first-order simulation’ OR ‘threshold analysis’ OR ‘years of healthy life’ OR ‘decision problem’ OR ‘transition probabilities’ OR ‘discount rate’ | KW tobacco control policies OR tobacco control policy OR smoking cessation OR smokeless tobacco OR cession treatment policies OR population smoking prevalence OR tobacco elimination OR cessation programs OR cigarette consumption OR smoking OR snus OR electric cigarettes OR SU Smoking Cessation OR Tobacco Smoking OR Smokeless Tobacco OR TX smokeless OR ‘Smoking’ OR ‘Tobacco’ OR ‘Smoker’ or ‘Smokers’ OR Cigar* OR ‘Smokeless’ OR E-cigarette* OR Electronic cigarette* OR ‘Snus’ OR ‘Nicotine’ OR ‘smoking-attributable deaths’ OR ‘smoking attributable deaths’ | Restriction: English and Human |
the reason for exclusion when multiple reasons exist will be as follows: (1) the article was not available in English; (2) the article did not contain an original analysis; (3) the study did not include a projected outcome; or (4) the study did not include a tobacco-related outcome. The remaining studies will be retained for inclusion in the systematic review.

Data extraction
The ISPOR-SMDM Modeling Good Research Practices Task Force published a series of papers that provide recommendations for best practices in developing and reporting on mathematical models. An online data extraction form will be developed based on the ISPOR-SMDM Modeling Good Research Practices and will contain items regarding the study objective, purpose, model structure, inputs and outcomes. We will approach form development with the expectation that model objectives will fall into one or more of three categories: (1) to evaluate the effects of a population-level policy, legislative, or regulatory action (‘policy study’); (2) to assess the economic implications of a policy or programme (‘economic study’); and (3) to estimate the effect that tobacco use changes or trends in tobacco-related disease would have on future morbidity or mortality outcomes (‘disease study’). Owing to the variability in the types of models and inputs assessed in this review, and the novel nature of this type of review, this form will undergo significant pilot testing. During this process, the form will be revised to facilitate data collection for technical and conceptual aspects of included papers.

Data synthesis
After the data are collected, we will perform a qualitative synthesis of the included studies. An initial paper will provide an overview of our findings. This overview will include a conceptual framework, based on the model objective categories we identified, that will be used to organise existing tobacco modelling studies. We will also identify methodological commonalities across papers. Subsequent papers will provide greater detail on results within each study objective category and an assessment of the risk of bias of these grouped studies; to conduct these analyses, we will perform additional rounds of data extraction with subgroups of the included studies. Given the large scope of this review and heterogeneity of included model structures and outcomes, we do not expect to conduct meta-analyses of model results. An additional outcome of this effort will be to determine if meta-analyses might be possible at some future point by identifying homogenous subgroups of studies, and recommending common methods and measures for ongoing and future studies that would permit meta-analyses and data pooling.

POTENTIAL LIMITATIONS
Potential limitations of this study include the risk of bias introduced by restricting the search to English language studies and peer-reviewed literature. Our ability to conduct quality assessments of the included studies may also ultimately be limited due to the nature of mathematical modelling methods. That is, there are numerous ways that a modeller can choose to structure his or her model, and this decision impacts the model outcomes. As noted in a report of the ISPOR-SMDM Modeling Good Research Practices Task Force, many a time choices regarding model structure “are made on the basis of expert opinion, or influenced by concerns for simplicity, feasibility of implementation, and so on. This process leaves much room for uncertainty, but it is very difficult to quantify and analyse this uncertainty.” While this characteristic of mathematical modelling may make it difficult to assess the internal validity of some models, the results of this systematic review will allow us to assess the cross validity of models by comparing different types of models that address similar research questions.

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Contributors ACV conceived the idea for this study. SF and ED drafted the protocol and developed the search strategy, with support from ACV, JP, GZ and RN. ACV, JP, GZ and ED will conduct the title and abstract review. SF, ED and AG will perform data extraction. ACV is the guarantor of the review. All authors provided input on inclusion and exclusion criteria.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This study is a systematic review of the literature and thus, uses data that are already publicly available.

Ethics and dissemination This review synthesises published literature; ethical approval is not required for this study. The results of this study will be disseminated in a peer-reviewed journal.

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