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Association of smoking reduction and mortality: protocol for a systematic review and meta-analysis of longitudinal observational studies

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ABSTRACT

Introduction Strong evidence shows that smoking cessation decreases mortality. Much less is known regarding the association between reduction in cigarettes per day (CPD) and mortality. The primary aim of this systematic review is to compare the mortality risk between smokers achieving a sustained reduction of CPD and smokers maintaining their smoking rate. The secondary aims are to compare the mortality risk between smokers achieving complete, sustained smoking cessation and (1) smokers maintaining their smoking rate and (2) smokers who achieved a sustained reduction in smoking rate.

Methods and analysis MEDLINE, Web of Sciences and Embase will be searched using a prespecified search strategy, up to 23 November 2020, and will be limited to studies published in English and in French. Longitudinal observational studies using individual data including smokers with at least two distant CPD assessments and a follow-up period of systematic mortality data recording will be included. The main outcome will be the all-cause mortality. The secondary outcome will be specific mortality. The Newcastle-Ottawa Scale will be used to assess the risk of bias of individual studies. Outcomes will be analysed using HRs. All other outcomes' effect size reported in included studies will be converted in HRs using validated methods.

Ethics and dissemination We intend to publish the results of our review in a peer-reviewed journal and to present the findings at national and international meetings and conferences.

PROSPERO registration number CRD42019138354.

Strengths and limitations of this study

► The systematic review will be conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
► Exposure will be defined using at least two distant cigarettes per day assessments.
► The meta-analysis associated with this review will allow quantifying the magnitude of the association between smoking reduction and mortality compared with maintained smoking intensity and smoking cessation.
► Heterogeneity, particularly differences in exposure and follow-up durations, may limit the strengths of the associations and conclusions.
► As evidence will be derived from observational studies, a conclusive answer on causality will not be provided.

INTRODUCTION
Rationale

Increased mortality among cigarette smokers has long been well established, reaching two to three times the mortality rate of never smokers. Smoking results in the reduction in life span by an average of 10 years.[1–6] The main causes of excess mortality among smokers are neoplastic, vascular, respiratory and other smoking-induced diseases.[3 4 7] All-cause mortality provides a measure of the excess mortality attributable to smoking that integrates all these causes and also captures mortality related to currently unidentified associations of smoking with health issues.[3] A clear dose–response relationship between smoking intensity (ie, cigarettes per day (CPD)), duration of smoking and mortality has consistently been reported.[2 5 6 8 9]

Smoking cessation reduces the risk of major chronic diseases and extends life expectancy by decreasing all-cause mortality.[1–4 10 11] Therefore, complete and definitive smoking cessation as soon as possible is considered the best avenue for smokers.[3 6 10 11] However, while well aware of this public health message, many smokers continue to smoke, probably because they feel unable or are unwilling to quit.[12] For these smokers, harm reduction or harm minimisation strategies have been suggested,[12] some of which being increasingly popular (ie, by using electronic nicotine delivery systems),[13 14] but for which the effectiveness in reducing the mortality risk compared with unchanged cigarette smoking rate remains to be comprehensively assessed.

According to the latest Surgeon General report,[3] reductions in the number of

cigarettes smoked per day are much less effective than smoking cessation in reducing the mortality associated with smoking. The reality or the extent of such a possible benefit of smoking reduction in avoiding smoking-related mortality risks has however not been analysed in the report. A qualitative review reported in 2006 that a reduction in the number of CPD is associated with an increased probability of future smoking cessation but was unable to conclude about a change in disease risk.[15] A systematic review published the following year examined the possible health benefit of reduced tobacco consumption and concluded that smoking reduction improves cardiovascular risk factors and respiratory symptoms and reduces the incidence of lung cancer.[16] However, the review found no evidence of an association between a reduction in CPD (compared with unchanged CPD) and all-cause or most specific mortality rates except for a borderline significant decline in risk of tobacco-related cancers. It is noteworthy that the analysis of the association between reduction in CPD and mortality relied on a single observational study in this review.[17] Since its publication in 2007, a number of additional studies reported contrasted findings regarding the extent of the possible association of reduction in CPD and mortality.[18–22] The purpose of our review protocol is to update and synthesise the currently available data regarding the association between smoking reduction and mortality.

Objectives

The primary aim of this systematic review is to compare the mortality risk between smokers achieving a sustained reduction of CPD and smokers maintaining their smoking rate. The secondary aims are comparing mortality risk between smokers achieving complete, sustained smoking cessation, and (1) smokers maintaining their smoking rate (CPD), (2) and smokers achieving a sustained reduction. Depending on the CPD categories reported in the studies included in the review, comparison of the mortality risk between different levels of CPD reduction will be performed if appropriate.

METHODS

This protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines.[23 24]

Eligibility criteria

Studies (published in English or in French) will be selected according to the criteria outlined below.

Study design

We will include longitudinal observational studies using individual level data; reports using aggregated data will be excluded. Figure 1 is a schematic diagram of data on participants (smokers), exposure (CPD change categories: maintainers, reducers, quitters) and outcome
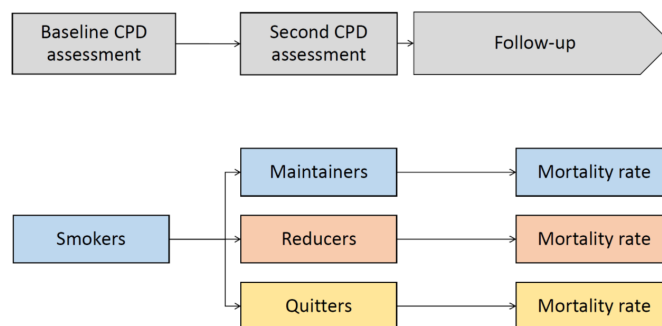
Figure 1 Schematic diagram of participants (smokers), exposure (CPD change categories: maintainers, reducers, quitters) and outcome (mortality rate). CPD, cigarettes per day.

(mortality rate) required for the eligible studies in the review.

Participants

Current smokers at baseline.

Exposure

The primary exposure of interest is cigarette smoking, expressed as the number of CPD, or as a CPD category (eg, 1–10, 11–20 and >20). CPD can be self-reported. CPD has to be measured at least twice: at baseline, and at a second and distant assessment. Individual change in CPD (or in CPD category) should have been assessed and reported.

Comparators

Three groups of participants' outcomes will be compared:
► Smokers having reduced their smoking rate (CPD) at a second assessment.
► Smokers having maintained (or increased) their smoking rate at a second assessment.
► Smokers having quit smoking at a second assessment.

Outcome

The main outcome will be all-cause mortality. Included studies must have systematically collected mortality records during a follow-up. The secondary outcome will be system specific mortality (ie, cardiovascular, cancer, respiratory and other…).

Information sources

We will search MEDLINE (1948 onwards) and EMBASE (1980 onwards). To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews identified through the search. We will also search the authors' personal files to make sure that all relevant material has been captured.

Search strategy

The search will be performed up to 23 November 2020, and be limited to studies published in English or in French. The MEDLINE search strategy is included as follows: (smok*[Title] OR cigarette*[Title] OR tobacco[Title]) AND cigarette*[Abstract]) AND

(mortality[Title/Abstract] OR death[Title/Abstract]) AND reduction*[Title/Abstract].

Web of Sciences and EMBASE searches will be started after completion of the MEDLINE search with subject headings and syntax of Web of Sciences and EMBASE. Further, the authors will check for additional relevant cited articles if not identified previously.

Study records
Data management
Literature search results will be uploaded and stored in Zotero (https://www.zotero.org); duplicates will be removed.

Selection process
At least two review authors will independently screen the titles and abstracts according to the eligibility criteria. Full reports with uncertain eligibility criteria will be checked. Identified full reports will be again checked for eligibility criteria before including them into the review. Online supplemental material 1 will be consulted if the information provided in the main published article is insufficient to assess whether or not the eligibility criteria are met. Between-review author disagreements will be resolved through discussion. Reasons for excluding trials will be recorded and reported.

Data collection process
Information will be extracted from all studies meeting eligibility criteria. Two reviewers will independently complete the data extraction form (see online supplemental table 1). Discrepancies will be resolved through discussion and/or consultation with the primary reviewer. We will contact study authors to resolve any uncertainties.

Data items
The data information form is structured in eight sections (online supplemental table 1):
► Study characteristics: setting, design, year of publication.
► Participants: characteristics of the study population such as country/region, age and sex distribution and the size of the population; the sampling methods used.
► Exposure/comparators: date of (and age at) baseline and second CPD assessment, CPD categories definition, CPD reducer definitions, health status at the beginning of the follow-up period.
► Outcomes timing/follow-up: date of (and age at) end of follow-up, duration of follow-up, specific mortality reported.
► Statistical analyses: the method for the main statistical analysis, the main effect measure, the magnitude of effect, with CIs will be recorded. We will record unadjusted and maximally adjusted estimates as appropriate and we will note the covariates used.
► Newcastle-Ottawa Scale (NOS) for cohort studies—scoring details in the three dimensions:
– Selection assessment.
– Comparability assessment.
– Ooutcome assessment.

Outcomes and prioritisation
The primary outcome of interest will be the all-cause mortality rate. The secondary outcomes will be specific mortality rate. Specific mortality will be classified according to the 2014 Surgeon General's Report[3]:
► Cancer: lung cancer; other cancers (cancers of the lip, pharynx and oral cavity, oesophagus, stomach, pancreas, larynx, cervix uteri (women), kidney and renal pelvis, bladder, liver, colon and rectum; also acute myeloid leukaemia.
► Cardiovascular and metabolic: coronary heart disease; other heart disease (includes rheumatic heart disease, pulmonary heart disease and other forms of heart disease); cerebrovascular disease; other vascular disease (atherosclerosis, aortic aneurysm and other arterial diseases).
► Respiratory: pneumonia, influenza, tuberculosis; chronic obstructive pulmonary disease (includes emphysema, bronchitis and chronic airways obstruction).

We expect to prioritise exposure definition, that is, the definition of CPD reduction: the primary analysis will use the study authors' main definition of CPD reduction, or if not defined, change to any lower CPD group will be used. Alternative reduction definitions will be used in secondary analyses.

Risk-of-bias assessment (in individual studies)
The NOS for cohort studies will be used to assess the risk of bias of individual studies.[25] Briefly, this scale contains eight items, categorised into three dimensions including selection, comparability and outcome. For each item, a series of response options is provided. A star system allows a semiquantitative assessment of study quality, such that the highest quality studies are awarded a maximum of one star for each item with the exception of the item related to comparability that allows the assignment of two stars. The NOS ranges between 0 and 9 stars. Risk-of-bias assessment will be conducted independently by two reviewers. Discrepancies will be resolved through discussion and/or consultation with the primary reviewer.

Data synthesis
Outcomes will be analysed using HR. All other outcome effect size measures will be converted into HRs, using validated methods.[26–28] We will conduct meta-analyses (using inverse variance weighting) to calculate a pooled effect estimate.

Statistical heterogeneity will be tested using the I^2 statistic (0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; 75%–100%: considerable heterogeneity). If high levels of heterogeneity among the trials exist ($I^2 \geq 50\%$ or $p<0.1$) the study design and characteristics will specifically be analysed.

We will attempt to explain the source of heterogeneity by subgroups (study setting, study design, study country, sex distribution, reducer definitions, health status at the beginning of the follow-up period) and meta-regression analyses (baseline date, participants age, time between baseline and second CPD assessment, mean age at the end of the follow-up, duration of the follow-up period) or sensitivity analyses (risk of bias). The statistical software Comprehensive Meta-Analysis V.3.0 will be used for the meta-analysis calculations.

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies.

Risk of bias in meta-analysis

Publication bias assessment will be based on funnel plots. In case of asymmetry, Duval and Tweedie's Trim and Fill method will be used.[29]

Confidence in cumulative evidence

We will use the Grading of Recommendations, Assessment, Development and Evaluation guidelines to assess the quality of evidence for our research questions.[30] This assessment of quality of evidence considers criteria subject to decrease confidence (risk of bias, imprecision, inconsistency, publication bias and heterogeneity across studies) or to increase confidence (strong association, dose–response gradient, opposing residual plausible confounding and bias). Strength of evidence will be judged as 'high' (further research is unlikely to change our conclusion), 'moderate' (further research is likely to alter our conclusion) or 'low' (further studies are required to answer the research question with a high degree of confidence/increase confidence).

Patient and public involvement

No patient or public are involved.

Ethics and dissemination

We intend to publish the results of our review in a peer-reviewed journal and to present our findings at national and international meetings and conferences.

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Supplementary table 1

Data extraction form

Study name:		
Item	**Variable**	**Data**
1	**Study design and characteristics**	
1.1	Study setting (*general or specific population, health status*)	
1.2	Study design (*i.e. retrospective cohort prospective cohort*)	
1.3	Year of publication	
2	**Population**	
2.1	Brief description of source and/or study population (*the source population is the wider population from which the study population, is drawn*)	
2.2	Sample size (*Number of smokers at baseline*)	
2.3	Age (*mean age at baseline*)	
2.4	Sex distribution	
2.5	Source/study population selection or sampling methods (*eligibility criteria/exclusions for studies based on e-health record and administrative databases*)	
2.6	Study country/world region	
3	**Exposure**	
3.1	Date of baseline CPD assessment	

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Supplemental material

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3.2	Date of second CPD assessment	
3.3	Mean age at second CPD assessment	
3.4	Time between baseline and second CPD assessment (years)	
3.5	Baseline CPD categories definition	
3.6	Second assessment CPD categories definition	
3.7	Main CPD reducer definition (if any)	
3.8	Other CPD reducer definitions	
3.9	Health status at the beginning of the follow-up period	
4	**Outcomes**	
4.1	Date of the end of the follow-up	
4.2	Mean age at the end of the follow-up	
4.3	Duration of the follow-up period (years)	
4.4	Specific mortality reported (i.e cardiovascular, cancer, respiratory, other…)	

5	**Statistical analyses**	
5.1	Statistical analysis method used and main effect measure reported (*e.g. prevalence (%), (incident) relative risk, hazard ratio, odds ratio*) If more than one type of analysis is conducted, report both analyses separately	
5.2	Magnitude of effect, with CIs. Include both crude and maximally adjusted effect measures for each comparison (i.e. reducers vs. maintainers, quitters vs. maintainers, quitters vs. reducers) and for each reducer definition	
5.3	Adjustment for confounding: list which covariates were included in the (fully) adjusted model.	
6	**Newcastle-Ottawa Scale (NOS) selection assessment**	
6.1	Representativeness of the exposed cohort	
6.2	Selection of the non exposed cohort	
6.3	Ascertainment of exposure	
6.4	Demonstration that outcome of interest was not present at start of study	
7	**Newcastle-Ottawa Scale (NOS) comparability assessment**	
7.1	Comparability of cohorts on the basis of the design or analysis	
8	**Newcastle-Ottawa Scale (NOS) outcome assessment**	
8.1	Assessment of outcome	
8.2	Was follow-up long enough for outcomes to occur	
8.3	Adequacy of follow up of cohorts	

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