Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes

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PECO formulation guidance

A clearly-framed question creates the structure and delineates the approach to defining research objectives, conducting systematic reviews and developing health guidance [1, 2]. To assess the association between exposures and outcomes, including in the field of nutrition, environmental and occupational health, the concept of defining the Population (including animal species), Exposure, Comparator, and Outcomes (PECO) as pillars of the question is increasingly accepted [3, 4]. Thus, the PECO defines the objectives of the review or guideline. Furthermore, the PECO informs the study design or inclusion and exclusion criteria for a review, as well as facilitating the interpretation of the directness of the findings based on how well the actual research findings represent the original question.

Previously, we have recognized the importance of PECOs for directing the assessments of benefits and harms, identification of exposures as risk factors or within risk assessments, and evaluation of the impact of interventions that prevent or mitigate an exposure or risk [3]; however, in debating PECO questions in our work, we found no guiding framework for operationalizing the PECO approach and the types of PECO questions researchers and decision-makers can answer. We identified only limited indirect guidance based on the development of Population, Intervention, Comparator, and Outcomes (PICO) questions where the general concept originated [1]. The Cochrane Collaboration emphasizes the importance of a well-formulated research question to guide an intervention review and provides clarity about the individual PICO components [5]; however, a review of 313 research studies reported that over half (54%) of the studies did not report on the four PICO components [6].

In environmental, public and occupational health research, specific challenges exist with identifying the exposure and comparator within the PECO. In fact, in these fields there are fundamental differences to formulating questions about interventions and comparators in the PICO framework [1]. The Cochrane Handbook, widely recognized as reference guide for systematic reviews, does not specifically address the development of questions for *reviews of exposures* [5]. Other organizations have reported adapting PICO to PECO for studies of unintentional exposure [7-9]. For example, the Collaboration for Environmental Evidence recognizes the transition from PICO to PECO for questions about the effect of an exposure [7]. The Navigation Guide, the National Toxicology Program's Office of Health Assessment and Translation, the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) and the European Food and Safety Association (EFSA) emphasize the role of the PECO question to guide the systematic review process for questions about exposures [8-10]. EFSA also proposes a back-calculation of PECO elements to define an exposure (if the effect on the outcome is known among a determined population) [10]. Typically review authors have used approaches to PECO questions that are reflective of two of the scenarios that we will present, specifically cases where the research question aims to evaluate whether an exposure is associated with a health outcome(s). However, the PECO can also be focused in ways that can make the systematic review perhaps better suited to inform decision-makers and these are illustrated in three scenarios we will present. These latter PECO approaches are seldom used; in part this may be due to the fact that a fully developed framework for operationalizing the development of PECO questions does not exist.

Given the lack of such guidance, research studies and systematic reviews often fail to explicitly state the PECO question. On the other hand, when reviews do start with a well-developed PECO

question, the purpose of the research is more clearly defined for the reader. For example, a recent systematic review broadly explored whether or not exposure to serum or plasma perfluorooctanoic acid (PFOA) among humans before or during pregnancy is associated with fetal growth [11]. The authors reported that a 1 ng/mL increase in serum or plasma perfluorooctanoic acid (PFOA) is associated with an 18.9 g decrease in birth weight. The review appropriately specified the population, exposure, comparator and outcome and it focused on exploring the presence or absence of an association. This approach is often chosen when little is known about the exposure and its potential relationship to an outcome. An alternative way to characterize with the impact of PFOA on health outcomes could better inform decision-makers. For instance, one might ask which exposure level would lead to a dangerous decline in birth weight or negative health outcomes in this population. If pursuing this strategy, evidence would be needed to define the outcome of interest; in this example, although challenging, the protocol would need to qualify the level of decline in birth weight that is considered harmful. Neither of the two former approaches is superior or inferior; they simply describe different research questions or phases in exploring the impact of exposures on outcomes. In fact, the general approach to phrasing PECO questions will depend on a number of factors, including a) the context; and b) what might be known about the effects of an exposure on an outcome at a given time. However, because of the dependence on the research and decision-making context, clarifying these aspects for the purpose of developing a PECO is crucial.

To address these issues, we developed a framework to formulate PECO questions that includes five paradigmatic scenarios. These scenarios are common for researchers conducting individual studies and authors of systematic reviews. Our framework proposes solutions with examples (related to the topic of hearing impairment) to facilitate the creation of PECO questions with a

strong focus on the ‘E’ and ‘C’ domains (Table 1). This is because we consider defining the population (including animal populations) and outcomes as more straightforward given their relation to the existing PICO literature. We attempted to support our framework by examples.

Furthermore, for practical reasons our primary focus is on environmental health and we drew on selected examples from these fields; however, these scenarios are relevant to other disciplines, including broader public health questions and nutrition. Since the exploration of the existence of an association between an exposure and a comparator is the building block for any further evaluation, we will describe that scenario first. We follow with scenarios in which this evaluation has been done or, for some scenarios, the decision-making context may be known. As stated above, none of the approaches is superior to another and they are influenced by the context of what is known as we will lay out in this brief article.

Insert Table 1.

Quantifying the exposure

Research to understand and quantify the exposure is needed to properly address scenarios 2 to 5 and formulate the PECO questions for them. In our first scenario, we describe what typically precedes those scenarios when little or nothing is known about the relationship between an exposure and outcome. Research addressing this scenario can provide information on the mean levels of exposure, ranges of exposures, and the nature of the association with the health outcome. In fact, for many organizations these are the most common questions asked. We will then present the remaining four scenarios with the assumption that research informing scenario 1 is available.

To implement the framework, researchers can utilize a number of sources to inform and facilitate the quantification of an exposure and, specifically, to define the criteria for the comparator. We refer to this in many examples as a cut-off value. We use the term cut-off to broadly to refer to thresholds, levels, durations, means, medians, or ranges of exposure. In this commentary, our examples are informed by previously published primary research or systematic reviews and government identified thresholds (e.g. Occupational Safety Health Administration [OSHA]); however, other sources may include current legislation or a level which is considered to produce a minimally-important change.

PECO Scenario 1

The first scenario facilitates the identification of a comparison when little or nothing is known about the association between exposure and the outcome, including the nature of the relationship. This PECO, as stated one of the most common situations in environmental health, aims to explore the impact of different levels of exposure on health outcomes and the nature of the relationship. The comparator includes the entire range of exposures (e.g. an incremental increase in exposure). Here, all comparators are predefined by what the observed data will show. The objective may be to define whether or not there is an association between the exposure and health outcome and, if there is an association, to identify the nature of the relationship, e.g., linear, logarithmic or u-shaped. For example, we present a summary of the results from two systematic reviews wherein this explorative PECO scenario leads to differing findings. In the first, a systematic review examined the association between 10 ng/mL increments of exposure to vitamin D and a range of health outcomes, including prostate cancer. The review reported no association between the 1,25(OH)2D biomarker to measure vitamin D with development of prostate cancer [12]. The second review examined the association between short-term exposure

to particulate mass with aerodynamic diameter less than 2.5μm ($PM_{2.5}$) and suggested a positive linear relationship with mortality from stroke [13].

In conjunction with Table 1, we provide additional examples to illustrate these scenarios using the topic of hearing impairment. To explore postnatal hearing impairment as a result of prenatal noise exposure, one may choose to examine an incremental increase in decibel (dB) exposure. Research suggests a linear dose-response relationship between the level of noise (i.e. dBs), duration of exposure, and health outcome of hearing impairment [14]; however, little is known about the effect of prenatal noise exposure on newborn hearing impairment [15]. Since there is insufficient information to isolate a specific comparison when examining prenatal noise exposure, we would develop a PECO that explores the association between incremental increase in exposure and hearing impairment. The size of the increments of the comparator may be informed by existing rationale or, if no evidence exists, they may require a more arbitrary identification. When developing a scenario about prenatal noise exposure, we present a hypothetical PECO question to reflect this situation, understanding that the 'E' and the 'C' could represent different values or smaller increments to measure change in the outcomes. For this example, we derived the incremental increase from the OSHA's Standardized Threshold Shift for occupational noise exposure of 10 dB [16].

P: Among newborns, what is the effect of

E: 10 dB exposure to noise during gestation versus

C: 10 dB incremental increase on

O: Postnatal hearing impairment

PECO Scenario 2

In the second scenario, we are interested in comparing health effects of different exposure levels but either do not know naturally occurring exposure levels or are unsure about which cut-offs to choose. This scenario is often a direct consequence of scenario 1 and may be addressed in the same systematic review as scenario 1 from which it would follow. Scientists often present data in ordinal groups (e.g. quartiles) in such situations. For example, we previously reported the effects of different levels of antioxidant blood and serum levels on pulmonary function and respiratory health [17-19]. The choice for the exposure and comparator in a systematic review may therefore be based on measures of distribution of the exposure in the included studies (e.g., central tendency values; highest versus lowest exposure groups such tertiles, quartiles, or quintiles). Ideally, the included studies describe the rationale for presentation of the exposure distribution to facilitate defining the cut-offs for the systematic review. This scenario requires exploration of the data to determine the specific exposure and comparator. It requires iterative development of the PECO based on findings from the systematic review or information from risk-management conclusions, which, nevertheless, should be pre-specified in a protocol. An additional example examines the effect of prenatal exposure to noise on postnatal hearing impairment.

P: Among newborns, what is the effect of

E: Highest noise exposure during pregnancy versus

C: Lowest noise exposure during pregnancy on

O: Postnatal hearing impairment

In addition, this second scenario could be informed by baseline risk data from a population-level study that allows specifying the exposure of the comparison. For example, by using the disaggregated population-weighted mean concentrations of $PM_{2.5}$ [20].

PECO Scenario 3

Our third scenario addresses formulating a PECO question in which we might have information about a certain exposure level for a population of interest but want to compare that to the impact of a different level of exposure on a certain health outcome. In this situation the mean cut-offs from an external or general population (from other research) may serve as the comparator. For example, we may be interested in comparing the impact of exposure to $PM_{2.5}$ from one country to either a different country or a global mean. To do this we could use the data reporting $PM_{2.5}$ levels on the outcome of airflow obstruction from a nationally-representative survey in China as our exposure and outcome of interest. The comparator could then be informed by either the mean concentration of $PM_{2.5}$ levels in a different country or the global population-weighted mean concentration of $PM_{2.5}$ levels [20]. The systematic review would address the following PECO: "In people exposed to particulate matter, what is the impact of levels of exposure identified in China compared to other countries or the global mean on airflow obstruction?" Of course, the ensuing analyses would have to carefully account for potential covariates or confounders.

A second example focuses on the impact of noise exposure among commercial pilots on hearing impairment exposure-level estimates from a cohort study conducted in Sweden [21]. To compare the risk of hearing impairment among commercial pilots with other occupations or the general population, we could conduct a systematic review of the effects on hearing impairment using a references of exposure levels from other occupations.

P: Among commercial pilots, what is the effect of

E: Noise corresponding to their occupational exposure versus

C: Noise exposure experienced by people in low-exposure occupations on

O: Hearing impairment.

PECO Scenario 4

In the fourth scenario, we may have sufficient information about the exposure and outcome to quantify a dose-response relation. Specifying the exposure and comparator will include using existing exposure cut-offs (e.g., thresholds, levels, durations, means, medians, or ranges of exposure) associated with the health outcomes of interest. For example, we may want to explore long-term exposure to occupational noise levels greater than 80 dB, which increase the risk of hearing impairment compared to lower levels [22].

P: Among industrial workers, what is the effect of

E: Occupational noise exposure < 80 dB versus

C: Occupational noise exposure ≥ 80 dB on

O: Hearing impairment.

The difference between this and the next scenario lies in the exploration (i.e. comparison) of what an intervention can achieve and outcomes that are associated with defined exposure levels. In other words, the PECO elements may be driven by the difference between a context which is concerned with setting a limit (such as a permissible occupational exposure level) versus a

context concerned with estimating the potential efficacy of an intervention to modify an exposure and the outcome which is the topic of our fifth and last scenario.

PECO Scenario 5

The fifth scenario typically occurs when there is evidence suggesting an association between an exposure and the outcome, such as the research suggesting a dose-response relationship between the level of noise and health outcome of hearing impairment referenced previously [14] (based on a PECO following scenario 1, table 1). If a decision-maker is interested in a specific exposure cut-off or intervention to mitigate the exposure through known interventions, they will ask systematic reviewers to conduct a review using the PECO framework that appropriately describes the health effects of exposures that are achievable or realistic in relation to a comparator.

A policy maker may want to know, in the absence of evidence evaluating the impact of an intervention or in the context of new interventions for which high certainty evidence is available, what the potential impact of that intervention is on health effects. As direct evidence evaluating the intervention is not available, the exposure cut-offs in the PECO question would be informed by the implementation of an intervention (e.g. the potential introduction of a novel street surface that can reduce noise levels by 20 dB) compared to not implementing the intervention. Note that this will still only provide indirect evidence for the effects of the intervention but can be helpful for modelling the impact if intervention studies are not available. The discrete PECO formulation of this example would be as follows:

P: Among the general population, what is the effect of

E: Noise levels that are 20 dB lower than

C: Current noise levels on

O: Hearing impairment.

Summary and conclusions

Formulating informative questions is a prerequisite for conducting an evidence synthesis in systematic reviews. The PECO approach to question formulation supports the conduct of a systematic review, including formulating search and eligibility criteria, presenting outcomes, and the wording in guidelines of final recommendations. We found little guidance about how to formulate questions that deal with unintentional exposures and, therefore, developed a framework based on existing examples and in-depth discussion that will help those designing research studies and authors of systematic reviews dealing with all populations and outcomes.

Our framework supports understanding the nuances and differences that exist between the review (research) question, the subsequent and sometimes iterative definition of inclusion and exclusion criteria from the PECO (they may or may not cover the PECO very narrowly or broadly) and the interpretation of the directness of the identified evidence. The framework can also provide guidance for those conducting individual studies dealing with exposures. We recognize that additional considerations would be required to develop a PECO framework aimed at animal studies or systematic reviews that include consideration of epidemiological and animal studies to discern whether a chemical has an effect on a health outcome. We encourage further testing and feedback on the use of this framework and include Figure 1, as a brief guide to facilitate the identification and development of an optimal PECO question.

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Author contributions

RLM and HJS conceptualized the approach and PW and KAT contributed to it. RLM and HJS wrote the manuscript. PW and KAT critically revised the manuscript for important intellectual content. All authors approved of the final version.

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Table 1. Five paradigmatic approaches and examples for identifying the exposure and comparator in systematic review and decision-making questions

Potential systematic-review or research context	**Approach**	**PECO example**
1. Calculate the health effect from an exposure; describing the dose-effect relationship between an exposure and an outcome for risk characterisation.	Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review.	Among newborns, what is the incremental effect of 10 dB increase during gestation on postnatal hearing impairment?
2. Evaluate the effect of an exposure cut-off on health outcomes, when the cut-off can be informed iteratively by the results of the systematic review.	Use cut-offs defined based on distribution in the studies identified in the systematic review.	Among newborns, what is the effect of the highest dB exposure compared to the lowest dB exposure (e.g. identified tertiles, quartiles, or quintiles) during pregnancy on postnatal hearing impairment?
3. Evaluate the association between an exposure cut-off and a comparison cut-off, when the cut-offs can be identified or are known from other populations.	Use mean cut-offs from external or other populations (may come from other research).	Among commercial pilots, what is the effect of noise corresponding to occupational exposure compared to noise exposure experienced in other occupations on hearing impairment?
4. Identify an exposure cut-off that ameliorates the effects on health outcomes.	Use existing exposure cut-offs associated with known health outcomes of interest.	Among industrial workers, what is the effect of exposure to < 80 dB compared to ≥ 80 dB on hearing impairment?
5. Evaluate the potential effect of a cut-off* that can be achieved through an intervention to ameliorate the effects of exposure on health outcomes.	Select the comparator based on what exposure cut-offs can be achieved through an intervention.	Among the general population, what is the effect of an intervention that reduces noise levels by 20 dB compared to no intervention on hearing impairment?

* Cut-offs is a broad term referring to thresholds, levels, durations, ranges, means, medians, or ranges of exposure. dB: decibel; PECO: population, exposure, comparator, outcome(s).