CME

Biases Including Confounding and Effect Size Modification in Clinical Studies and Their Mitigations

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An association analysis is an integral part of almost every clinical study. To determine the existing relationship of an exposure (e.g., smoking; treatment) with its expected respective outcome (e.g., coronary heart disease (CHD); improvement) accurately, one has to ensure the quality of data. Regardless of the types of association measures depending on various study designs (to be discussed separately), the association/relationship of exposure with an outcome may often get distorted due to the presence of various biases, including confounding and effect size modifications in the collected data. In spite of following each of the major research methodology steps required under a clinical study, to ensure the quality of data, one needs to minimize/nullify each of the numerous probable biases, including confounding and effect size modifications in the data. Hence, the focus of the present write-up is to briefly describe these biases so that researchers can be aware and take care of them in their clinical study.

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Introduction

Under epidemiological studies using various study designs (to be discussed separately), as an attempt to measure the relationship of exposure (e.g., smoking) with an outcome (e.g., CHD) accurately, one has to ask oneself whether the measured association level is due to prevailing biases in the data. Further, if the answer is no, could the measured association level may be due to confounding and/or effect-modifying variables? Again, if the answer to confounding/effect modification is no, ruling out the role of chance in measured association level has meaning. Ultimately, suppose a data set is complete in all aspects, including the availability of data on all possible confounders/effect modifiers. In that case, the answer to all of them relies on an appropriate regression analysis. To be more specific, analytical results under a regression model get influenced due to various components like the quality of data (i.e., free from biases),[1-4] a number of additional independent variables along with considered exposure variable,[4,5] scale of measurement of each independent variable, presence of colinearity among independent variables,[5] missing potential confounding and/or effect modifying variables,[4] and non-consideration of effect modifying variables as effect modifiers.[1-5] Although a host of literature is available on the topic, the present write up is aimed to briefly describe each of the above components to keep the researchers/readers aware so that they can take care of them while planning/doing any clinical research.

Bias

Bias in research is literally known as a systematic error that may result in deviation from the truth. In other words, there may be involvement of a process at any stage of the study that is likely to produce results that differ systematically from the truth.[1] To clarify further, any inappropriate step in the data collection, its analysis & interpretation, and publication or related systematic review altering summary and implications that are deviated systematically from the truth.[2] There may be various types of biases, which are briefly described below:

Selection bias

An inappropriate method used in the selection of a sample[4,6] from the study population may distort its

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representativeness of the study population. In other words, due to an inappropriate selection method, the potential characteristics of the selected sample may be different than those of the study population, which may obviously alter the study results from the truth. It is known as selection bias. It may be of various types:

Prevalence-incidence or Neyman bias

This bias may often occur when prevalent cases are being used to study the relationship between exposure (e.g., smoking) and disease (e.g., coronary heart disease). As such, a person diagnosed with a disease may change the habit that might have contributed to the disease. To be more specific, a smoking person diagnosed with coronary heart disease (CHD) might become a non-smoker. Likewise, out of frustration, a non-smoking person diagnosed with CHD might become a smoker. In other words, due to this behavior change[3], the relationship of exposure with disease might get inaccurately diminished/magnified from the truth.

Sometimes, this bias may also arise due to a relatively longer gap between exposure and selection of study participants. For example, due to a longer gap in planning/conducting the study, considerably a large number of deaths might get missed under natural disasters and disasters like the Bhopal Gas Disaster. It may make the relationship between exposure (e.g., toxic gas) and outcome (e.g., death) totally spurious. Also, such bias may crop up in studies on short-term/fatal diseases. For instance, in a hospital-based case-control study of acute myocardial infarction (AMI) and smoking, a large number of AMI cases may not arrive at a hospital due to their sudden death, among which the majority may be smokers. As a result, available cases at hospitals may have a lower frequency of smoking, away from the truth. As obvious, such distortion in data may provide an underestimated level of the association between smoking and AMI. It may also distort the association of other factors with AMI.

To overcome the above biases, we need to adopt due strategies while collecting data. For example, those regarding the above-described behavioral changes may be minimized through a detailed history of smoking, like have you ever been a smoker, how long and per day average smoking. As obvious, cross sectional data collection (e.g., current smoking: Yes or no) on such aspects will undoubtedly add biases in data. Likewise, to know the exact number of deaths due to a disaster, one may need to ask about all family members before a disaster. Further, studies on short-term diseases and/or short-term fatal diseases need to be preferred as community-based studies.

Admission rate or Berkson's Bias

In a hospital-based case-control study, the characteristics of cases and/or controls may be altered by the admission rate of related patients in that hospital. Such bias may occur mainly because of the prevailing burden of considered disease and patients' ability/choice to have access to that hospital. Further, patients being considered as controls from a hospital may also suffer from a particular disease. As such, they differ from healthy controls in the community. To be more specific, hospitalized patients are more likely to be involved in smoking and/or alcohol drinking than non-hospitalized/healthy controls. Hence, a case-control study using hospital-based controls examining smoking/alcohol drinking as risk factors may provide distorted results. For instance, to examine the association between smoking and coronary heart disease (CHD), consideration of cancer patients as controls may balance smoking between CHD cases and controls. In other words, smoking may not turn up to be a risk factor for CHD. Sometimes, as an unacceptable result, smoking may erroneously emerge to be a protective factor for CHD. Likewise, consideration of patients suffering from other diseases like respiratory disease as controls for which smoking is a risk factor may not be an appropriate choice.[4,7]

Unmasking/Detection bias

This bias is mainly due to differences in approach (e.g., different vigor, methods or criteria) of determining outcomes between the groups, for example, between toxic gas exposed and non-exposed population groups in Bhopal. To be more specific, one may tend to verify outcomes among the exposed group differently than those among the non-exposed group. This bias is also referred as an observer bias, ascertainment bias, or assessment bias.

Friend/Relative Control Bias

In a case-control study, if closely related individuals (e.g., family members, friends, relatives, neighbors) are considered as controls, they are likely to have similar habits or exposures (e.g., smoking & dietary habits). Therefore, extent of the association between smoking/dietary habits and considered disease/outcome may get underestimated.[4]

Response Bias

In a case-control study, a varying response rate among cases and controls is often related to exposure (e.g.,

smoking) and/or disease (e.g., CHD). Further, the replacement of controls that were originally decided but could not be contacted or refused to participate may also be related to exposure and/or disease. For example, investigating the efficacy of screening by breast examination in reducing mortality from breast cancer, cases and controls may be identified from the household survey. Often, designated women in the control group may not be at home at the time of the interview while collecting data on various aspects, including exposure (screening). Hence, the originally designated women may be replaced by the neighboring household's women. It may be that women who were not at home tend to be employed and employed women may be more likely to have had screening than those unemployed. Intuitively, having unemployed women (controls) would underestimate the effect of screening on breast cancer.[4,7]

Information Bias or Misclassification Bias

An inaccuracy in data collection on exposure (e.g., smoking) and/or outcome (e.g., CHD) is referred to as information bias or misclassification bias. In other words, due to an inaccurate measurement of exposure and/or outcome, the relationship between exposure and outcome may get distorted even if other potential variables are measured accurately. Like in the case of selection bias, it may also alter the study results from the truth. Further, it may also be of various types:

Recall bias

The persons suffering from a particular disease (i.e., cases) remain more likely to recall what might have caused (i.e., exposure) their disease. On the other hand, persons free from that disease (i.e., controls) may not have such motivation about considered exposure. Further, in comparison to controls, cases may be questioned about considered exposure more comprehensively. For instance, to cross-check many case-control studies reporting abortion as an increasing risk factor for breast cancer, a comparison of histories of prior abortions obtained by one to one interview against available medical records may reveal systematic underreporting of abortions among controls (but not among cases) that might contribute to false results. This bias is a major issue to be dealt with in clinical studies.[8,9]

Family Information Bias

Under clinical studies, information on family history about considered disease and exposure is often required. A family member who develops a disease may have better information about exposure and disease among parents and/or other family members. In other words, a diseased person in a family is more likely than his or her non-diseased family members to know that a parent/other family members have a history of that disease. As an example, a person who is diabetic may be more likely than his or her non-diabetic family members to know that a parent/family member has a history of diabetes. Hence involving such respondents in data collection may help in avoiding family information bias.[4]

Diagnostic Suspicion Bias

Due to a known probable cause (i.e., exposure) of a disease, there may be a more extensive search for the disease among those exposed. For instance, there might be an extensive search for HIV infection among intravenous drug users than that among their counterparts. Likewise, there might be extensive search for bladder cancer among rubber workers than among their counterparts. One needs to have similar approach to identify cases among exposed (e.g., intravenous drug users; rubber workers) and unexposed people.[9]

Exposure Suspicion Bias

Conversely, due to a known probable suffering (i.e., disease) because of an exposure, there may be a more extensive search for the exposure among the diseased. As an example, while using case records, only 10 of 36 medical records of thyroid cancer patients might originally contain positive statements regarding exposure to radiation. However, by asking direct questions, out of a total of 36 children with carcinoma of thyroid cancer, 17 (47%) might give a history of previous exposure to radiation. One needs to have similar approach to collect data on exposure among diseased (e.g., thyroid cancer patients) and non-diseased people.[8]

Measurement Bias

The quantitative biological markers like blood pressure and blood sugar may get often misread. Further, change in their scale of measurements (e.g., from quantitative to categorical forms) may also be carried out without retaining their original associations with considered clinical outcomes (e.g., CHD). Sometimes used tools for data collection like food frequency questionnaire do not provide data on diet accurately to detect important association between diet and disease like cancer. Because of presence of such bias in collected data, derived results from the collected data remain spurious and lead to distorted implications.[4,5]

Inaccuracy

There may also be various reasons to fuel inaccuracies in the collected data, for example, misunderstanding of questions by a respondent being interviewed and/or inability or unwillingness to give the correct response for sensitive questions.[1]

Confounding Bias and Effect Size Modifying Bias

Confounding bias

Confounding bias[1] is literally known as the distortion in the extent of relationship between exposure (e.g., smoking) and disease (e.g., CHD) due to failure to take into account the role of some potential risk factors (e.g., drinking; no physical activity) other than the exposure of interest (i.e., smoking). In other words, another factor (e.g., physical exercise) is known as a confounder if it is found to be associated with both, the exposure (e.g., smoking) and the outcome (e.g., CHD), and is not causally in between as a mediator. To be more specific, a variable (e.g., Physical exercise) is known as a confounder if the strength of relationship between the exposure (e.g., smoking) and the outcome (e.g., CHD), differs overall, versus within values for that variable (i.e., Physical exercise). This may be depicted as shown in Fig. 1.

Mediation

A variable (e.g., high HDL) is known as a mediator[1] if it is causally in the pathway by which the exposure (e.g., smoking) leads the outcome (e.g., CHD). This may be depicted in Fig. 2.

Effect size modification

A variable (e.g., physical activity) is known an effect size modifier[1] if the strength of relationship between the exposure (e.g., smoking) and the outcome (e.g., CHD) differs within varying levels of that variable (i.e., physically active, and non active). It is similar to statistical interaction, but in public health, effect modification is also related to the biology of disease, not just a data observation. This may be depicted in Fig. 3.

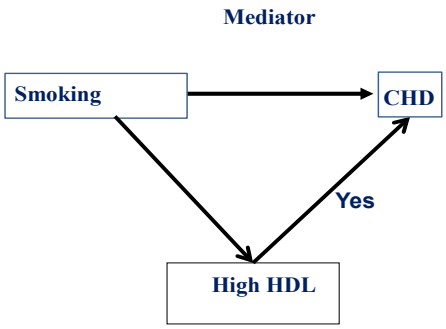

Fig. 2: Mediator

Both: confounder and effect modifier

A variable (e.g., physical activity) may be both, confounder and effect size modifier, for the relationship between exposures (e.g., smoking) and outcome (e.g., CHD) if it fulfils earlier described required conditions for both, to be a confounder and effect size modifier. This may be depicted in Fig. 4.

Neither: confounder nor effect modifier

A variable (e.g., physical activity) may neither be confounder nor effect size modifier for the relationship between exposures (e.g., smoking) and outcome (e.g., CHD), if it does not fulfil earlier describe required conditions for both, to be a confounder and effect size modifier. This may be depicted in Fig. 5.

To summarize, a variable in a data set collected under any of the study designs (to be communicated separately) may be assessed to be possible confounder and/or effect modifier for the relationship between exposure

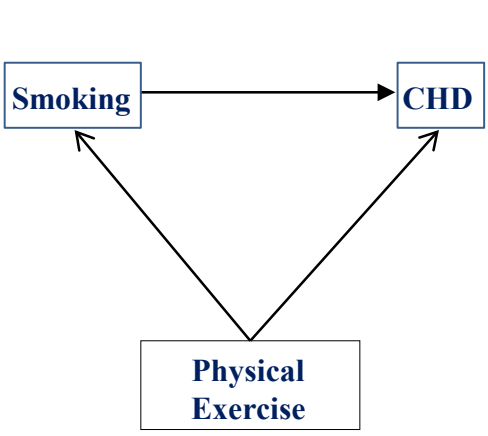

Fig. 1: Confounder

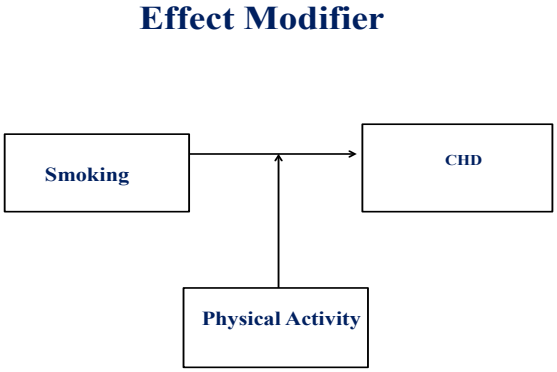

Fig. 3: Effect modifier

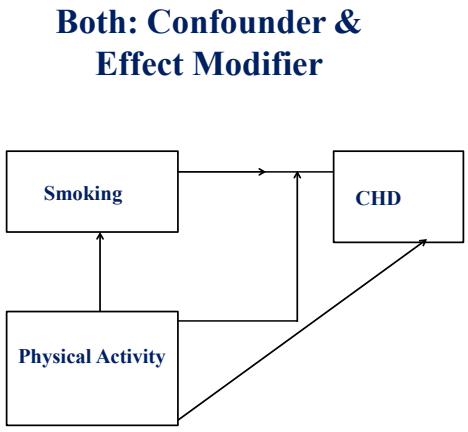

Fig. 4: Both- confounder & effect modifier

and outcome. To be more specific, they may be easily understood by analytical results of hypothetical data sets involving measures of association [e.g., odds ratio (OR)] under case control studies. For related specific clues, crude OR; adjusted OR; and strata specific ORs through stratified analysis (to be communicated separately) may be used.[4] To be more specific, a variable (e.g., physical activity) may be only confounder for the relationship between exposure (e.g., smoking) and outcome (e.g., CHD), if crude and adjusted ORs vary with a margin of at least 10% where as strata specific ORs remain similar. On the other hand, a variable (e.g., physical activity) may be only effect modifier for the relationship between exposure (e.g., smoking) and outcome (e.g., CHD), if crude and adjusted ORs remain similar where as strata specific ORs vary with a margin of at least 10%. Further, a variable (e.g., physical activity) may be both, confounder as well as effect modifier, for the relationship between exposure (e.g., smoking) and outcome (e.g., CHD), if crude and adjusted ORs vary along with variation in strata specific

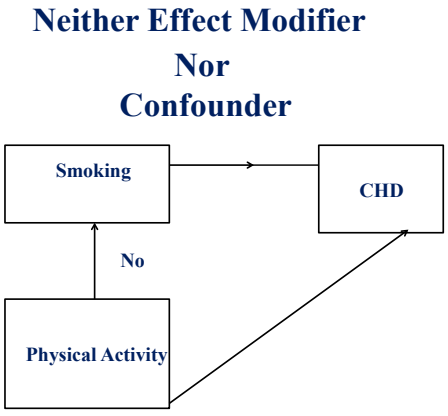

Fig. 5: Neither confounder nor effect modifier

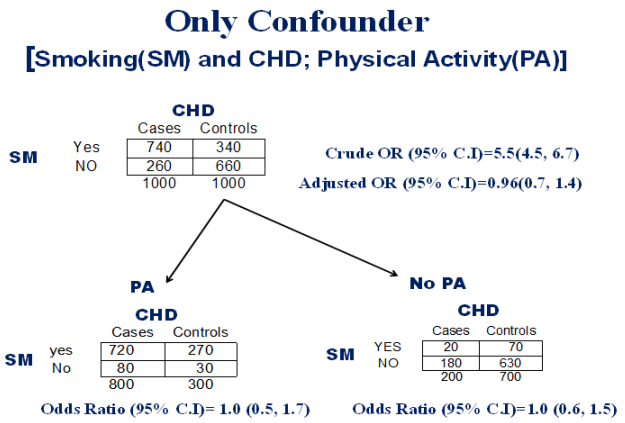

Fig. 6: Only confounder

ORs, with a margin of at least 10%. Likewise, a variable (e.g., physical activity) may neither be confounder nor effect modifier, for the relationship between exposure (e.g., smoking) and outcome (e.g., CHD), if crude and adjusted ORs do not vary along with no variation in strata specific ORs. They are further explained with specific examples using hypothetical data sets as follows:

Example 1: *Only confounder*

The hypothetical data and related analytical results depicted below clearly show that ORs (without and with adjustment in relation to physical activity) describing relationship between smoking and CHD vary with a margin of at least 10%. However, strata specific (i.e., physically active group (PA) and physically non-active group (No PA)) ORs remain to be similar. Therefore, physical activity is a confounder for the relationship between smoking and CHD, but not an effect size modifier (Fig. 6).

Example 2: *Only effect modifier*

The hypothetical data and related analytical results depicted below clearly show that ORs (without and with adjustment in relation to physical activity) describing relationship between smoking and CHD do not vary with a margin of at least 10%. But, strata specific (i.e., physically active group and physically non-active group) ORs vary with a margin of at least 10%. Therefore, physical activity is not a confounder for the relationship between smoking and CHD, but remains to be an effect size modifier (Fig. 7).

Example 3: *Both-confounder and effect modifier*

The hypothetical data and related analytical results depicted below clearly show that ORs (without and with adjustment in relation to physical activity) describing relationship between smoking and CHD vary with a margin of at least 10%. Also, strata specific (i.e., physically

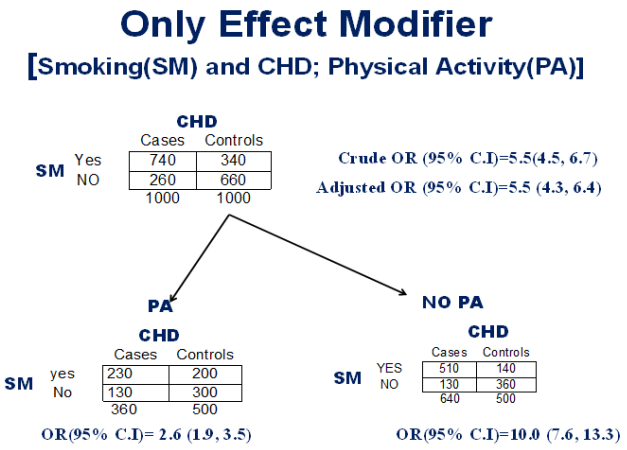

Fig. 7: Only effect modifier

active group and physically non-active group) ORs vary with a margin of at least 10%. Therefore, physical activity is both, a confounder as well as an effect modifier, for the relationship between smoking and CHD (Fig. 8).

Example 4: *Neither confounder nor effect modifier*

The hypothetical data and related analytical results depicted below clearly show that ORs (without and with adjustment in relation to physical activity) describing relationship between smoking and CHD do not vary with a margin of at least 10%. Also, strata specific (i.e., physically active group and physically non-active group) ORs do not vary with a margin of at least 10%. Therefore, physical activity is neither a confounder nor an effect modifier for the relationship between smoking and CHD (Fig. 9).

Exploration of confounders and effect size modifiers

The analytical results under above described four examples are listed in the Table 1 along with their respective decision making which may help in exploring potential confounders and effect size modifiers:

To take the decision regarding confounder and / or effect modifier specific steps may be listed here. Under a data set using any of the study designs, to identify variables (e.g., physical activity) as potential confounders and effect size modifiers regarding a relationship between an exposure (e.g., smoking) and outcome (e.g., CHD), to begin with, appropriate crude association measure needs to be worked out. Then, stratify the data as physically active and non-active groups, and calculate stratum specific association measures. If stratum specific association measures are different, physical activity will be an effect modifier for the relationship between smoking and CHD. In this case, stratum specific association measure needs to be used.

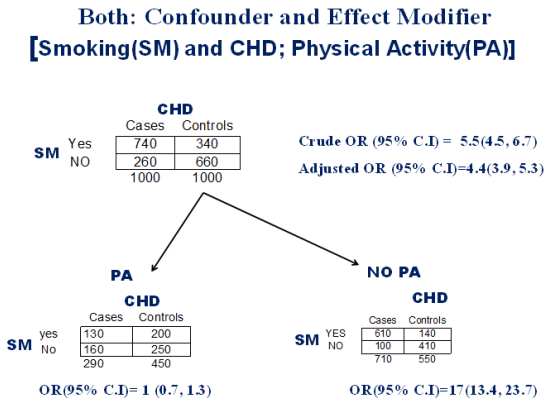

Fig. 8: Both- confounder & effect modifier

With effect modification, the crude estimate is expected to be between the stratum-specific estimates. Further, if stratum specific association measures emerge to be similar, physical activity will not be an effect modifier. In this case, adjusted association measure needs to be calculated. If crude and adjusted association measures emerge to be similar, physical activity will not be a confounder for the relationship between smoking and CHD. One has to use crude association measure. But, if crude and adjusted association measures emerge to be different, physical activity will be a confounder for the relationship between smoking and CHD. As such, in this case, adjusted association measure needs to be used.

To explore potential confounders in a study, information on all the expected confounders needs to be collected. Further, study needs to be powered in terms of minimum sample size,[4,10] so that the potential confounders may be explored. There should not be matching on potentially important confounders. Otherwise, the matched variable may not be examined regarding its effect. Taking into account the identified confounders in the data set, the statistical methods (e.g., Extended Mantel-Haenszel method, multiple regressions)

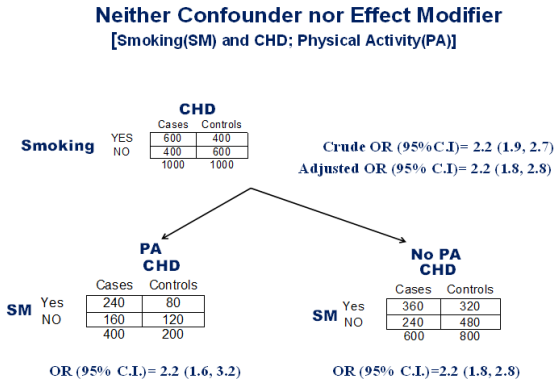

Fig. 9: Neither confounder nor effect modifier

Table 1: Decision taking

Exposure	Odds Ratio for CHD				Interpretation
	Crude	Adjusted	No PA	P A	
Smoking	2.2	2.2	2.2	2.2	Neither confounder Nor Effect Modifier
	5.5	.96	1	1	Only Confounder
	5.5	5.5	10	2.6	Only Effect Modifier
	5.5	4.5	17	1	Both: Confounder & Effect Modifier

may be used to calculate the "adjusted" estimate of association measure between exposure and outcome.

Like in case of confounders, to explore potential effect modifiers in a study, information on all the expected effect modifiers also needs to be collected. Further, study needs to be powered in terms of minimum sample size[4,10] so that the potential effect modifiers may be explored. There should not be matching on potentially important effect modifiers. Otherwise, the matched variable may not be examined regarding its effect modification impact. The effect size modifiers need to be identified to find out high-risk subgroups for preventive measures; to achieve higher precision in estimated association measure; to strengthen the ability to compare various studies that have different proportions of effect-modifying sub-groups, and to help in developing a causal hypothesis for the disease. If effect modification is identified, stratum- specific estimates of association measure needs to be used. Further, separate stratified models may be considered; otherwise an interaction term may be incorporated in an epidemiological modelling. For example, in case of assessing a relationship between an exposure (e.g., smoking) and outcome (e.g., CHD), if physical activity emerges as an effect modifier, multiplication of smoking (e.g., yes, no) and physical activity (e.g., yes, no) has to be incorporated as non smoker and physically active; non smoker and physically inactive; smoker and physically active; and smoker and physically inactive categories. This inclusion will result into three dummy variables in the model considering category at least risk (i.e., non smoker and physically active category) as a reference category.

Summary

A study needs to be designed in such a way that all possible biases are minimized/avoided. The biases described above may often be controlled/avoided at planning stage of the study through following every step of research methodology.[11] Further, there is need to collect data on all the potential confounders/effect modifiers, missing to collect data in relation to even a single such variable may make the study findings questionable. Once quality data is available, one needs to identify possible confounders. In addition, co linearity present among all the potential confounders needs to be explored. Out of two highly correlated variables, only one of them needs to be included in a subset of variables to be finalized for development of an epidemiological model. Also, at least selected first order potential effect modifiers need to be explored and included in the modeling (to be communicated separately). Just for an ease of interpretation, such consideration is often ignored by the researchers.

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