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STUDIES OF ENVIRONMENT AND HEALTH: SOME CHALLENGES FOR STATISTICIANS

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1. Introduction

This paper is concerned with statistical issues arising in connexion with studies of health and the environment. The examples and comments, however, have a wider relevance. In contrast to research work in statistical methods, scientific application of statistics has to deal with all of the following items:

1. Scientific hypothesis or research question:
   - formulation of the substantive hypothesis
   - notions about the underlying mechanism generating the data
   - data relevant to the hypothesis, etc.
2. Study design
3. Data collection and data quality assurance: correctness, missing values, etc.
4. Scientific value of the data:
   - relevance to the scientific question at hand
   - reproducibility, accuracy, precision, etc.
5. Choice of adequate statistical models:
   - in view of the hypothesis / research question (item 1)
   - incorporating the knowledge from items 1 to 4 as well as from previous studies

6. Estimators, tests and their statistical properties, as derived from the statistical models
7. Data analysis using the chosen statistical models
8. Scientific conclusions

Most statistical publications are concerned only with items 2, 6 and 7. In applied statistical work, however, one is forced to deal with all of these items. According to an informal estimate, most time in applied statistical work is spent on items 3, 4 and 7. This paper will comment chiefly on items 1, 4, 5, 7 and 8. It is organised around a few examples, each of which was chosen to make one or more general points. These pertain to scientific applications of statistics in general, but especially to statistical work in studies of health and the environment.

2. Dealing with inter-subject variability

2.1. Some general remarks about studies of health and the environment

Studies of environmental effects on health deal with a particular set of causal or contributing variables: environmental conditions, be they natural or man-made. Of interest is the exposure of individuals to such environmental conditions and the resulting health effects. The reliable assessment of such exposures is difficult due to two facts:

- Environmental conditions are variable: there is spatial variability, mainly on a large scale, and there are sudden and slow temporal variations as well.
- Individuals are mobile: They move around in changing environments, picking up exposures at varying rates on their way. In addition individuals have varying susceptibilities.

Epidemiologists mostly consider the health effect of environmental conditions to be proportional to lifetime exposure. What is then the best way of assessing environmental effects in view of varying and difficult to measure exposures and susceptibilities?

2.2. Stratified analysis

A successful approach relies on stratified analysis, using each person as a stratum i.e. as its own control. This is possible, provided there is more than one health observation per person and exposure status. The following example about a chemical accident at Schweizerhalle in 1986 illustrates this approach.

Example 1. In fall of 1986, a fire destroyed a storage facility for chemicals near Basle, Switzerland, leading to wide spread air and water pollution. With regard to air pollution, there was the urgent question of how it affected the respiratory health of children. By coincidence, data for a study designed to investigate the relationship of respiratory illness in children and climatic conditions was being collected in the area during the same time. This study was based on a random sample of pre-school children. For each child, the daily presence or absence of a number of respiratory symptoms (cough, running or stuffy nose, sore throat, ear ache, fever) was recorded by the parents in a diary for 6 weeks [1]. For some children the study period covered time before and after the fire. A simple assessment of the effect of the accident on the respiratory health of pre-school children could then be obtained with a stratified analysis as proposed by Mantel and Haenszel , considering each child a stratum, and with exposure replaced by period (before and after the fire).

This analysis has the following advantages:

- It takes into account varying exposure and varying susceptibility simultaneously.
- As there is no need to assess individual exposures and susceptibilities explicitly, nor to model their effect on the health response, the method in a sense is robust, providing an assessment of the association between exposure and health effect which is interpretable.
- It is simple and easily explained. This is an important asset for the fruitful collaboration with scientists.

In its simplest form, its drawbacks include the loss of the data for children without symptoms in any one period. This can be avoided using more sophisticated statistical methodology. The method can be extended to incorporate covariables eg. by using stratified parallel conditional logistic regression [4].

More sophisticated methods, such as time series analyses can also be applied to this situation. Such methods will allow the quantification of the delay between accident and effect [5]. As a rule, these sophisticated methods need to be applied to health data aggregated over children (i.e. ignoring variations in individual exposure and susceptibility), a fact which may reduce their advantage and appeal.

2.3. Results, limitations, conclusion

Both stratified analysis and time series analysis showed a pronounced, statistically significant increase of the incidence of respiratory symptoms in children after the fire [2].

With regard to the list in the introduction, this example touched on item 1 (scientific question - hypothesis) as we have found that only rather limited questions about the global effect of the accident can be answered with any confidence. It touches on item 2, as a study plan involving observations on each child before and after the accident is needed.

Apart from having to rely on data distributed finely in space and time, it is not evident which statistical methods would need to be used or developed to assess the impact of changes in single components of environmental exposures, such as smoke, NO_x, etc. This could be an area of further research into statistical methodology which would need to take into account knowledge from medicine, atmospheric physics, chemistry and combustion.

3. Problems of health perception

3.1. Questionnaire studies: reliability of information

In order to assess environmental effects on health, one must measure health, a difficult task in itself. In large scale epidemiological studies, assessment of health is often done via questionnaires. This complicates matters further, as such subjective assessment can be influenced by the person observing and reporting the data. The following example illustrates this [6]. In this study, adolescents and their parents were separately asked the same questions about the adolescents' respiratory symptoms.

Table 1. Questionnaire based study of respiratory health of adolescents. Agreement between parental and adolescents' answers to the same questionnaire on respiratory health of adolescents.

Who is reporting which symptom (in %)?

P = Parents A = Adolescents

Symptoms	P&A	P only	A only	A	P
Wheeze	4.6	2.2	6.1	10.7	6.8
Asthma ever	9.2	2.6	4.4	13.6	11.8
Nocturnal dry cough	5.1	6.0	14.8	19.9	11.1

Table 1 shows that agreement between parents and adolescents regarding the adolescents' respiratory symptoms is not complete. It is indeed most amazing that in a certain percentage of cases, only parents report symptoms and not the adolescents themselves. Their own threshold of recognition of such symptoms may be higher than their parents'. It is therefore not entirely clear who is providing the more accurate results. This is certainly a problem which cannot be resolved by statistical methods alone. However, statisticians need to be aware of it. Statistical methods can also help to exhibit it, alleviate it and maybe find explanations for this phenomenon.

3.2. Factors affecting the reliability of response to health questions
Even more shocking is the recognition that the agreement between parents' and adolescents' responses depends on other factors, as is shown in Table 2. The statistical measure used here is Cohen's k which measures how far the agreements exceed the agreement to be expected by chance alone ($k = 0$). Perfect agreement would result in $k = 1$ [7, 8].

Table 2. Agreement between parent's and adolescent's responses to the question asthma ever.

Classification of respondents by:		Agreement k
Parental education:	low	0.44
	medium	0.71
	high	0.70
Family history of asthma:	yes	0.73
	no	0.63
Parents smoking:	yes	0.62
	no	0.74
Adolescents smoking:	yes	0.55
	no	0.70

This is a problem which is difficult to resolve, but one must be aware of potential distortions in the relationship between environmental conditions and respiratory health due to variation in the composition of different groups of responders. Partial remedies would be to stratify or correct for responders' smoking and educational status etc. when analysing respiratory health responses. In this manner, one could assess the effect of these variables on the outcome. However, such distortions will always produce increases in the variance of effect estimates.

3.3. Conclusions

What can be learned from these two examples? Firstly, we must be aware of the quality and properties of the variables in a statistical analysis before we can begin with statistical inference. This is certainly not a problem of statistical inference proper, but it is an important problem of scientific inference.

With regard to the list in the introduction, the above example shows the importance of assessing data quality (item 4) before delving into the building of elaborate statistical models. It also touches on items 7 and 8, because only certain analyses are possible and make sense with these data and because only scientific conclusions which are in accordance with the quality and reliability of the data are warranted. This also illustrates that in studies of environment and health relying on health surveys, efforts need to be divided appropriately between finding and constructing adequate statistical models and assuring the suitability of the data being used with these statistical models.

Finally, Table 2 illustrates the need and opportunity of developing further the statistical tools for analyzing survey based health responses, taking into account possible variations in the reliability of health responses according to some identifiable respondent characteristic.

4. Determination of exposure

4.1. A description of the problem

Environmental variables are usually expensive to collect and hence available only for a small number of points in space, often over extended periods of time, however. On the other hand, it is commonly assumed that individual health responses depend on the exposure accumulated by an individual as he or she moves through time and space. The common technique of replacing unknown personal exposures by measurements obtained from fixed stations has several undesirable effects:

- The effective sample size of a study is determined by the number of independent environmental monitoring stations. Each population segment monitored by one station in essence contributes only one time series of health observations.
- There is, for most individuals, substantial exposure misclassification with all its attendant detrimental effects.

4.2. Proposals to improve exposure assessment

Several proposals have been made to mitigate the effect of sparse exposure data.

4.2.1. Local adjustments based on spot measurements

Spot measurements can be obtained expressly for a study using relatively inexpensive accumulating measuring devices. These spot measurements can be used to calculate local adjustment factors for the stationary measurement device, thus refining the exposure assessment and increasing the number of different exposure situations [9, 10].

4.2.2. Local adjustments based on spot measurements and questionnaire information

A variant of the previous method is based on combining spot measurements and questionnaire information. For a study of respiratory disease in children, categories of living situations with typical NO_2 concentration distributions determined from a questionnaire combined with local spot measurements were used to assign an annual mean NO_2 exposure to each child. The spot measurements allow the derivation of statistical relations between global pollution as measured by a continuously operating fixed monitoring station and local conditions using robust regression methods. If done carefully, this has two beneficial effects:

- A reduction in the exposure misclassification for most individuals, increasing the reliability of the study findings.
- A corresponding increase in the number of differently exposed sub-populations. This increases the power of the study as well as the possibilities of checking/ selecting competing statistical models relating health status to environmental conditions.

4.3. Exposure situations

Let us stop for a moment to consider what one can obtain from studies of the relationship of health outcomes and environmental conditions. Except for very detrimental environmental conditions where one observes acute effects immediately after exposure, health outcomes are determined by the accumulated combined effect of prevalent combinations of environmental noxes, as given by their development over time. Thus, all one can hope for is to characterise certain distinct exposure situations and to investigate health differences between individuals exposed to different situations. Only in special circumstances will it be possible to investigate the effect of, eg., a change in annual mean ozone level alone on respiratory symptoms, as the mean ozone level is always correlated to the annual mean NO_2 level (see Figure 1).

Figure 1. Statistical relationship of annual mean ozone concentration (O3) and annual mean NO_2 concentration (NO_2), both in μ g/m^3, rural areas, from [9].

4.4. Statistical prediction

The relationship shown above is purely statistical and depends on other factors too. We have operationalised these factors with "location": sections within cities more or less exposed to traffic, more or less centrally located and rural areas. Due to variations in the ozone - NO_2 relationships between locations, the researchers were able to separate the effects of ozone and NO_2 on respiratory symptoms in the study in question, as it had enough sufficiently disparate locations. Similarly, empirical relationships between various environmental variables were used to predict certain (few!) unobserved mean annual ozone concentrations using mean annual NO_2 concentrations.

4.5. Interpolation

Another possibility to estimate individualised exposures is by interpolation. This was attempted in a study of the health effects of radio wave exposure near a short wave transmitter. However, due to periodic changes in the main transmission direction, the transmitter's electromagnetic field emissions showed large variation. Thus, one would have needed a measured time series of electromagnetic field strengths at a very large number of points to be able to estimate the energy surface depending on the transmission direction. The solution finally adopted was the use of the nearest measurement point, averaging over time using the known time pattern of transmissions. That is, more weight was given to averaging over time, keeping the rather crude location approximations of using the nearest point of measurement for each person [11].

4.6. Relevant measure of exposure

When analysing health outcomes, one always has to consider which functional of the pollutant time series (eg. its annual mean, or the time above certain levels) is the most relevant feature with regard to health effects. For the rough characterisation and trend analysis of environmental conditions, annual mean levels of selected pollutants are usually sufficient. If accumulated dose is relevant for health effects, then the annual mean exposure will be optimal. If, on the other hand, only exposures above a certain threshold lead to health damage, annual numbers and duration of transgressions of this threshold need to be considered. Field studies will usually not provide detailed enough data to allow pinpointing the most relevant functional of the pollutant time series. Research into statistical methods helping to discriminate between the two mechanisms of health damage (damage due to accumulated dose or threshold transgression) would meet with keen interest.

An added difficulty is the differential development of regions over time with respect to pollutant mix. These are problems which have not received much attention.

4.7. Summary and conclusion

Taken together, a promising route for the estimation of exposure seems to be via environmental exposure situations. For the SCARPOL [9, 10] respiratory health study, the exposure situations were characterised by:

- location urban centre, heavy traffic
  urban centre, little traffic
  suburb, heavy traffic
  suburb, little traffic
  suburb, elevated
  rural
- annual mean NO_2 concentration
- annual mean suspended particle concentration

This classification proved to be useful for Switzerland, where much of the air pollution comes from vehicles. The approach may have to be modified for other countries. The drawback of using environmental exposure situations is that one renounces the aim of determining the effects of the various environmental pollutants separately. The only admissible interpretation of an association between a health response and exposure is then via mixtures of pollutants. This is certainly somewhat less than desirable.

With regard to the introductory list of relevant items for a scientifically sound statistical analysis, the discussion of this section was centered on item 4 (scientific value of the data), and there mostly on the questions of accuracy and relevance of measures of exposure. The conclusions under item 4 affect the answer to item 1 (which scientific hypotheses can be answered with the data at hand?), as well as item 5 (which statistical models are adequate, accumulation or threshold models?).

Statistical research questions arising out of this section might concern the best methods of improving exposure estimation, eg. through the combination of exposure measurements and qualitative information obtained from respondents to health questionnaires as well as the questions related to statistical methods to find the data series functional best suited to predict health effects.

5. Problems of exposure misclassification

5.1. Introduction

Sections 3 and 4 have illustrated the fact that in studies of health and the environment, one has to reckon with misclassification of individuals with respect to health responses as well as exposures. In the sequel, we deal with the consequences of exposure misclassification, disregarding health response misclassification.

Estimated exposures are different from actual exposures due to:

- individual mobility;
- observations being too sparse in space;
- too little data about the temporal development of exposures (short or incomplete time series, lack of measurements).

As an approximation, the resulting exposure misclassification may be considered random (not systematic) and non-differential between individuals with different health outcomes.

In bivariable studies of exposures vs. health outcome this has the following consequences [12, 13].

1. If one finds a *significant estimated exposure effect* in the presence of random misclassification only, likely
   - the direction of the estimated effect will be the same as the direction of the true effect
   - the size of the estimated effect will be smaller than the true effect
   - the variability of the effect estimate will be larger than in the situation without random misclassification.
2. If, on the other hand, one *fails to find a significant exposure effect* under the above conditions, no conclusions can be drawn: There could be an effect masked by misclassification or there could be no effect.

The situation is considerably worse in the case of *multivariable analyses*, where nothing general can be said about the direction and size of effects as soon as there is random misclassification in more than one of the covariables [14]. This is a serious and wide spread problem.

5.2. A scientific question and a data set

With the following example, we illustrate a way of dealing with this problem. The example concerns a study of radon and lung cancer mortality [15]. There is a consensus among epidemiologists that the risk of lung cancer is determined mainly by smoking, occupational exposure, air pollution and in-home radon exposure. The scientific question of the study concerned the potential effect of in-home radon exposure on lung cancer mortality. With respect to this question, the variables representing smoking, occupational exposure and air pollution are potential confounders: they are associated with lung cancer mortality, and they may also be associated with in-home radon exposition. Our study provided the following information:

Table 3. Data for the study of radon and lung cancer mortality.

Data:	radon exposures: averages and standard deviations by district; mortality: by age, sex and district; population: by age, sex and district
Missing information:	smoking information; occupational exposure information; air pollution information
Misclassification:	radon exposure shows considerable local variation; mobility of the population

What can be done to obtain a scientifically sound inference which is not affected unduly by missing information and misclassification? There are several possibilities which we will examine in turn.

5.3. Comparing results of sub-population

Poisson models are commonly used to model incidence data, such as the number of occurrences of some event or deaths from some cause [16]. The Poisson distribution has the property that its mean is equal to its variance, which can be used to assess the adequacy of any statistical model for the Poisson mean (see eg. the model proposed below). If the variance of the fitted Poisson model exceeds its mean, we speak of a model with overdispersion; the opposite case is called underdispersion. Overdispersion is an indication for a poorly fitting model, eg. one in which an important covariable is lacking. Underdispersion should occur rarely, as it corresponds to less variation than one would expect purely by chance.

For a first analysis of the radon data, we decided on a Poisson regression model. The outcome variable was the number of lung cancer deaths per district-sex-age group; the explanatory variables were the number of people exposed (as a multiplyer), age group, an indicator variable for urban districts (as a proxy for the impact of smoking, occupational and air pollution) as well as mean radon exposure per district in Bq/m^3. This Poisson model was applied separately to the mortality data for males and females, since smoking history, occupational exposures and in-home radon exposure differ between genders.

The **fitted model based** on the data for all males showed considerable overdispersion (Table 4, [15]). This is to be expected, as smoking, occupational and air pollution are important confounders missing in the model. In order to check the hypothesis that the observed overdispersion was due to the missing confounders, a strategy of progressively restricting the sample to individuals less and less exposed to these confounders was adopted. The sub- populations fitted are given in the following table.

Table 4. Various sub-populations with number of persons at risk (in millions), number of lung cancer deaths 1979–90 and estimates of radon-effect (Gamma) and overdispersion (Q).

Population	Code	no. of persons at risk (in 10^6)	number of lung cancer deaths	Gamma	Q
all men	1	2.49	27'491	-0.402	1.76
men < 60	3	1.84	2822	0.216	1.16
men, countryside	2	1.76	18'716	-0.331	1.67
men, countryside, < 60	4	1.31	2008	0.362	1.14
all women	5	2.66	4638	0.71	1.27
women < 60	7	1.79	693	0.438	0.98
women, countryside	6	1.82	2613	1.071	1.09
women, countryside, < 60	8	1.25	434	0.541	0.94

In the models applied to these sub-populations, the influence of these confounders, and hence the overdispersion, should be reduced. One would also expect larger radon effects when restricting the analysis to younger people, since with lung cancer, several decades will pass between initial cell damage and manifest cancer or death (latency period) and the noxious influence of radon begins at age 0, while smoking and occupational exposures usually do not begin before age 15 or 20.

Table 4 shows that the analyses were based on fairly large numbers. Table 4 and Figure 2 show that the data from sub-populations less exposed to the effects of the confounders (women, younger people, people from the country side) tended to fit to models with successively less overdispersion. In addition, better fit (lower values of Q) and less exposure to confounders tended to go together with larger radon effect estimates.

The tentative conclusion from fitting this series of models was that there indeed is evidence for an interdependency of lung cancer mortality and mean radon exposure per district. This conclusion is supported by several of the subsamples independently. From studies of uranium miners, it may be assumed that radon is causally related to lung cancer incidence and mortality [18, 19]. Hence, in the presence of a statistically well established association between lung cancer mortality and radon exposure in dwellings, a causal interpretation becomes plausible.

Figure 2. Radon effect and overdispersion for various subpopulations.

Ordinate, lower curve: estimates of radon effect (est, times 10^3); upper curve: overdispersion (Q), (no overdispersion: $Q = 1$)
Abscissa: Subpopulations in decreasing order of Q(1 = all men, 2 =rural men, 3=all women, 4=men < 60, 5=rural men < 60, 6=rural women, 7=women < 60, 8=rural women < 60)

5.4. A Bayesian analysis

One complication that was not mentioned in the previous analysis is the fact that the data on radon exposure as well as lung cancer exhibit spatial correlations. In a further analysis [20] these spatial correlations were modelled for one of the sub-groups using a modified statistical model. The radon effect estimate turned out to be 77% of the former estimate once the spatial covariance structure was taken into account. The main effect of the spatial structure was to adjust standard errors to about 80% of the value previously estimated (Section 5.3). Hence, the p-values were almost identical.

From the point of view of model stochastics, though not from the point of view of sample data, this amounts to an independent confirmation of the previous analyses: the conclusion that there is a radon effect on lung cancer mortality holds up independently of the stochastic assumptions made in the two analyses. Indeed, the two types of models are contradictory with respect to their stochastic structure: the analyses described in Section 5.3 are based on the assumption of independence between districts, while in *the Bayesian framework* this assumption is refuted.

5.5. Errors in the measure of exposure

The fact that the exposure estimate was a global one for each district, thus incorporating a measurement error for each individual was considered in this third analysis of the data. A Bayesian analysis using a heteroscedastic errors-in-variables Poisson model and a mixture of normals as the distribution of the radon measurements resulted in a somewhat larger estimate of the radon effect [21]. This was to be expected, as incorporating errors-in-variables generally leads to an increase in effect estimates. This new analysis again strengthens the conclusion reached in sections 5.3 and 5.4 above.

5.6. Conclusions

In order to reach a scientific conclusion concerning the effect of radon exposure on the Swiss population, one has to view all three analyses (and maybe further ones) together. The general correspondence of the findings suggests that a radon effect is indeed present. It is much more difficult to give an estimate of the likely effect of radon exposure on lung cancer rates in Switzerland.

This example has addressed items 4 to 7 of the process of scientific statistical work outlined in the introduction. It aims at illustrating how knowledge about data quality or (lack of it) can be incorporated in a series of statistical models. Each model covers certain aspects of data inadequacy. Taken together, the analyses based on these various, possibly contradictory, models provide guidance in arriving at a scientifically sound conclusion.

6. Final remarks

In this paper, an attempt was made to illustrate the role of statistical modelling, estimation and testing in the process of scientific enquiry. Little was said about the role of statistical thought in the design and planning of studies, although these domains are of equal importance. The examples, from the simple to the more complex ones, show that the assumptions underlying a statistical model may be violated in a practical application; nevertheless, the same model may contribute valuable insights concerning the scientific problem. Indeed, several partially conflicting statistical models were used to arrive at a scientific conclusion in the final example discussed. No single analysis of these data could have provided the insights which were reached via this combined sifting of the study evidence. At the moment, the judicious choice of competing as well as complementary statistical models to deduce solid scientific conclusions is an art. It is an open challenge to develop the elements of a suitable statistical theory to guide practitioners in this field.

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