cated to end of life care.[12] Unsurprisingly, therefore, our understanding of the effective treatments, patient preferences, and best ways to include patients in decisions remains patchy. The best way to answer the practical difficulties of effectively including terminally ill patients in treatment decisions is through more appropriate training, suitable care infrastructure, public debate, and research rather than by professionals making decisions unilaterally.—Irene J Higginson

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Teleoanalysis: combining data from different types of study

Nicholas J Wald, Joan K Morris

Teleoanalysis can provide the answer to questions that would be obtained from studies that have not been done and often, for ethical and financial reasons, could never be done

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Once a causal link has been established between a risk factor and a disease it is often difficult, and sometimes impossible, to determine directly the dose-response relation. For example, although we know that saturated fat intake increases the risk of ischaemic heart disease, the exact size of the effect cannot be established experimentally because long term trials of major dietary changes are impractical. One way to overcome the problem is to produce a summary estimate of the size of the relation by combining data from different types of study using an underused method that we call teleoanalysis. This summary estimate can be used to determine the extent to which the disease can be prevented and thus the most effective means of prevention. We describe the basis of teleoanalysis, suggest a simple one-step approach, and validate the results with a worked example.

What is teleoanalysis?

Teleoanalysis can be defined as the synthesis of different categories of evidence to obtain a quantitative general summary of (*a*) the relation between a cause of a disease and the risk of the disease and (*b*) the extent to which the disease can be prevented. Teleoanalysis is different from meta-analysis because it relies on combining data from different classes of evidence rather than one type of study.

Randomised trials with disease end points are often not enough to determine dose-response relations; their results tend to be limited by factors such as dose, duration of treatment, and a limited age range of subjects. We also need data from observational epidemiological studies (particularly large cohort studies) and often knowledge of the mechanism of action. Short term trials using drugs or vitamins are also helpful because a drug can have a large specific effect that is not otherwise achievable.

It may also be necessary to quantify the individual effects that relate to separate steps in a causal pathway—that is, the effect of factor A on disease C is determined from the estimate of the effect of A on an intermediate factor B and the estimate of the effect of B on C, rather than by directly measuring the effect of A on C. The exercise is like putting together the pieces in a jigsaw puzzle.

The adverse effects of interventions always need to be considered, and including them in the analysis will

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Teleoanalysis can provide the answer to public health problems such as the most effective dose of folic acid to prevent fetal neural tube defects

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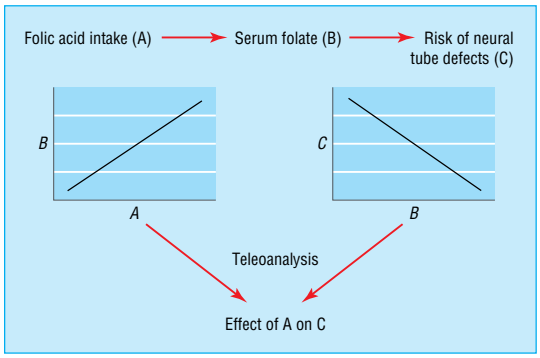
Details of the statistical method for the one-stage process are available on bmj.com

give an assessment of the benefit to harm ratio. However, inclusion of adverse effects relies more on monitoring than on interpretive analysis, and we will not consider it further in this article.

In contrast to meta-analysis, which increases the precision of summary estimates of an effect within a category of study, teleoanalysis combines different categories of study to quantify the relation between a causative factor and the risk of disease. This is helpful in determining medical practice and public health policy. Put simply, meta-analysis is the analysis of many studies that have already been done; teleoanalysis provides the answer to questions that would be obtained from studies that have not been done and often, for ethical and financial reasons, could never be done.



Teleoanalysis to estimate the effect of taking folic acid on risk of fetal neural tube defects

Examples of teleoanalysis

Dietary cholesterol and ischaemic heart disease

An example of the value of teleoanalysis is in quantifying the relation between diet (A) and the risk of ischaemic heart disease (C). This relation can be fully recognised only through some of the important intermediate factors—for example, serum cholesterol concentration (B). A meta-analysis of randomised trials suggested that a low dietary fat intake had little effect on the risk of ischaemic heart disease.[1] But the effect of a significant reduction in dietary fat can easily be underestimated, even when it is based on the results of randomised trials. The difficulty is that diet in the general population cannot readily be changed on a large enough scale for long enough to give interpretable results. Randomised trials answer the pragmatic question of the efficacy of the dietary advice offered but do not indicate the efficacy of some more effective means of reducing dietary fat—for example, dietary stanols, which lower cholesterol concentrations.

The problem can be overcome by using serum cholesterol concentration as an intermediate factor in the causal pathway. We can then examine the effect of lower dietary fat intake on serum cholesterol concentration (which can be done in small scale experimental studies) and the effect of serum cholesterol concentration on the risk of ischaemic heart disease (which can be done in epidemiological cohort studies and in trials of cholesterol lowering drugs).[2–4] Data from several sources need to be reconciled quantitatively to assess the effect of dietary fat on disease.

Dietary folate and neural tube defects

Increasing maternal intake of folic acid prevents fetal neural tube defects. In the Medical Research Council vitamin study, women who took folic acid 4 mg/day around the time of conception had an 83% reduced chance of having a child with a neural tube defect.[5] Other evidence supported the preventive effect of folic acid,[6 7] but the dose-response relation remained unknown. This made it difficult to advise women planning a pregnancy on the appropriate dose and an illogical two dose policy emerged; despite the absence of adverse effects, women who had had an affected child were advised to take 5 mg a day but women in the general population were advised to take only 0.4 mg a day.[8] The problem of dose was unresolved and the effect of fortifying flour with folic acid on the risk of a neural tube defect also could not be predicted. Too few satisfactory studies had examined different doses of folic acid supplementation to quantify its preventive effects.

By using teleoanalysis to integrate different sources of data and different classes of evidence, it was, however, possible to resolve the issue.[6] Several studies have examined the effect of increasing folic acid intake (A) on serum folate concentrations (B), showing that an absolute increase in folic acid intake leads to an absolute increase in serum folate concentration. A cohort study established the dose-response relation between maternal serum folate (B) and the risk of having a neural tube defect pregnancy (C), showing that a proportional increase in serum folate concentration leads to a proportional decrease in risk of neural tube defects.[9] Combining results from these sources in a two-stage model produced a simple quantitative summary that linked folic acid intake to the prevention of neural tube defects (figure).[10]

Teleoanalysis in one step

Teleoanalysis can also be done with a statistical method that integrates all the available data in one step, in

Predicted serum folate concentrations for specified increases in folic acid intake and predicted reduction in risk of neural tube defect risks in women of childbearing age according to background serum folate with two-step model[10] and one-step model

Extra folic acid intake (mg/day)	Background serum folate 5 ng/ml				Background serum folate 10 ng/ml			
	Two-step model		One-step model		Two-step model		One-step model	
	Serum folate (ng/ml)	% reduction in risk	Serum folate ng/ml (95% CI)	% reduction in risk (95% CI)	Serum folate (ng/ml)	% reduction in risk	Serum folate (ng/ml) (95% CI)	% reduction in risk (95% CI)
0.2	6.9	23	6.8 (6.4 to 7.2)	21 (8 to 36)	12	13	12 (11 to 12)	12 (5 to 21)
0.4	8.8	36	8.6 (7.8 to 9.4)	35 (14 to 54)	14	23	14 (13 to 14)	21 (8 to 36)
1	14	57	14 (12 to 16)	55 (26 to 77)	19	41	19 (17 to 21)	39 (17 to 60)
2	24	71	23 (19 to 27)	70 (36 to 88)	29	57	28 (24 to 32)	55 (26 to 77)
5	52	85	50 (40 to 60)	84 (49 to 96)	57	75	55 (45 to 65)	74 (39 to 91)

For further detail see www.smd.qmul.ac.uk/wolfson/folicntd

Summary points

Trials to determine the dose-response relation between risk factors and disease are often difficult or impossible to do

Quantification of such dose-response relations therefore relies on combining epidemiological data with data from other sources

Teleoanalysis is an underused method that combines different categories of data to produce a summary estimate of the size of the relation

The method is valuable in public health as it can estimate the extent to which a disease can be prevented and thus help determine the most effective means of prevention

effect performing both steps simultaneously. This model can be implemented in a statistical computer package WinBUGS (based on a bayesian conditional independence model), which is currently available free from the internet.[11] The details of the statistical method are available on bmj.com.

The table compares estimates of the effect of folic acid on neural tube defects obtained by the one-step method with those derived by the two-step approach.[10] The two methods give nearly identical results. In effect, each validates the other and confirms a dose-response relation of considerable public health importance. The models show the extra benefit of using a 5 mg a day supplement in the prevention of neural tube defects instead of 0.4 mg per day, as is currently recommended for women in general. With a background serum folate concentration of 5 ng/ml this would yield an 84% (95% confidence interval 49% to 96%) reduction in the risk of neural tube defects compared with a 35% (14% to 54%) reduction with the currently recommended dose. The one-step method estimates confidence intervals directly but the two-step method requires a separate simulation.

Although the two-step approach is simpler to carry out with conventional software and is easily explained to non-statisticians, the one-step approach may be preferred because it automatically provides an indication of the precision of the estimates. Given the availability of the necessary software, there is no reason why teleoanalysis should not become standard. Use of the technique will formalise a method that has been used in isolated situations over the past decade and should help to encourage the use of intermediate markers in quantitative analyses. Teleoanalysis alone does not prove that a particular agent causes a disease, but once this has been established—for example, in a single dose drug trial—it is a useful method to quantify the effect and indicate the dose-response relation.

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Contributors and sources: The authors have worked for many years in aetiological epidemiology seeking to identify preventable causes of disease and quantifying these effects.

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One hundred years ago

The advantages and disadvantages of the profession of medicine

The choice of an occupation for life, or, as it may be, the recognition of a vocation, is, in the majority of cases, an anxious process, alike to the neophyte who is about to enter on his novitiate of professional life, and even more to those to whom his happiness and future usefulness are of the first concern. The cause of this anxiety is the difficulty of arriving at a momentous decision on evidence which is usually not in clear perspective, often misunderstood, sometimes insufficient, and always more or less embarrassing in its rival claims. The profession of medicine, like every other, has its advantages and its disadvantages, and those who entertain the idea of entering it should weigh for themselves the one against the other so that they may know what they have to expect. For the more definite their idea of the life they will have to lead the more accurately will they, their parents and guardians, be able to judge of their fitness for it, and the more surely will they be able to avoid the stones of stumbling that will bestrew their path. The idea of fitness should certainly have as its foundation considerations of physical constitution, and control of what are familiarly known as ways and means, as well as considerations of intellectual capacity, aptitude, and liking for the study of natural objects, and qualities of character such as diligence, perseverance, patience, and moral strength. With the object of helping young runners about to enter on the race of life to avoid making a mistake in a matter of such vital importance as the choice of a profession, we now lay before them a dispassionate statement of what lies before one who adopts medicine as a career—the work he will be called upon to do, the rewards he may fairly look for, the sacrifices he may have to make, and the disappointments that may fall to his lot. It must be understood that we speak here of the man of average abilities, with no particular advantages in the way of money or influence, who will take up medicine for a livelihood, and will expect a fair return for the time and money spent on his education.

(*BMJ* 1903;ii:501)