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Incidence of the Bertillon and Gompertz effects on the outcome of clinical trials

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HIGHLIGHTS

- Death rates of non-married persons are about twice the rates of married people.
- At age 82 mortality rates are 40 times higher than at age 37.
- Therefore, the marital status of elderly participants greatly affect death numbers.
- The previous problem cannot be corrected through randomization alone.
- Recommendations are given to remedy this source of bias.

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ABSTRACT

The accounts of medical trials provide very detailed information about the patients' health conditions. On the contrary, almost no vital data such as marital status or age distribution are usually given. Yet, some of these factors can have a notable impact on the overall death rate, thereby changing the outcome and conclusions of the trial. This paper focuses on two of these variables.

The first is marital status; its effect on life expectancy (which will be referred to as the Bertillon effect) may double death rates in all age intervals.

The second variable is the age distribution of the oldest patients. Because of the exponential nature of Gompertz's law changes in the distribution of ages in the oldest age group can have dramatic consequences on the overall number of deaths. One should recall that the death rate at the age of 82 is 40 times higher than at the age of 37.

It will be seen that randomization alone can hardly take care of these problems. Appropriate remedies are easy to formulate however. First, the marital status of patients as well as the age distribution of those over 65 should be documented for both study groups. Then, thanks to these data and based on the Bertillon and Gompertz laws, it will become possible to perform appropriate corrections.

Such corrections will notably improve the reliability and accuracy of the conclusions, especially in trials which include a large proportion of elderly subjects.

1. Introduction

This is a rather unusual paper. Written by a theoretical physicist with a long-standing interest in demography (e.g. Refs. [1,2]), this note concerns a key-aspect of clinical trials, an aspect which is closely connected with a basic law of demography. Our point is very simple.

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- According to the Bertillon effect [3,4] in all age groups (over 20) the death rate of divorced or widowed males is twice the death rate of married people.
- Gompertz's law [5, Figs. 1,2] giving the death rate as a function of age is an exponential. Roughly speaking after the age of 40, the age-specific death rate doubles every 10 years. In the age group 80–84 it is 40 times higher than that in the age group 35–39.

When these two results are combined it becomes clear that special precautions must be taken for dealing with groups comprising many persons of old age, a fairly common occurrence in clinical trials testing drugs for heart disease. For instance it is not sufficient to ensure that the placebo and drug groups have the same total numbers of men and women. One must also make sure that the oldest age group comprises the same number of men and women. In addition one must have the same age distribution in the two study groups. If these conditions are not fulfilled the results of the trial must be corrected appropriately.

This note will proceed as follows. In Section 1 we present the problem. In Section 2 we present the Bertillon and Gompertz effects. In Section 3 we present a specific clinical trial. In Section 4 we examine the incidence of the Bertillon effect on the outcome of this trial. In Section 5 we examine the incidence of the Gompertz effect through a thought experiment. In Section 6 we show that in any group the fraction of people over 65 is a much predictor of group mortality than the median age which is the standard variable given in the accounts of medical trials. The paper ends with a conclusion section which outlines a number of recommendations. The most important is that in all trials, and especially in those comprising many elderly people, it is imperative to give the density (or distribution) functions of ages in the two groups, namely the placebo group and the one who gets the real drug. Other statistical characteristics such as the median/average age or the interquartile range[1] do *not* permit to control (and correct for) the effect of age on mortality in the two groups during the duration of the trial.

In recent decades clinical trials have become highly technical and standardized procedures. There is even a scale, the Jadad scale, which assesses the methodological quality of a clinical trial, particularly regarding randomization and blinding. The accounts commonly contain the following sentence: "The participants in the two study groups (i.e. placebo versus drug group) were well balanced with respect to major risk factors". In support of this claim the papers provide a table entitled "Baseline characteristics of the trial participants according to study group". Table 1 reproduces the non-medical factors as given in the account of the LIPID [6] trial. Other accounts (e.g. Refs. [7,8]) contain similar tables.

Yet, it seems that two important factors are commonly omitted which can substantially affect the outcome in terms of overall death rate,[2] namely the marital situation (*MS*) of the patients and the age distribution of the fraction older than 65 ($F65$).

- The first point is related to the fact that the death rate by heart disease or by cancer is highly dependent (by a factor 2 as shown in Fig. 1) upon the marital status of the subjects. For the sake of brevity this effect will be referred to as the Bertillon effect.[3]
- Most accounts of clinical trials give the median age (*MA*) in the placebo (P) and drug (D) groups. It will be shown that the median age is a very poor indicator of overall expected mortality in any group of people. This is due to Gompertz's law for death rates according to which death rates increase as an exponential function of age.[4] Roughly speaking, after the age of 35 the age-specific death rate doubles every 10 years. Therefore it is not surprising that the fraction of elderly people is a much better indicator of expected death rate (see Fig. 4).

One could argue that the previous observations do not really matter because the randomization procedure will take care of that and ensure that the P and D groups are identical with respect to *MS* and $F65$. This is not true however.

Randomization may indeed result in groups having similar *MA* because in any set of groups this variable has a low dispersion. However, this does not tell us anything significant about death rates. In contrast, the more significant $F65$ variable has a much higher dispersion. For a given sample of US counties its coefficient of variation ($CV = \sigma/m$) is 3 times the *CV* of *MA*. For *MS* the randomization is also a tricky operation because there are 5 different marital situations, namely: single, married, non-married partners, divorced, widowed, each of which has a different expected mortality. As the rates are different for males and females one needs in fact 10 categories. Thus, it is nearly impossible to balance the population numbers for each of these groups.

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[1] Let us recall that the interquartile range is: $IQ = Q_3 - Q_1$ where Q_1 and Q_3 are the first and third quartile, respectively. For instance for the following set of 12 integers $E = \{1, 11, 15, 19, 21, 24, 28, 35, 37, 47, 50, 60\}$, the three quartiles are: $Q_1 = 15$, Q_2(median) $= 26$, $Q_3 = 37$.

[2] In this paper we focus on clinical trials in which the number of deaths occurring in each group (placebo versus drug) is a key-result. This is for instance the case of trials involving drugs for the treatment of heart diseases.

[3] After Louis-Adolphe Bertillon [3] who stated the rule for overall death rates in every age interval above 20. Subsequently [4, p. 474], he reported a similar observation for suicide rates. In this case the effect is about 1.5 times stronger than for over-all death rates. Some twenty years later his study was revisited and expanded by Emile Durkheim [9, Part 2, Chapter 3].

[4] For ages over 35 and in the conditions of medical trials one can neglect the age-independent Makeham component of the mortality rate.

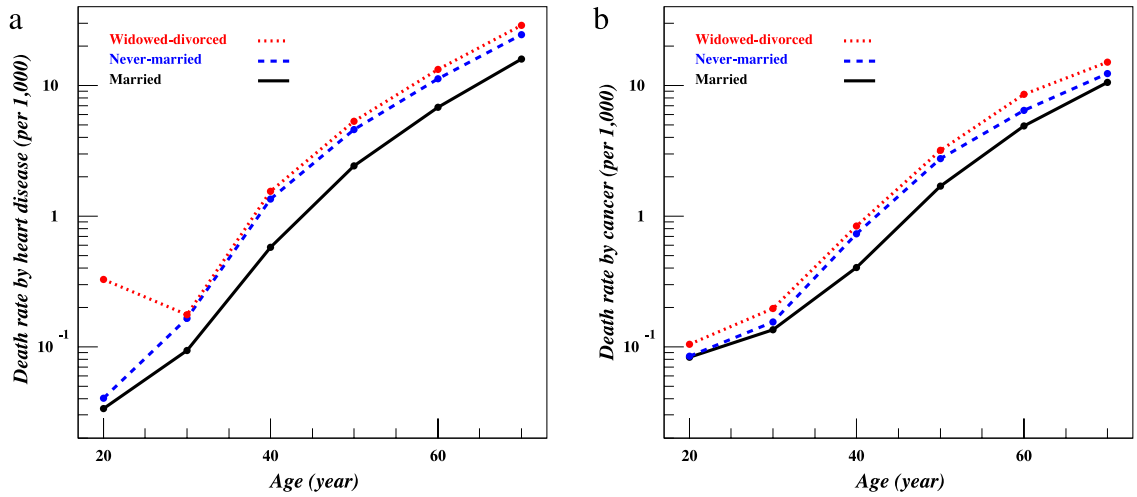

Fig. 1. Bertillon effect. Death rate through heart disease or cancer by marital status, males, United States, 1980. The death rate of married people is about two times smaller than the death rate for non-married persons. There is a similar effect for global (all causes) death rates. More precisely, one can notice the following results. When one combines heart disease and cancer one gets the following ratios: **Heart + cancer, males** (1) age 40: non-married/married = 2.2 (2) age 70: non-married/married = 1.6. Moreover, for all causes of death (data not shown here) one gets: **All causes, males** (1) age 40: non-married/married = 3.2 (2) age 70: non-married/married = 1.7. **All causes, females** (1) age 40: non-married/married = 2.0 (2) age 70: non-married/married = 1.4. **All causes, males + females** (1) age 40: non-married/married = 2.6 (2) age 70: non-married/married = 1.55. On these graphs, for the sake of clarity, widowhood and divorce cases were lumped together. However, a more detailed analysis shows that widowed people have markedly higher death rates than divorced persons especially for young people. In this connection it should be observed that the data point for 20-year old men which seems to be out of line is not spurious. It is observed as well in other countries and in various years. It is due to the very high death rate of young widowers.
Source: Number of deaths: Vital Statistics of the United States, 1980, Vol. 2: Mortality, Part A, pp. 316–317. Population by age and marital status: 1980 Census of population, Marital Characteristics, p. 1; Statistical Abstract of the United States 1981, Table 49.

2. The Bertillon and Gompertz effects

2.1. Bertillon effect

Although, as already mentioned, the influence of marital status on death rates has been known for a long time, knowledge of this effect separately for different causes of death (as summarized in Fig. 1) is more recent.

As a matter of fact, such evidence can only be obtained in a country such as the United States which has a large population. For instance, in 1979 the number of widowed males who died from cancer in the age group 35–44 was only 62 for the whole country; in 1980, it was 48 which shows that despite being small these death numbers are nevertheless fairly stable (Vital Statistics of the US, 1979 and 1980).

2.2. Gompertz law

Discovered in 1824, Gompertz's law was probably the first major law in the field of demography. As shown in Fig. 2, it is not only valid for overall death rates but also separately (with only slight variations) for different diseases.

In what follows we will adopt the following parameters:

$$y = g_0 \exp(ax) \qquad x: \text{ age (in years)}, \qquad y: \text{ death rate per 1000}, \qquad a = 0.082, \qquad g_0 = 0.11. \tag{1}$$

It will be seen below that they lead to death number predictions which are consistent with what is observed in medical trials.

3. Statistical information given in trial reports

As already said, trial reports are highly standardized. Every report has a table entitled: "Base-line characteristics of the randomized subjects". Almost 90% of the data given in such tables are medical data. For instance the Table of WOSCOR [10] has 21 lines of which only one is non-medical; it gives the median age. The Table of Jupiter [7] has 29 lines of which only 2 are non-medical; they give the median age and the interquartile range. The Table of LIPID [6] has 42 lines of which 8 are non-medical. These 8 lines are reproduced in Table 1. Our purpose in selecting the LIPID trial is to show that even such accounts which provide more information than is customary do not contain the data which would be really needed.

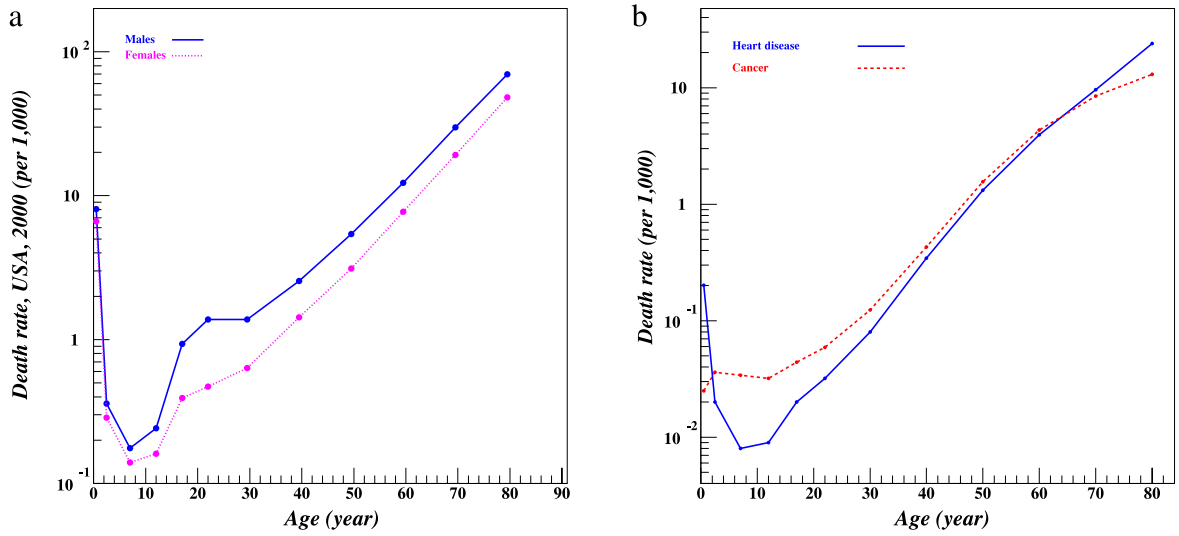

Fig. 2. Gompertz's law: Age-specific death rates in the United States in 2000. The graph illustrates the exponential growth of death rates as a function of age. This constitutes Gompertz's law. The curves for males and females are parallel (graph on left-hand side). There is also a similar exponential growth for *separate* causes of death provided they are due to diseases (e.g. cancer, heart disease, cerebrovascular accident, pulmonary disease, etc.). On the contrary, the rates for causes of death that are not diseases (e.g. suicide, accident) do *not* increase exponentially but at a much slower rate.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, Compressed Mortality File. This database is commonly referred to as the WONDER database.

Table 1
Base-line characteristics of patients in the LIPID [6] trial.
Source: LIPID [6].

	Placebo group		Pravastatin group	
Age characteristics				
All ages	4502	100%	4512	100%
31–54	1021	23%	1065	24%
55–64	1708	38%	1706	38%
65–69	1087	24%	1081	24%
70–75	686	15%	660	15%
Median age	62		62	
Interquartile range $Q_3 - Q_1$	55–68		55–67	
Sex characteristics				
Male	3741	83%	3756	83%
Female	760	17%	756	17%
Deaths from any cause (over 6 years)	633		498	

Notes: the table is reproduced in the very same form as given in LIPID [6]. Although several vital characteristics are given, they all fail to describe the precise composition of the oldest age group. The thought experiment delineated in Fig. 3 shows that these characteristics greatly matter as far as the overall expected mortality is concerned.

LIPID [6] gives 6 characteristics which are recalled in Table 1. Yet, on the basis of Gompertz's law one quickly comes to realize that these characteristics are not sufficient. They do not put any constraint on the distribution of ages within the *oldest* age group.

In any trial in which mortality rates matter, an important parameter is the difference of death numbers in the placebo and death numbers. In LIPID it was: $(633-498)/[0.5(633+498)] = 24\%$. This is a fairly standard difference for a successful trial. For WOSCOPS 1, WOSCOPS 2 and JUPITER it was 24%, 15% and 22% respectively.

Even the mere difference in the numbers of the oldest age group (660 versus 686) will have an incidence. Based on Gompertz's law this difference will result in 6 more deaths in the placebo group which represents 4.4% of the overall death difference of 135 between the two groups. Although small, this correction should not be omitted.

For the sake of clarity we will analyze separately the implications of the Bertillon and Gompertz effects but one should keep in mind that the two effects are closely connected. The fact that the death rate of non-married persons is twice the rate of married persons is true at all ages but it has no observable consequence for age groups under 60 that is to say as long as the death rate remains small. It is only for high death rates (age groups above 70) that the effect will significantly affect the total number of deaths recorded in clinical trials.

Table 2
Expected incidence of marital status and gender on death numbers in the LIPID trial.
Source: Data given in Figs. 1 and 2.

	Placebo group	Diff.	Pravastatin group
1. *Incidence of marital status*			
Hypothesis on 70–75 age group	Only non-married persons		Only married persons
Death rate (per 1000)	39		25
Expected number of deaths	160		99
Expected difference		61 (45%)	
2. *Incidence of gender*			
Hypothesis on 70–75 age group	Only men		Only women
Death rate (per 1000)	30		20
Expected number of deaths	122		78
Expected difference		44 (32%)	
3. *Combined (marital stat. + gender)*			
Hypothesis on 70–75 age group	Only non-married men		Only married women
Death rate (per 1000)	46.5		14.0
Expected number of deaths	191		55
Expected difference		136 (101%)	

Notes: all three assumptions are compatible with the vital characteristics given in the account of the trial. In the LIPID trial there were 633 deaths in the placebo group and 498 in the drug group which gives a difference of 135. The numbers in the lines "Expected difference" give the expected death differences solely on the basis of the composition of the groups that is to say under the assumption that both groups receive the same placebo. The numbers within parentheses give the percentage with respect to 135. It can be seen that the combined marital status plus gender effect accounts for the totality of the placebo-drug difference.
The death rates were derived from the data in Figs. 1 and 2. For instance: $39 = 1.55 \times 25$ and so on. The numbers of death were computed over the 6 years of the LIPID trial with initial numbers in the 70–75 age group equal to 686 and 660. For instance: $0.686 \times 39 \times 6 = 160$ (this is an approximation but which is sufficient for our present purpose) and so on.

4. Incidence of the Bertillon effect on trial outcomes

As noted above, randomization will hardly be able to balance exactly the proportions of different *MS* in the study groups. This problem becomes more serious as the average age of the study group increases because, not surprisingly, the proportion of widowed people increases with age (especially in the female population). At age 50, 85% of the US population was married (in 1980), but for the age group over 75 years, 46% were married, 45% widowed, 5% single and 2% divorced (Statistical Abstract of the US 1981, Table 49).

As the order of magnitude of the Bertillon effect is around 100%, even a partial imbalance can matter because the difference in the number of deaths between *P* and *D* groups is usually of the order of 20%–30%.

In order to quantify this effect while at the same time keeping the argument as simple as possible we will consider the data of LIPID [6] and make a fairly extreme assumption.

The data given in the account of the trial (and reproduced in Table 1) give only the total number of men and women. Let us assume that all 686 persons in the placebo age group 70–75 are males while on the contrary, all 660 persons in the pravastatin age group 70–75 are females.[5]

Needless to say, a randomization procedure is not likely to result in a 70–75 year placebo group with 100% men. However, as already mentioned, for the 4 main sub-groups (namely married versus non-married, male versus female) randomization will not ensure equal numbers on the placebo and pravastatin sides and especially not for the 70–75 age group which is the smallest, yet also the most important. There will be fluctuations and Table 2 shows that the effect of such fluctuations will not be small. Even if the percentages that we found (namely 45%, 32% and 101%) are divided by 4 or 5 the effect will still be significant. In order to be able to make a mere precise statement one would need to know how exactly the randomization procedure was carried out. Obviously, the patients were not drawn from a standard population for in this case, as 77% of the samples are over 55, there would be more females than males while in fact we observe the opposite.

Once one has got precise information about the randomization procedure, the magnitude of the fluctuations can be predicted. Making several subgroups is a multinomial process. One knows that for subgroup X_i the coefficient of variation *CV* will be given by: $CV(X_i) = \sqrt{(1 - p_i)/Np_i}$ where N is the total number of elements from which the drawings are performed and p_i the probability that a drawn element belongs to subgroup i. Just in order to be more specific, let us assume that there are q subgroups whose probabilities are equal. In this case: $p_i = 1/q$ and $CV(X_i) = \sqrt{(q - 1)/N}$. This formula shows that, as expected, the coefficient of variation increases when there are more subgroups or when N decreases. As an example, for $q = 4$ and $N = 1000$, one gets $CV = 6\%$, while for $q = 8$ and $N = 100$, one gets $CV = 28\%$.

[5] In addition we assume that the additional males ($3742 - 686 = 3056$) in the *P* group and the additional females ($756 - 660 = 96$) in the *D* group are distributed in younger age groups so that they will not bring about any notable additional difference in death numbers.

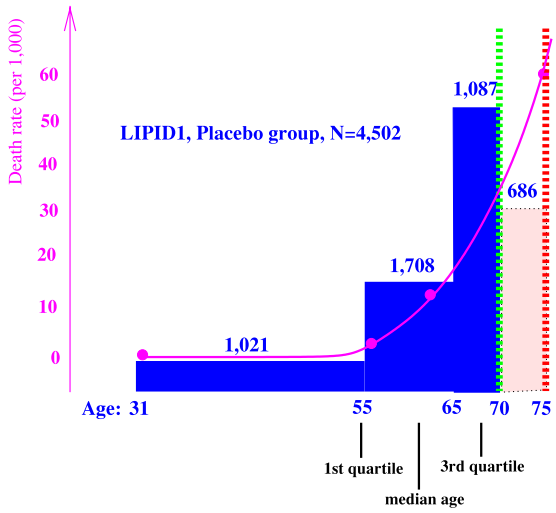

Fig. 3. Changes that do not affect the reported statistical characteristics but significantly change the overall number of deaths. The histogram corresponds to the age groups of the LIPID [6] trial. The oldest age group has been drawn in a different color because the statistical data reported in the paper (and reproduced in Table 1) do not put any constraint on the distribution of subjects *within* this group. Three cases are represented: uniform distribution (pink), only 70-year old subjects (dotted green line on the left-hand side of the uniform distribution), only 75-year old subjects (dotted red line on the right-hand side of the uniform distribution). Depending on the assumption, the number of deaths (all causes) for the whole trial may change by as much as 11%. In LIPID [6] the oldest age group represented only 15% of the whole study groups; needless to say, the Gompertz effect will be stronger when this percentage is higher. The effect becomes also stronger as the age of the oldest age group increases. Note that the scale on the left-hand side is for the smooth death rate curve; the scale for the histogram is not shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Source: LIPID [6].

5. Incidence of the Gompertz law on trial outcomes

We wish to show that for the highest age group the detailed age distribution matters. In line with the method already used in the previous section, we consider extreme cases. This is done through a thought experiment which conveys the main idea. This thought experiment is based on the fact that the vital characteristics given in Table 1 do not give any information about the age-distribution within the oldest age group.

Thus, by modifying this distribution one can substantially change the expected number of deaths.

How did we carry out this analysis? For each age Eq. (1) gives the corresponding death rate. As the trial lasted 6 years, the calculation will involve the following steps. If (e.g. in the P group) there are initially n_1 subjects aged 61, some $m_1 = n_1 y(61)$ will die in the first year. As a result, at the beginning of year 2 there will be $n_2 = n_1 - m_1$ remaining patients. Similarly, during the second year, some $m_2 = n_2 y(62)$ will die. By repeating this calculation first for the 6 years of the trial, and then for all ages, and by summing all death numbers one gets the expected death number during the whole trial. In this way, one obtains the following results (this is for the placebo group[6]):

31–54 : 31, 55–64 : 180, 65–69 : 200, 70–75 : 190, total: 601 (instead of 633).

The fact that the actual number of deaths, namely 633, is slightly higher than the expected number may be due to the selection of the patients. All of them had a history of myocardial infarction and also a fairly high cholesterol level. On account of this, for subsequent calculations the coefficient g_0 will be multiplied by the following renormalization factor $633/601 = 1.053$.

Now, we are ready to carry out the experiment described in Fig. 3. The numbers of deaths in the age group 70–75 were calculated under the following assumptions:

- Whole group at age 70
- Uniform distribution
- Whole group at age 75

and lead to the following results.

Placebo group. Age 70: 164 deaths, Uniform: 198 deaths, Age 75: 235 deaths
Pravastatin group. Age 70: 158 deaths, Uniform: 190 deaths, Age 75: 225 deaths.

6 Because the age end-points (31,75) are only given for the whole sample, we had to assume that they are identical for the placebo group.

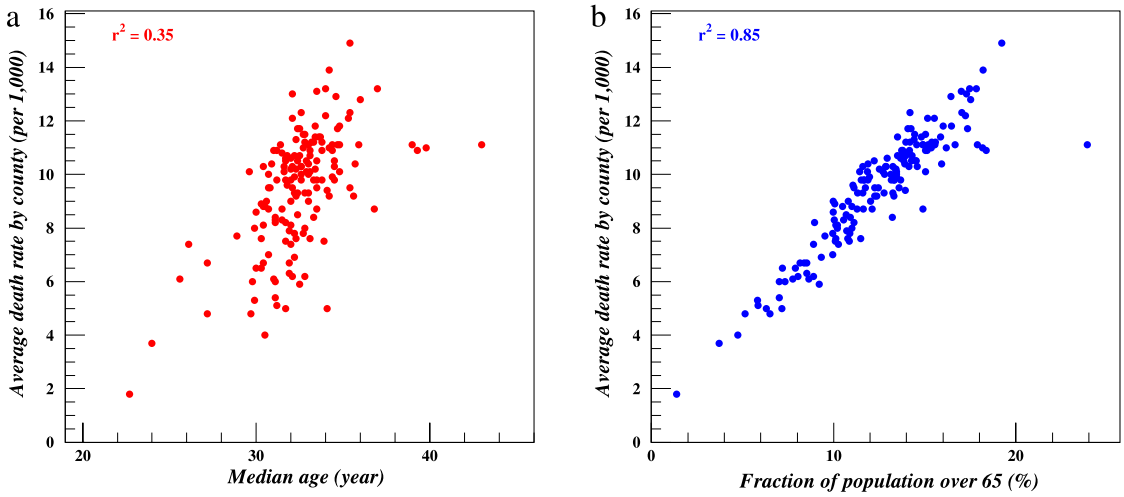

Fig. 4. Relationship between median age (left) or fraction over 65 (right) on the one hand and average death rates on the other hand for the counties of Georgia. The poor correlation ($r^2 = 0.35$) between median ages and death rates is a consequence of Gompertz's law. Indeed, the fact that the death rate at age 82 is 40 times higher than at age 37 implies that the addition of young persons will lower the mean age without notably changing the death rate. On the contrary, just a few more persons over 80 will lift the death rate without substantially shifting the mean age. The median age is even less sensitive to such changes than the mean age. Note that in the graph the median age and $F65$ are for the year 1990 whereas the death rates are averages over 1979–1998. The least-square estimate of the regression line between $F65$ and the death rate d (per 1000 population) reads: $d = aF65 + b$, $a = 0.61 \pm 0.04$, $b = 1.8 \pm 0.13$. There are similar results in other states; for instance in Texas (254 counties) the r^2 of the correlation ($F65$, d) is 0.92 and the parameters a, b of the regression line are: $a = 0.59 \pm 0.02$, $b = 1.3 \pm 0.11$.
Source: Average age: Bureau of the Census, USA Counties website. F65 and average death rates: Centers for Disease Control and Prevention, National Center for Health Statistics, Compressed Mortality File (commonly called "WONDER" database).

Thus, for a placebo group composed solely of persons of age 75 and a pravastatin group composed solely of persons of age 70, the expected difference in death numbers will be $235 - 158 = 77$ which represents 57% of the difference (of 135) between the placebo and pravastatin groups.

In other words, just by changing the age distribution within the oldest age group one can generate a difference in death numbers which is more than one half of the difference attributed to the effect of the drug.

6. Determinants of death rate

As a proof of the fact that the median age is not a useful variable, we show that it is a poor predictor of overall death rates. In contrast, the population fraction over 65, $F65$, is a very good predictor of death rates.

The data shown in Fig. 4 are for the 159 counties of Georgia. For what reason was Georgia selected? Altogether there are some three thousand counties in the United States but the numbers of counties per state vary greatly. Texas and Georgia are among the states with the largest numbers of counties which is why they were selected.

7. Conclusion

In this paper we emphasized that, due to the Bertillon effect, the marital status of the subjects taking part in a trial is of cardinal importance because it may increase death rates due to heart disease or cancer by as much as 100%. Although for the sake of brevity we focused our attention on these two major causes of death, there is a similar effect (of the same magnitude) for other causes of death such as cerebrovascular accidents or pulmonary diseases. This observation leads to the recommendation to include the information about marital status in the table giving the characteristics of the two study groups.

Secondly, we emphasized that, due to the Gompertz effect, it is important to describe the oldest fractions of the study groups in great detail. In several study accounts we were not even able to find the limits of the age intervals of the study groups. The most appropriate information would be the density functions of the age groups over 65 as a function of age. If, for some reason, this is not possible then one should give at least the percentage fraction over 65 ($F65$) and the age of the oldest subjects in each group. We have seen that the median age is almost useless because it is a poor predictor of overall death rates.

By giving the possibility of performing appropriate corrections, the two points made here should permit to improve the accuracy of trial results. As this can be done at little cost there is really no reason to discard such an improvement.

A last remark may be worthwhile.

One of the referees asked why this paper was submitted to a physics journal rather than to a medical journal? The answer is very simple.

It was indeed submitted to two medical journals, one of them being the NEJM in which all the trial accounts under discussion in the present paper were published. Yet, the editors' assessments were that the topic was not of "sufficient interest" for the paper to be sent to reviewers.

In recent years double screening (i.e. pre-selection based on the editor's feelings prior to the real reviewing process) has become more and more frequent in many journals.

Fortunately, in physical journals such subjective judgments about the possible interest of a topic are carefully avoided by most editors.

Some two centuries ago the first articles about electricity were concerned with the contraction of the legs of frogs. That was probably not very useful in itself but who would have guessed that it would lead to radio-waves and computers?

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