Abstract   The accounts of medical trials provide very detailed information about the patients’ health conditions. On the contrary, only minimal data are usually given about demographic factors. 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; this effect, which will be referred to as the Bertillon effect, may change death rates by over 100%. The second is the age of the oldest patients; because of the exponential nature of Gompertz’s law, the distribution of ages in the oldest age group can have dramatic consequences on the overall number of deaths. 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.

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Overview

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 (1998) trial. Other accounts (e.g. Jupiter 2008, WOSCOPS 2007) 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[^1], 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[^2].

- 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[^3]. Roughly speaking, after the age of 35 the age-specific death rate doubles every 10 years. In the age group 80-84 it is 40 times higher than in the age group 35-39. 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

[^1]: 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.

[^2]: After Louis-Adolphe Bertillon (1872) who stated the rule for overall death-rates in every age interval above 20. Subsequently he reported (Bertillon 1879, p.474) a similar observation for suicide rates. In this case the effect is about 1.5 times stronger. Some twenty years later his study was revisited and expanded by Emile Durkheim (1897, Part 2, Chapter 3).

[^3]: For ages over 35 and in the conditions of medical trials one can neglect the age-independent Makeham component of the mortality rate.
\( CV = \sigma/m \), 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 will be nearly impossible to have balanced population numbers for each of these groups. This problem becomes more serious as the average age of the study group increases. 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).

### Incidence of the 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).

As noted above, randomization will hardly be able to balance exactly the proportions of different MS in the study groups but it may also be argued that randomization is not likely to result in huge imbalances. However, such imbalances may be produced indirectly. For instance, if one wishes to compare groups of males and females over 65 years one must be aware that the proportions of widowed subjects will be very different in the two cases: about 8% for males compared to 40% for females (Statistical Abstract of the United States 1980).

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

### Incidence of the Gompertz effect

This section proceeds in three steps. Firstly, the Gompertz law is recalled. Secondly, We present a thought experiment which conveys the main idea. Thirdly, we emphasize that the population fraction over 65 is a much better predictor of the overall death rate than the median age.

**Gompertz law**
The death rate of married people is on average two times smaller than the death rate in the two other categories. More precisely, the ratios single/married and widowed/married are as follows:

age 40, heart: \( s/m = 2.3, \ w/m = 2.7 \); cancer: \( s/m = 1.8, \ w/m = 2.1 \)

age 50, heart: \( s/m = 1.9, \ w/m = 2.2 \); cancer: \( s/m = 1.6, \ w/m = 1.9 \)

For the sake of graphical 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. 

Sources: Number of deaths: Vital Statistics of the United States, 1980, Vol.2: Mortality, Part A, p.316-317. Population by age and marital status: 1980 Census Census of population, Marital Characteristics, p.1; Statistical Abstract of the United States 1981, Table 49.

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:

\[ y = g_0 \exp(ax) \quad x: \text{age (in years)}, \quad y: \text{death rate per 1,000}, \quad a = 0.082, \quad g_0 = 0.11 \] (1)

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

**Thought experiment based on LIPID (1998)**

The LIPID (1998) experiment was selected because it provides much more information than usually given about the demographic characteristics of the study groups. Whereas many accounts give only the median age, LIPID (1998) gives 6 characteristics which are recalled in Table 1 and Fig. 3. Yet, on the basis of Gompertz’s law one quickly comes to realize that these characteristics are not sufficient and not well chosen. They are not sufficient because they do not give enough information about the oldest subjects in each group. For instance, the account says that the subjects’ age interval was 31 to 75 but it does not give the intervals separately for the two study groups. Moreover, the characteristics that are given do not put any constraint on the distribution of ages in the *oldest* age group.

### Table 1 Base-line characteristics of patients in the LIPID (1998) trial.

| Age characteristic | Placebo group | Pravastin group |
|--------------------|---------------|-----------------|
| All ages           | 4,502         | 4,512           |
| 31 – 54            | 1,021         | 1,065           |
| 55 – 64            | 1,708         | 1,706           |
| 65 – 69            | 1,087         | 1,081           |
| 70 – 75            | 686           | 660             |
| Median age         | 62            | 62              |
| Interquartile range| 55 – 68       | 55 – 67         |
| Deaths from any cause (6 years) | 633 | 498 |

Notes: The table is reproduced by keeping all figures in the very same form as given in the source. Two observations are in order. (i) Although several statistical characteristics are given, they all fail to describe the 4th quartile, i.e. the fraction of the 25% oldest people in each group (which comprises the age-group 70-75 because $686/4502=15\%$) The thought experiment delineated in Fig. 3 shows that these characteristics greatly matter as far as the overall expected mortality is concerned. (ii) In the source the fraction 70-75 was rounded to the closest integer, namely 15%. More precise values are $F'70 = 15.24\%$, $14.63\%$. The difference $686-660$ will result in an expected number of 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.

Source: LIPID (1998).

Thus, by modifying this distribution one can substantially change the expected number of deaths.
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 (1998) 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, only 75-year old subjects. Depending on the assumption, the number of deaths (all causes) for the whole trial may change by as much as 11%. In LIPID (1998) 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 death rate curve; the scale for the histogram is not shown. Source: LIPID (1998)

How did we carry out this analysis? For each age equation (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):

$31 - 54 : 31, \ 55 - 54 : 180, \ 65 - 69 : 200, \ 70 - 75 : 190, \ \text{total: 601 (instead of 633)}$

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 $633/601 = 1.053$.

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4Because 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.
Now, we are ready to carry out the experiment described in Fig. 3. The number 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.

Age 70: 164 deaths,  Uniform: 198 deaths,  Age 75: 235 deaths

The difference between the cases “70” and “75” is 71 deaths which represent 11.2% of the total number of 633 deaths in the placebo group. This is one half of the difference between the placebo and drug groups, namely \((633 - 498)/633 = 21.3\%\).

**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, \(F_{65}\) is a very good predictor of death rates.

The data shown in Figure 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.

**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 same magnitude) for other causes of death such as cerebrovascular accidents or pulmonary diseases. This observation leads to the recommendation to include 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 (\(F_{65}\)) 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
Fig. 4 a,b  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 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 \( F_{65} \) are for the year 1990 whereas the death rates are averages over 1979-1998. The least-square estimate of the regression line between \( F_{65} \) and the death rate \( d \) (per 1,000 population) reads:

\[
d = aF_{65} + b, \quad a = 0.61 \pm 0.04, \quad b = 1.8 \pm 0.13.
\]

There are similar results in other states; for instance in Texas (254 counties) the \( r^2 \) of the correlation \((F_{65}, d)\) is 0.92 and the parameters \( a, b \) of the regression line are: \( a = 0.59 \pm 0.02, \quad b = 1.3 \pm 0.11. \)

Sources: Average age: Bureau of the Census, USA Counties website. \( F_{65} \) and average death rates: Centers for Disease Control and Prevention, National Center for Health Statistics, Compressed Mortality File (commonly called “WONDER” database).

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 in terms of additional text in account papers there is really no reason to discard such an improvement.

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