**SUMMARY**

**Background:** In a general way at all ages and for almost all diseases, male death rates are higher than female death rates.

**Findings:** Here we report a case in which the opposite holds, namely for tuberculosis (TB) mortality between the ages of 5 and 25, female death rates are about two times higher than male rates. What makes this observation of interest is that it occurs in all countries for which data are available (e.g. Britain, Switzerland and United States), and in all years from the end of the 19th century up to the time in the 1960s when TB became a very rare disease in all developed countries. The fact that this regularity holds despite a drastic reduction in the number of deaths is also noteworthy.

**Practical usefulness:** So far, the reason of this anomaly remains an open question but the effect is so accurate that it can be used for probing the reliability of mortality records. This will be explained in the case of developing countries. For instance, it turns out that in South African TB death data as published (and revised) by the “World Health Organization”, female deaths were certainly under-estimated by a factor of two.

*Version of 31 January 2018*

Key-words: death rate, death ratio, male, female, tuberculosis

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Introduction

Because this question can serve to illustrate the methodological discrepancy between the approach of physics on the one hand and of biology on the other hand, we believe its significance extends beyond the specific problem investigated here.

After a short presentation of the excess-female mortality effect, in the two following subsections we explain why the answers proposed by epidemiologists and biologists appear unsatisfactory. Actually, the reason of this failure is quite simple; it is the inability or unwillingness to adopt a comparative perspective.

Excess-female mortality in tuberculosis

In human populations females have a lower mortality than males at any age and for almost all causes of death. However there are a few exceptions and it is therefore natural that they attracted the attention of epidemiologists. In the present paper we concentrate our attention on the fact that between the age of 5 and 25 the tuberculosis death rate of females is about 1.5 to 2.0 times higher than for males. It is true that there are a number of other infectious diseases (see below) which show a similar effect but almost all such diseases are childhood diseases (e.g. measles) which means that most of the cases occur prior to the age of 5. For instance, in 1901 in the UK, 94% of the measles deaths occurred between the ages of 0 and 5. In the (15 – 44) age interval, the only one in which there is a substantial excess female mortality, there are only 42 deaths (0.5% of the annual number). In other words, for all those diseases except tuberculosis, the excess-female mortality effect concerns a very small number of patients. On the contrary, for tuberculosis the age-specific mortality increases from the age of 5 to the age of 25 which means that, especially in the developing world, hundreds of thousands of patients are concerned by the female excess mortality effect.

Poor diet as a first suggested explanation

Several papers published in the past three decades from 1990 to 2017 (Anderson 1990, Hinde 2011, Janssens 2017) propose an explanation based on an inappropriate diet. The thesis can be summarized as follows (Hinde 2011, p.9).

“A widely held account is that a lack of bargaining power in the home associated with a shortage of paid work for women led to women having a much poorer diet than men, which lowered their resistance to infections. In 1990 Michael Anderson argued that this was the underlying reason for the relatively high female mortality compared to that of males observed [in 19th century Britain] in poor agricultural areas and regions dominated by heavy industry.”

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1 Above all the approach of physics means accurate well targeted measurements along with their comparative analysis.
A similar thesis was presented independently for the Netherlands by Angélique Janssens:

“We have been able to ascertain that a considerable part of maternal mortality in the period 1875-1900 can be attributed respiratory TB for which adequate nutritional intakes are highly relevant.”

What should one think of this explanation?

A piece of evidence that would provide a solid basis for this explanation would consist in statistics about the respective food intakes of boys and girls. Needless to say, no data of that kind are available at country level. Thus, one must rely on the belief that it made sense for families to favor their sons at the expense of their daughters.

However, the main problem with this explanation is the fact that the excess-female mortality is not limited to the 19th century. In fact, as will be shown below in Fig. 1, it extends well into the 20th century including to areas like California or New York State which are not “poor agricultural areas”. By extending their analysis to the 20th century, the aforementioned authors would have been able to identify this difficulty.

In short, we do not want to say that the diet effect played no role whatsoever, but it is certainly not the main explanation for this effect.

**An explanation based on the role of sex hormones**

In a sense the excess-female mortality effect could be called the “Garenne effect” after the name of the epidemiologist Michel Garenne who from 1991 to 1998 (Garenne et al. 1991, Garenne 1994, Garenne et al. 1998) devoted much time to the study of this effect.

The study started from an observation made in rural Senegal in 1990 showing female excess mortality after measles vaccination. Then, eight years later an explanation was proposed.

Positing a link between the hormonal and immunological systems seems of course a natural explanation for an effect which affects male and females differently.

In Garenne and al. (1998) the authors say that “there is growing evidence that sex hormones regulate the Th1/Th2 balance”. The Th1 and Th2 (T=Thymus where they originate, h=helper) are two sorts of white cells which eliminate foreign bodies, e.g. cells infected by a virus or cancer cells. It turns out that the female hormone progesterone promotes the production of Th2 cells whereas the male hormone testosterone rather favors the Th1 cells. To close the argument one only needs to observe that the Th2 cells seem to develop weaker resistance to bacteria than that provided by Th1 cells.

Obviously, this model was designed for the specific purpose of explaining the excess-
female mortality in an age interval during which the concentration of progesterone in the blood is fairly high. In order to be really convincing this model must explain other effects than the one for which it was designed. Unfortunately, the authors do not give any corroborating evidence. Once again, this denotes a lack of comparative perspective. In physics, when a new effect has been identified, the first task is to define its range of validity. For instance, surface tension explains why some insects (e.g. water striders) can walk on water and it explains also the “tears of wine” phenomenon.

Starting from the fact that high levels of progesterone inhibit the fight against TB-like bacteria, what additional observational tests can one propose?

First, we must find situations in which the progesterone level is particularly high. Such situations should be marked by an excess-female vulnerability to TB. (i) In men or postmenopausal women the concentration of progesterone in the serum of the blood is of the order of 1 nanogramme per milliliter of blood serum. (ii) For young non-pregnant females it is of the order of 5 ng/ml (low at the beginning of the 28-day cycle and higher at the end). (iii) Finally, during pregnancy it is on average of the order of 50 ng/ml. In short, the concentration is really much higher than in men only during pregnancy.

Thus, a testable prediction of the progesterone model would be a high incidence of TB in women who have several children in succession as compared with women who have only one child or none at all. Naturally all other conditions should be similar and in addition the test should be made on the years before the BCG vaccination became commonly used.

The authors of Garenne et al. (1998) mention a fact which, at first sight, seems to go in the right direction. They say that diseases such as rubella, influenza and tuberculosis “are more severe during pregnancy when the level of progesterone dramatically increases” but they give no evidence apart from the well known case of rubella, which however is of a different nature in the sense that it is the embryo which suffers rather than the mother.

**Death rate, incidence rate, fatality rate**

In the two previous subsections we discussed successively a sociological and a biological explanation, More generally, the death rate $\mu$ can be decomposed in the following way:

\[
\mu = \frac{\text{deaths}}{\text{population}}, \quad F = \frac{\text{deaths}}{\text{affected population}}, \quad I = \frac{\text{affected population}}{\text{population}}
\]

Death rate ($\mu$) = Fatality rate ($F$) $\times$ Incidence rate ($I$)
The fatality rate which describes the severity of the disease is likely to be of biological nature, whereas the incidence rate which describes how fast the disease spreads is a mixed factor which reflects both biological features, e.g. the mode of transmission and sociological conditions, e.g. the frequency of social interactions.

**Accurate measurements**

In previous studies the data from many countries and many years (typically 1950-1989) were lumped together. Thus, in Garenne (1994) the smallest areas considered are whole continents: Europe, North America (which mixes the US and Mexico), Latin America and so on. In Garenne et al. (1998) the graphs are drawn for the whole world. Such a procedure of data aggregation precluded any serious comparative analysis.

On the contrary, in the present paper we consider single countries (or even subareas of countries) over time intervals that were especially calibrated to be the smallest intervals able to keep the statistical fluctuations at an acceptable level.

This procedure will allow us to make a number of preliminary observations. Moreover, more precise conclusions will become possible once incidence and fatality rate data become available.

**Anomaly of the female/male death ratio for TB: evidence**

As already said, broadly speaking for most age groups and most diseases the number of female deaths is markedly smaller than the number of male deaths. In the US, in the 1950s for all causes of death and averaged over the age interval 5-30 the death ratio male/female is about 1.5.

However, here we report a case in which there are about two times more female deaths than male deaths. This effect is seen between 1880 and 1960 for tuberculosis (TB) between the ages of 10 and 25 (Fig. 1a,b,c,d). In the decades after 1970 the number of deaths due to TB became very small (except in old age). For instance, in the US in the time interval 1999-2015 and for all the age groups from birth to 45 years the annual number of deaths due to respiratory TB averaged only about 40. For that reason the effect becomes impossible to test after 1960.

The fact that this effect is seen not only in the US but also in Switzerland and Britain indicates that it is probably not due to a statistical artifact. For the sake of brevity it will be referred to as the $f/m$ effect.

Fig. 2 shows the $f/m$ death ratio for all causes of death for several European coun-

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2This observation seems to hold not only for humans but also more generally for primates (Bronikowski et al. 2011), mammals and vertebrates (Clutton-Brock et al. 2007).
Fig. 1a,b  TB death ratio female/male by age in Switzerland and the US. More precisely TB refers to TB of the lungs. In the Swiss statistics it is the word “phthisis” which is used instead of TB. The error bars are defined as $\pm \sigma$ where $\sigma$ is the standard deviation of the average. The insets show separately the female (upper line in red) and male (lower line in black) TB death rates. Sources: Switzerland: Mouvement de la population de la Suisse 1877-1885, the data are available on the website of the “Office Fédéral de la Statistique”, in the years after 1885 the death data by cause, age and sex were no longer included. USA: Bureau of the Census, Mortality Statistics, various years.

Fig. 1c,d  TB death ratio female/male by age in 3 US states (white population only) and in Britain. The error bars are rather small and have been omitted for the sake of clarity; on average the coefficient of variation is of the order of 4%. Sources: Vital Statistics of the United States; website of the British “Office of National Statistics”, many thanks to Ms. Justine Pooley for her help.

It can be seen that the age interval in which $f/m > 1$ is basically determined by the TB death ratio.

\[3\text{In addition it can be noted that for Japan the curve is very similar.}\]
Fig. 2  All causes death ratio, female/male  The fact that the curves follow fairly closely the TB death ratios (although of course with a smaller amplitude) shows the key role played by TB mortality. Source: Bunle (1954).

Discussion of the effect

Female excess or male curtailment?

Is this effect due to an excess of female deaths or to an “abnormally” low number of male deaths? In an attempt to answer this question separate male and female data are shown in Fig. 1a,b. (male in black, female in red). Now, what should one understand by “normal” curves? The term “normal” is understood here as “most common”. The common pattern is that in a log-log plot the infant death rate is a downward straight line until the age of 10 after which it starts fairly suddenly to go upward (Berrut et al. 2016). The inset graphs in Fig. 1a,b show that the female curves begin to level off already around the age of 4. As a result they come above the curves of the male death rates and remain higher until the age of 25. Thus, it is the female rate (not the male rate) which behaves in an unusual way. In other words, the phenomenon is indeed an excess-female mortality.

Exogenous or endogenous?

As always in such situations, once the possible incidence of a recording artifact has been excluded, the effect can be due to exogenous or endogenous factors. Here exogenous would mean more contacts with pathogens or other external factors whereas endogenous would refer to physiological factors.

A possible exogenous factor which comes to mind is an occupational hazard. Let us examine this possibility more closely. The age interval over which the effect is observed is fairly broad. However, it is the
starting age which really matters. Why? Because, once TB cases in excess have appeared the disease will develop through its own dynamic in the sense that it will progress in each affected individual and also spread by contagion to other persons. If this argument is accepted, how should one determine the starting age? In the graph the data points are shown with error bars which correspond to ±σ. In order to raise the confidence level from 0.68 (which corresponds to ±σ to 0.96 (which corresponds to ±2σ we will consider that the starting point occurs when the ratio becomes equal to 1 + 2σ. This leads to a starting age of 5 in Switzerland and 6 in the US. The important point is that these ages are well before any industrial occupational activity. The only kind of activity that one can think of at that age would be domestic, for instance farm work. In most countries, the age of 6 marks the beginning of school attendance although it is far from clear why this should lead to an $f/m$ effect.

**Are there other diseases with more female than male deaths?**

One should remember that in the first half of the 20th century tuberculosis was the first cause of death. This makes the previous anomaly quite noteworthy. However one needs also to examine whether there are other diseases for which female deaths outnumber male deaths. More precisely, we wish to see if there are other diseases which show a female/male death ratio over 1 in the age interval 5-25?

A systematic investigation of British data for all the diseases mentioned in the International Classification of 1901 leads to the following findings.

- **Code 60, measles.**
  
  $0 - 5 : f/m = 0.88$, $5 - 15 : f/m = 1.14$, $15 - 44 : f/m = 2.00$

- **Code 740, anaemia and leucocythaemia (nowadays rather called leukocytosis, i.e. white cells in excess).**
  
  $f/m \sim 3$ in the age interval 10-45. However, there are only few deaths. In successive 5-year age groups the numbers of deaths for this code number are under 100.

- **Code 1060, cerebral haemorrhage and embolism.**
  
  $f/m \sim 2$ in the age interval 1-25. There are less than 30 deaths in each 5-year age group.

- **Code 1810, burns and scalds.**
  
  This was the most puzzling finding. In the age interval 5-20, $f/m \sim 3$; then in 20-45, $f/m \sim 1$; finally from 45 to 85, $f/m$ is again about 3.

In short, apart from the case of burns, for the age intervals under consideration, the other cases are of minor importance in terms of death numbers.

**Tuberculosis death ratio in developing countries**
In developed countries TB mortality has become close to zero except in old age.
However, in many developing countries TB is still an important disease. The question
that we wish to address is whether the \( f/m \) effect can be observed in such
countries?

**Defects of the WHO data base**

Before we can answer this question we must examine what statistical data are avail-
able. The data of the “World Health Organization” (WHO) provide a broad coverage
for almost all countries and TB features at the top of the list of diseases. However
for the objective that we have in mind there are three difficulties.:

- The data by age are limited to only three age groups, namely: \( I_1 = 0 − 15, \ I_2 = \)
  \( 15 − 60, \ I_3 = 60^+ \).
- In many developing countries the quality and completeness of the data is not
good. The WHO distinguishes 3 categories which are represented by 3 colors: “ma-
genta” means very incomplete, “cyan” means fairly complete, “blue” means good
quality data. Developed countries are blue, semi-developed countries are cyan and
almost all African countries are magenta. For our purpose this is of course most
unfortunate because it means that for the countries where TB may be most preva-
lent there are in fact no reliable data. That is why we will focus on semi-developed
countries.
- There is another cause of uncertainty which is due to the way the data are re-
ported. In the table the numbers of deaths are expressed in thousands but as there
is only one decimal digit a number such as 0.1 could mean 0.051 or 0.149 which
means that there is an uncertainty of \( (0.149 − 0.051)/0.1 = 100\% \). In other words,
the smaller the number of deaths, the lower its accuracy. For the same reason all
data for developed countries are reported as being 0.0; this means only that the real
death numbers are less than 0.05 thousands = 50. In countries with a small popula-
tion this may still represent a sizable death rate.

**Test of the \( f/m \) effect in developing countries**

Because of the limitation in the number of age-groups we cannot test the \( f/m \) effect
directly. The test must be done indirectly. How should one proceed?

For both \( I_1 \) and \( I_2 \) he WHO data allow us to compute the ratio \( f/m \). They are given
in Table 1b for several countries. Then, we must compare these ratios with the same
ratios for a country (for instance the US) for which the \( f/m \) effect is observed. It is

\footnote{In what follows age groups of older adults will be left aside. There are two reasons for that. The first is of course
because the \( f/m \) effect occurs in early years. In addition, one should remember that because of atypical clinical symptoms
the diagnosis of tuberculosis in elderly people is rather uncertain (Thomas et al. 2001).}

\footnote{Obviously this is not a sound way of reporting because it adds a “reporting uncertainty” to the “recording uncertainty”.
The data should be reported with the same number of digits whether the figures are small or large, e.g. 0.36 and 36 instead
of 0.4 and 36.1.}
at this point that a difficulty arises which must be considered more closely.

Fig. 3  TB death rate in the United States. From 1940 to the end of the 20th century the old-age component becomes more and more predominant. Sources: Linder et al. (1947, p. 248-254); Grove et al. (1968, p. 378-469); Wonder database of the Center for Diseases control” (CDC).

Table 1a  TB death ratios f/m and m/f in the age groups (0,15) and (15,60) in the US

| Year | female/male I₁ = (0,15) | male/female I₂ = (15,60) |
|------|-------------------------|--------------------------|
| 1910 | 1.2                     | 1.33                     |
| 1931 | 1.1                     | 1.27                     |
| 1943 | 1.2                     | 1.71                     |
| 1950 | 1.2                     | 2.16                     |
| 1954 | 1.1                     | 2.41                     |
| 1999 – 2015 | –                    | 2.64                     |

Notes: The symbol – means that the ratio is not well defined because the numbers of deaths are too small. It can be seen that for I₁ the ratio female/male remains stable around a value of 1.1. In contrast after 1931, as the deaths in the sub-interval (35,60) of I₂ become predominant, the ratio male/female increases from 1.3 to 2.6. Sources: Vital Statistics of the United States, Wonder database of the “Centers for Diseases Control” (CDC).

Fig. 3 shows that the parts of the curves in the age-interval (0,15) keep the same structure. On the contrary, in the age-interval (15,60) the old age component becomes more and more predominant especially in the decades after 1940. If one remembers that, as shown in Fig. 1b, f/m > 1 in the age-interval (15,30) but f/m < 1 in the age-interval (35,60), it becomes clear that over the interval (15,60) the ratio m/f will become larger as old-age deaths become predominant. This is indeed what appears in table 1a.
Table 1b  TB death ratios $f/m$ and $m/f$ in the age groups (0,15), (15,60) in various countries

| Country      | female/male $I_1 = (0,15)$ | male/female $I_2 = (15,60)$ |
|--------------|-----------------------------|-----------------------------|
| China        | 1.0                         | 1.60                        |
| India        | 1.2                         | 1.50                        |
| Philippines  | 0.91                        | 1.64                        |
| South Africa | 0.84                        | 3.51                        |
| Thailand     | 1.0                         | 1.67                        |

Notes: The data are for 2008. The value 3.51 for $I_2$ in South Africa is an outlier not only with respect to the other countries but also with respect to the whole range 1.3-2.6 displayed in Table 1a. Therefore, it is likely that this figure is not correct; probably female deaths were under-estimated by a factor of 2. Source: World Health Organization 2011: Mortality and burden of disease estimates for WHO member states in 2008.

With the exception of South Africa, the figures by country given in Table 1b are consistent with the longitudinal data for the United States given in Table 1a. The case of South Africa shows that, most likely, female deaths were under-reported by a factor of 2. With a $h/f$ ratio of 1.16, Iran is another outlier (this time the male deaths would seem to have been under-reported); however in this case the fact that only one decimal digit (male deaths=0.6, female deaths=0.7) is given in the WHO report makes the conclusion somewhat uncertain.

In other words the $f/m$ effect reported in this paper can be used to probe the reliability of the data published by national statistical agencies. As a matter of fact, according to the accompanying explanations, the data published in the WTO report are not exactly identical to the figures provided by member states but have been revised by the WHO to ensure “cross national comparability”. This makes the discrepancy observed in Table 1b even more surprising.

Conclusion

The female/male death rate ratio for TB in all industrialized countries for which appropriate data during the late 19th century through to the mid-20th century are available is greater than unity for the age range 10-35 whereas for all other diseases the ratio is less than unity. From our analysis we can deduce that in some developing countries (we pointed out the case of South Africa) deaths from TB are being under-reported by factors as large as two. Once detailed data for developing countries become available we shall be able to test the veracity of this prediction.

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6It has been suggested that such under-reporting may be the result of stigma faced by women with TB in developing countries.
Acknowledgments  We wish to express our sincere thanks to Ms. Justine Pooley of the “Office of National Statistics” for introducing us to detailed British mortality data.

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