Analysis of air pollution mortality in terms of life expectancy changes: relation between time series, intervention and cohort studies

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Abstract

Background:
Information on life expectancy change is of great concern for policy makers, as evidenced by the discussions of the so-called "harvesting" issue, i.e. the question how large a loss per death corresponds to the mortality results of time series studies.
Methods:
Whereas most epidemiological studies of air pollution mortality have been formulated in terms of mortality risk, this paper shows that a formulation in terms of life expectancy change is mathematically equivalent but offers several advantages: it automatically takes into account the constraint that everybody dies exactly once, regardless of pollution; it provides a unified framework for time series, intervention studies and cohort studies; and in time series and in intervention studies it yields the life expectancy change directly as a time integral of the observed mortality rate.
Results:
Results are presented for life expectancy change in time series studies. Determination of the corresponding total number of attributable deaths (as opposed to the number of observed deaths) is shown to be problematic. The time variation of the mortality after a change in exposure is shown to depend on the processes by which the body can repair air pollution damage, in particular on their time constants. Hypothetical results are presented for repair models that are plausible in view of the available intervention studies of air pollution and of smoking cessation. If these repair models can also be assumed for acute effects, the results of cohort studies are compatible with those of time series.
Conclusions:
The proposed life expectancy framework provides information on the life expectancy change in time series studies, and it clarifies the relation between the results of time series, intervention and cohort studies.

1. Background

There has been much debate about the significance of the mortality impacts (sometimes called "acute mortality") observed in time series (TS) studies, an issue often referred to as harvesting or mortality displacement [see e. g. references 1, 2]. The key question is whether the observed deaths have been advanced by only a few days or whether the loss of life expectancy (LE) is much larger. This issue is crucial for the monetary valuation and for policy implications [3, 4].

For a new perspective on this issue and on the relation between TS studies, intervention studies and cohort studies, the present paper formulates the analysis directly in terms of LE change, after showing that such a formulation is mathematically equivalent to the conventional formulation in terms of mortality risk. An LE formulation offers several advantages: it automatically accounts for the fact that everybody dies exactly once, regardless of pollution; it provides a unified framework for time series, intervention studies and cohort studies; and it yields directly a quantity of interest to policy makers.

The constraint of fixed total probability of death can be appreciated by comparing an accident that instantly kills individuals in normal health (the LE loss ΔL is equal to the entire remaining LE) with a mortality risk that reduces LE by a short amount of time ΔL. The time dependence of the mortality rates is different. Whereas for an accident the mortality rate changes only at the moment of the accident, for the risk with the short ΔL the mortality rate increases initially but then decreases (relative to a reference population without the risk) during the ensuing period ΔL because of the individuals who would have died then but whose deaths were advanced. The delayed decrease can be called "compensating change". Even though TS studies until now have not taken this constraint into account, it has not affected the results. For TS the compensating change becomes a more or less uniform background as a result of the fluctuations in concentration because there is a wide range of individual ΔL. In cohort studies the constraint is implicit in the study design, because they observe the net effect of chronic exposure. But the constraint is crucial for understanding the LE change in TS studies [see e.g. references 5, 6] and in intervention studies [7 - 10].

A unified framework for TS and cohort studies has also been proposed recently by Burnett et al [11] who show that both types of study measure essentially the same risk function. However, these authors do not take into account the time variation of the risk function due to the compensating change, i.e. that the increased mortality due to a pollution peak now implies a decreased mortality at a later time.

The present paper shows that the mortality fluctuations observed in TS studies are proportional to the instantaneous time derivative of the life expectancy. They are the result of exposures both in the recent and the distant past, but a strong correlation with the most recent exposure is observed since the fluctuations due to past exposures tend to average to zero. The acute LE loss due to a pollution peak can be calculated by integrating the mortality rate over the observation window of a TS study (typically 1 day) and results are presented for O_3 and PM_{10} (including studies that have extended the observation window to 60 days). In intervention studies the (approximately) constant difference between exposures before and after the intervention makes it possible to determine the LE change by integrating the change of the mortality rate over time. Cohort studies [12 - 14] measure a long term relative risk from which one can calculate [15 - 18] the ultimate LE gain that can be achieved by a permanent

reduction of air pollution; it is equal to the LE change at the end of a sufficiently long intervention study.

I also address the determination of deaths that can be attributed to air pollution. By contrast to the acute LE loss due to a pollution peak, the corresponding total number of deaths (in the sense of all deaths that are advanced by the peak) cannot be measured by epidemiology. The customary multiplication of mortality rate and relative risk increase of TS studies yields only a lower bound. This also prevents the determination of the LE loss per air pollution death.

Unfortunately the available data are not sufficient to determine all quantities of interest, for example the relation between the results of TS, intervention and cohort studies, and the contribution of acute mortality to the total LE loss from chronic exposure. Since one needs models for the processes by which the body repairs air pollution damage, the remaining sections of the paper are somewhat speculative. Whereas the phenomenon of repair is well documented by studies of smoking cessation [19 – 21], less is known about repair of air pollution damage [for a review see 22]. In view of the available information it is plausible to assume that the LE change due to air pollution is proportional to the time integral of past concentrations weighted by exponential decay factors. Using model parameters suggested by the data, results are plotted for the evolution of mortality after an intervention. They indicate that the change in mortality rate is largest soon after the intervention. After a time long compared to the longest time constant of the repair processes the mortality rate returns to a level close to the one before the intervention (even though the LE gain is permanent), a consequence of the fact that everybody will die sooner or later.

With these models the results of TS, intervention and cohort studies are remarkably compatible with each other. The contribution of acute mortality to the total LE loss of chronic exposure is equal to the relative risk increase times the time constant of the repair processes that are significant immediately after a pollution peak.

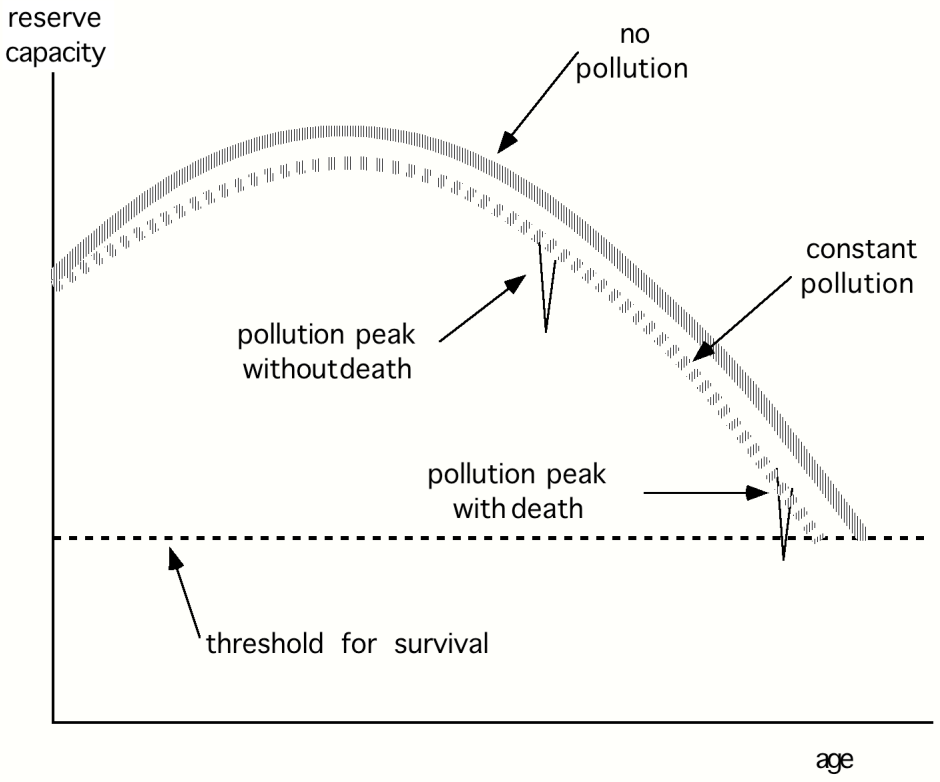
2. Methods

2.1. A Qualitative Model for Effects of Air Pollution

Discussions of acute mortality impacts are often phrased in terms of a pool of individuals who are so frail that they succumb to a pollution peak. A large stationary population always contains many individuals who are so frail that an additional stress imposed by an air pollution peak can advance their death. For example, at any moment roughly 1% of a stationary population with life expectancy 75 yr are within the last nine months of their life and thus extremely frail. Illness can cause temporary episodes of frailty.

But the fact that pollution-related deaths occur only in the frail pool does not mean that pollution has no effect on the rest of the population. Rather it contributes to reducing the reserve capacity of the body, as illustrated very schematically in Fig.1 without trying to give a precise definition of reserve capacity; it is inversely related to frailty (Fig.1 is inspired by a graph in chapter 4 of NRC [23]). A young healthy body has enough reserve capacity not to feel the relatively slight reduction due to acute or chronic pollution exposure. But the old or sick may be pushed below the threshold where death occurs. As individuals age they inevitably move into the pool of the frail. By diminishing the reserve capacity, pollution advances the passage into the frail pool and shortens life expectancy. On average the inflow to the frail pool equals the outflow. Time series studies measure the effect of pollution fluctuations on the outflow from this pool, as reflected in the number of deaths per day.

Fig.1. Schematic sketch of reserve capacity of the body as function of age, and effect of air pollution. There are natural fluctuations, e.g. due to illness, as suggested by the width of the lines. Air pollution lowers the curve. The effect of pollution on mortality (shown exaggerated for the sake of illustration) becomes observable in an epidemiological study only to the extent that there are individuals whose reserve capacity is so low that the extra stress pushes them below the threshold for survival.



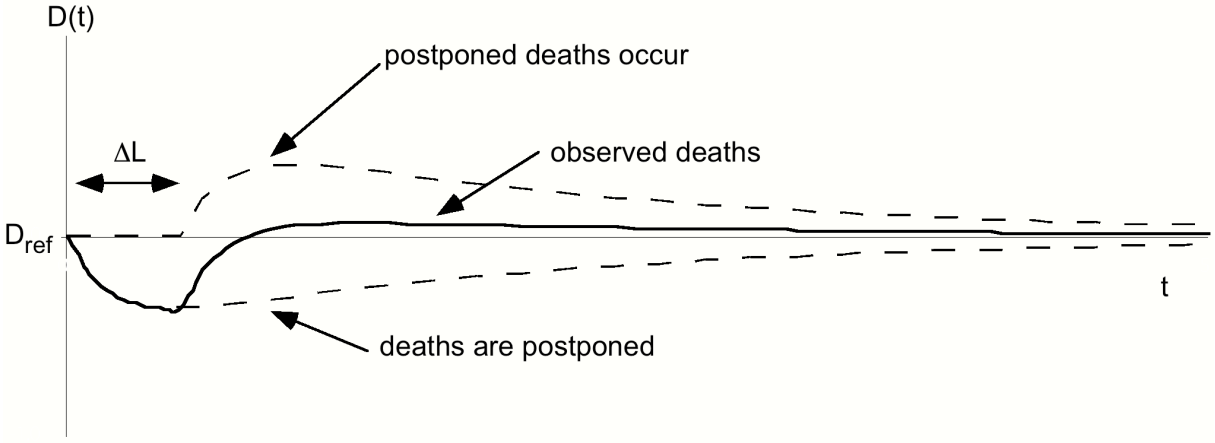
2.2. Change of Mortality After Change of Exposure

Fig.2 shows a qualitative picture of the effect of a reduction of exposure on D, the number of deaths per day in a stationary population. In these graphs the lower dashed line represents the individuals whose deaths are postponed, the upper dashed line the postponed deaths when they do occur. The dashed lines are not observable. Only the net effect can be observed, shown by the heavy solid line, which is the sum of these dashed lines. The exposure reduction is temporary in parts a) and b), permanent in c). In part a) all individuals enjoy the same LE gain ΔL, so the upper dashed line is the mirror image of the lower one, but shifted by ΔL. In part b) there is a distribution of different LE gains; it broadens the upper dashed curve. After the initial drop the solid line moves above D_{ref}; that is the compensating change mentioned in the Introduction. The onset of the compensating change gives a rough indication of ΔL.

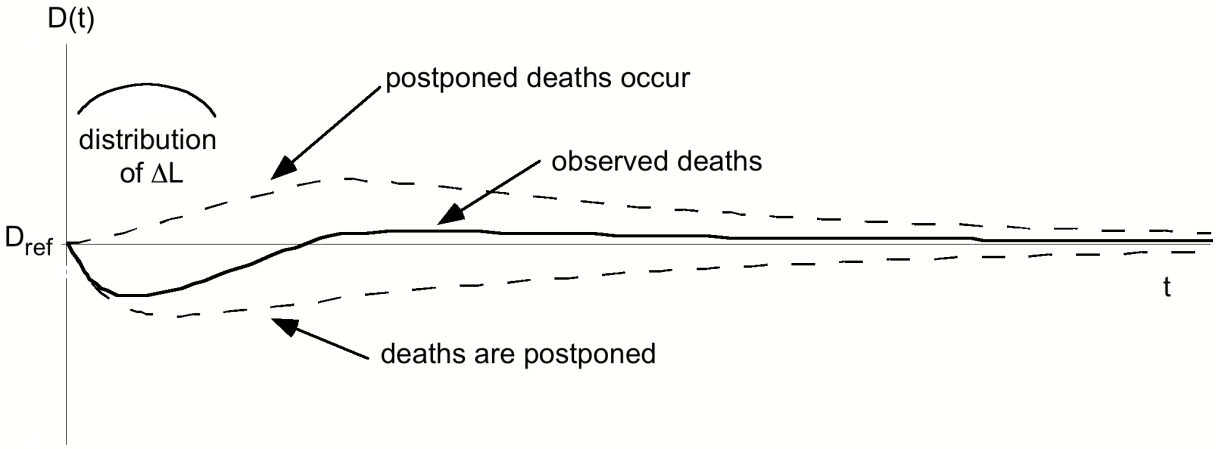
Part c) shows the effect of a permanent decrease of exposure (for simplicity for the case where all individuals enjoy the same LE gain ΔL). Now the postponed deaths reach a constant asymptotic level. The observable death rate drops at first, but then increases again, gradually reaching the original level even though the LE gain is permanent. That D must eventually return to the original level follows from the fact that in a stationary population the birth rate is constant and equal to D. Deaths have been postponed but not avoided. Eventually a new stationary state is reached, with a longer life expectancy and thus a larger population (for the same birth rate). The mortality rate is the ratio of D and population size; it decreases permanently whereas D returns to the original value.

Fig.2 Qualitative picture of the effect of a reduction of exposure on D, the number of deaths per day. Thick solid line = observable deaths, thin dashed line = deaths shifted by pollution.

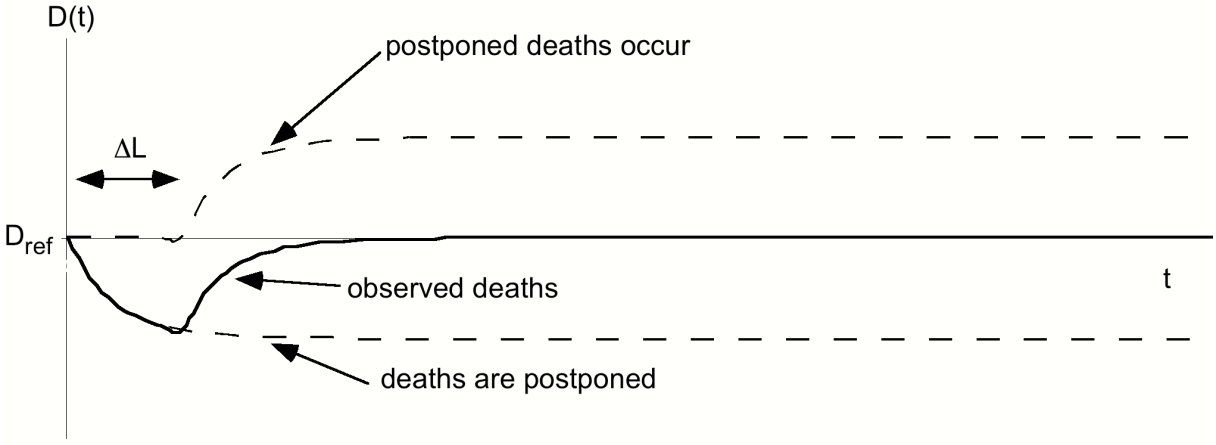
a) temporary reduction of exposure, all individuals have the same gain ΔL.



b) temporary reduction of exposure, distribution of different individual gains.



c) permanent reduction of exposure, all individuals have the same gain ΔL.



2.3. Relation between Age-specific Mortality and Life Expectancy (LE)

To obtain quantitative results it is helpful to recall some well known elements of survival analysis. Let $\mu(x)$ be the age-specific mortality rate, defined such that someone who has reached age x has a probability $\mu(x)\,\Delta x$ of dying between x and $x + \Delta x$ (usually one chooses $\Delta x = 1$ yr). The fraction of a birth cohort of initial age x_0 that survives to age x is called survival function $S_\mu(x_0, x)$. As shown in Appendix A, it is given by

$$S_\mu(x_0,x) = \exp\left[-\int_{x_0}^{x} \mu(x')\,dx'\right] \quad , \tag{1}$$

and the remaining LE of a cohort of age x_0 can be calculated as

$$L(x_0) = \int_{x_0}^{\infty} S_\mu(x_0,x)\,dx \quad . \tag{2}$$

If $\mu(x)$ is given, $S_\mu(x_0,x)$ and $L(x_0)$ are thus uniquely determined. Vice versa, the function L(x) determines $\mu(x)$, as shown in Appendix A. Because of the one-to-one relation between $\mu(x)$ and life expectancy L(x), the mortality impact of air pollution can be analyzed in terms of a change in mortality rate or in terms of the corresponding LE change ΔL. Here and throughout the paper ΔL is the change per person, averaged over the population or population segment under consideration.

2.4. Relation between LE Change and Mortality after Intervention

Let us evaluate the change in mortality and LE as a function of time t after a permanent reduction of exposure at $t = 0$, the population having been stationary before the intervention. Here I look only at the entire population; more detailed equations for the effect on a cohort of a given age are derived in Appendix B. Consider a large stationary population of N individuals and the number of deaths per time, designated by D. It will be convenient to look at D because its change can be related directly to the postponement of the individual deaths. The population-averaged mortality rate μ, i.e. the average of $\mu(x)$ over the age distribution, is the ratio

$$\mu = D/N \quad . \tag{3}$$

Let μ_{ref} be the mortality before, $\mu(t)$ the mortality after an intervention that reduces air pollution permanently by a constant amount. The relative risk is

$$RR(t) = \mu(t)/\mu_{ref} \tag{4}$$

and it corresponds to an LE change

$$\Delta Lt) = L(t) - L_{ref} \quad . \tag{5}$$

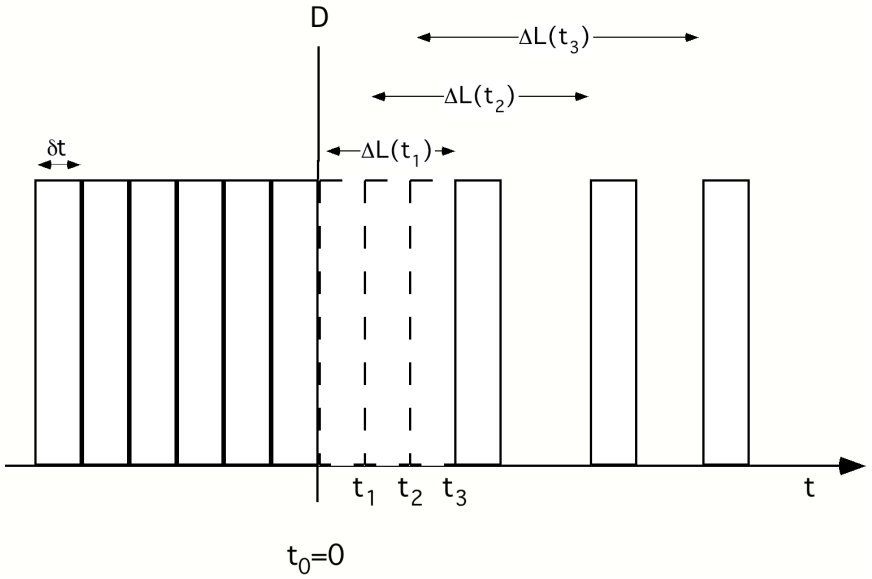
D and N are functions of the time t after the intervention. D and N before the intervention, designated by D_{ref} and N_{ref}, are independent of time because the population is stationary. D_{ref} is equal to the birth rate. To find the evolution of D(t) and N(t) after the intervention and the relation between $\mu(t)$ and $\Delta L(t)$, let us begin by assuming a homogeneous population in the sense that all individuals experience the same LE gain $\Delta L(t)$.

It is helpful to consider small discrete time steps δt and to plot D as a sequence of boxes of width δt, the height representing the number of deaths during δt, see Fig.3. Before the intervention D = D_{ref} = constant and the spacing of the boxes is uniform. After the intervention, the deaths occur later. The effect of this postponement of deaths on D can easily be understood by considering the shift of the boxes to the right, as shown in Fig.3 for t > 0. This results in an increase of the spacing between the boxes. D(t) is proportional to the density of the boxes.

If the entire gain occurred instantaneously at t=0, all deaths would be postponed by the same amount; thus the spacing would again be dense and uniform after the first shift. In reality the gain ΔL(t) increases gradually with t, and the resulting spacing depends on its rate of change

$$\Delta L'(t) = d\Delta L(t)/dt \quad . \tag{6}$$

Fig.3. Schematic sketch to illustrate the derivation of the evolution of the rate D of deaths per time after a step decrease of pollution. D is proportional to density of boxes (deaths per small time step δt). Dashed boxes show from where the boxes are shifted by the intervention. ΔL(t) = LE gain at time t after intervention.



To find the density of boxes, note that between $t_i + \Delta L(t_i)$ and $t_{i+1} + \Delta L(t_{i+1})$ there is one box. For small δt this time interval is $\delta t + \Delta L'(t_i)\,\delta t$, and the density is 1 box/$[\delta t + \Delta L'(t_i)\,\delta t]$. At time $t + \Delta L(t)$ the ratio of the density of boxes after and before the intervention is therefore

$$\frac{density\ at\ t + \Delta L(t)}{density\ at\ t < 0} = \frac{\delta t}{\delta t + \Delta L'(t)\delta t} = \frac{1}{1 + \Delta L'(t)} \tag{7}$$

and since D is proportional to the density one obtains

$$D(t+\Delta L(t)) = D_{ref}/(1 + \Delta L'(t)) \qquad \text{for } t > 0 \quad . \tag{8}$$

For a reduction of the exposure ΔL(t) increases with t, ΔL'(t) is positive and D is less than D_{ref}. For later reference I note that Eq.8 also holds for the case where the exposure increases and ΔL'(t) is negative. When the asymptotic gain ΔL_∞ has been reached, ΔL'(t) vanishes and D(t) is again equal to the initial value D_{ref} because the birth rate has remained constant. But

the mortality rate μ has decreased permanently because the population size N has increased in proportion to the LE.

So far I have assumed that all individuals have identical gains. In reality there is a distribution of different individual gains. Averaging the quantity 1 + ΔL'(t) over this distribution, the ratio $D_{ref}/D(t)$ is replaced by its average over the individual gains. For the small changes involved in air pollution studies the average of $D_{ref}/D(t)$ is very close to D_{ref} divided by the average D(t).

The LE gain ΔL(T) after a time T following the intervention can be obtained by integrating the measured data for $D_{ref}/D(t+\Delta L(t))$ of Eq.8

$$\Delta L(T) = \int_0^T \Delta L'(t)\, dt = \int_0^T \left(\frac{D_{ref}}{D(t + \Delta L(t))} - 1 \right) dt \quad , \tag{9}$$

since ΔL(0) is of course zero. This is an integral equation because ΔL appears on both sides. However, in practice one can approximate the result by integrating in steps, obtaining the gain at t_{k+1} from the one at t_k

$$\Delta L(t_{k+1}) = \Delta L(t_k) + \int_{t_k}^{t_{k+1}} \left(\frac{D_{ref}}{D(t + \Delta L(t_k))} - 1 \right) dt \quad . \tag{10}$$

The ultimate gain ΔL_∞ is the limit reached when $T \to \infty$; in practice the finite observation period yields of course only a lower bound (note that the integrand is positive-definite for a permanent pollution decrease), but a leveling off of the integrand would indicate that one is getting close to the ultimate gain. The units of ΔL(T) are the same as the ones chosen for t since the integrand is dimensionless. The result is the gain per person, averaged over the study population.

The mortality μ(t), and hence the relative risk, can be obtained by dividing D(t) by the size of the respective populations according to Eq.3. Since the birthrate is constant, the population size N(t) increases with LE, ultimately reaching

$$N_\infty = N_{ref}\, (L_{ref} + \Delta L_\infty)/L_{ref} \tag{11}$$

when new stationary conditions are established, L_{ref} being the LE before the intervention. Whereas D returns asymptotically to the initial value, the mortality rate μ is lower because people live longer and the population size has increased.

The exact time dependence of N(t) and μ(t) would require a more detailed calculation because during the transition to the new stationary state different age groups increase differently; but in any case N(t) is bounded by N_{ref} and N_∞. Since the population-average LE gain is short compared to L_{ref} (at most a few months compared to about 75 years, see Eq.17 below), the change of the population size is entirely negligible in practice considering the uncertainties of the data, and one can use the approximation

$$RR(t) = \mu(t)/\mu_{ref} \approx D(t)/D_{ref} \quad . \tag{12}$$

Since the change in relative risk ΔRR(t) due to typical exposures is small compared to unity, one can further approximate Eq.9, with negligible error, by

$$\Delta L(T) \approx - \int_0^T \Delta RR(t + \Delta L(t))\, dt \quad . \tag{13}$$

Stepwise integration as in Eq.10 can be used, although the ΔL(t) on the right hand side can be neglected if T is relatively short as shown by the example in Section 3.1.

To conclude this section I emphasize that the key result is Eq.9 (or 13) which yields the LE change after an intervention as time integral of the observed death rate (or change of relative risk). As written, it is appropriate for the entire population, but with the obvious addition of a label x for age it also holds for a constant age segment or for a birth cohort of age x, as shown in Appendix B.

3. Results

3.1. LE Change for Time Series

In the LE framework the mortality measured by typical TS studies corresponds to an intervention study that lasts only one day. Thus the LE change is given by Eq.13 with T = 1 day. It represents the acute loss of life immediately after a pollution peak. Let us insert into Eq.13 the relative risk for 10 μg/m^3 of PM_{10} found in the analysis of the NMMAPS data for 90 cities in the USA, as recently revised to correct for the GAM problem [24]; it is ΔRR(0) = 0.0021 for the GLM version of the analysis (the t = 0 indicates that this is for the first day). The result is

$$- \Delta L(1 \text{ day}) = \Delta RR(0) * 1 \text{ day} \tag{14}$$
$$= 0.0021 \text{ days for acute mortality from 1 day at 10 } \mu g/m^3 \text{ } PM_{10}.$$

It would be almost twice as high for the original GAM estimate of ΔRR(0) = 0.0041. The minus sign indicates a loss for a risk increase.

Recently Schwartz [2] and Zeger et al [1] have succeeded in extending the exposure duration up to T = 60 days, measuring in effect the average relative risk ΔRR_{av} corresponding to the average concentration Δc_{av} of PM_{10} during the period T. They find that $\Delta RR_{av}/\Delta c_{av}$ increases with T at least up to 60 days, the longest for which their method could be used. For all-cause mortality Schwartz found that $\Delta RR_{av}/\Delta c_{av}$ increased linearly with T and at 60 days was about twice that for one day. Fairly similar results have been found in other studies that have extended the observation window [10]. Since ΔRR_{av} is the average from t = 0 to T of the relative risk ΔRR(t) at time t, the result of Schwartz implies that

$$\Delta RR(t) = \Delta RR(0)\, (1 + 2\, t/60 \text{ days}) \quad . \tag{15}$$

Inserting this into Eq.13 yields

$$- \Delta L(T) = \Delta RR(0)\, T\, (1 + T/60 \text{ days}) \qquad \text{up to 60 days;} \tag{16}$$

it increases in linear plus quadratic fashion, reaching 0.0021 * 60 days * 2 = 0.25 days after 2 months. This is the population average LE loss per person. For sensitive subgroups the loss is

of course much higher, but at the present time not enough is known about individual sensitivities.

It is interesting to compare these numbers with the ultimate LE gain ΔL_∞ achievable by a permanent reduction of PM_{10}. That can be calculated on the basis of the cohort studies such as the one Pope et al [14] which are essentially steady state comparisons of the effects of different exposures. Several authors have published such calculations [4, 15 - 18], based on the cohort study of Pope et al [14], with essentially the same result for the same long term relative risk. For example, Rabl [4] found

$$-\Delta L_\infty = 92 \text{ days} \qquad \text{for lifetime exposure at 10 } \mu g/m^3 \text{ of } PM_{10}. \qquad (17)$$

This is very much larger than $\Delta L(1 \text{ day}) = -0.0021$ days of Eq.14, for two reasons: the latter is for a single day of exposure, and it includes only acute effects. The contribution of acute mortality to the LE loss from chronic exposure will be addressed in Section 4.2.

For O_3 only acute mortality has been measured until now. The meta-analysis by the World Heath Organization [25] provides a ΔRR for all-cause mortality of 0.003 per 10 $\mu g/m^3$ increase in the daily maximum 8-hour mean O_3. Analogous to Eq.14 the corresponding LE loss is $\Delta L(1 \text{ day})_{acute} = -0.003$ days.

3.2. LE loss per death

For acute mortality the LE loss per air pollution death can be obtained by dividing the LE loss of Eq.14 by ΔN_{deaths}, the number of acute deaths that are attributable to a pollution peak. If one calculates the latter by multiplying the daily mortality by the relative risk, one finds for a peak of one day

$$\Delta N_{deaths-} = (0.01/365) * 0.0021 = 5.8E\text{-}8 \qquad \text{for 10 } \mu g/m^3 \text{ } PM_{10}, \qquad (18)$$

taking a typical mortality for Europe and North America of $\mu = 0.01$ per yr per person together with $\Delta RR(0) = 0.0021$ (note that $\Delta N_{deaths-}$, like ΔL, is normalized per person). I have added the subscript – to indicate that this is a lower bound because it corresponds to the observed deaths, i.e. the solid black line in Fig.1. The corresponding upper bound for the loss per death is

$$\Delta L(1 \text{ day})/\text{death} < 100 \text{ yr/death} \qquad \text{independent of exposure} \qquad (19)$$

because both numerator and denominator are proportional to exposure. This is clearly an upper limit as indicated by the subscript +. Since the real loss per death is certainly much smaller, the number of attributable deaths must be much larger than what is observable.

The attributable deaths are all the deaths that have been advanced by pollution, i.e. the thin dashed line in Fig.1. Unfortunately that is not known. If everybody's death is advanced somewhat, even if only by an undetectably small amount, ΔN_{deaths} would be equal to (0.01/365). If only a fraction f_{sens} of sensitive individuals is thus affected,

$$\Delta N_{deaths+} = (0.01/365) * f_{sens} \qquad \text{independent of exposure,} \qquad (20)$$

and hence the lower bound is

$\Delta L(1\ \text{day})/\text{death} > 0.21\ \text{yr}/f_{sens}$ for 10 $\mu g/m^3$ PM_{10}, proportional to exposure. (21)

3.3. Models for the Repair Processes

Whereas all the results up to this point follow from the data, the rest of the paper invokes models of the action of pollution damage and is thus more speculative. A model is necessary to estimate how the mortality rate will change during an intervention study, beyond the period for which data are available (60 days for PM_{10}, at most a few days for O_3 and SO_2).

Let us assume that LE loss is proportional to the concentration c of the pollutant. Furthermore, past concentrations have less impact now because the body is able to repair some of the damage, an ability well documented in the case of ex-smokers [19 - 21]. To account for repair, it seems plausible to assume exponential decay for the effect of past exposures. If there is only a single time constant τ one obtains the following model for the LE loss at time t due to a sequence of concentrations $\{c(t')\}$ between t_0 and t

$$\Delta L(t) = - k \int_{t_0}^{t} c(t') \exp[-(t-t')/\tau]\, dt' \quad , \tag{22}$$

where c(t') is the concentration at time t' and k is a proportionality constant. The minus sign is introduced because concentrations are positive and ΔL is a loss. A more realistic model contains several terms with different time constants, as described in Appendix C. If the body could not recover, the time constant(s) would be infinite and the LE loss would depend only on the cumulative exposure, not on its distribution over time

Leksell & Rabl [15] reviewed the studies of ex-smokers, especially the one by Doll et al [20], one of the most comprehensive long term studies of smokers and ex-smokers. They found that the recovery can be approximated quite well by an exponential decay model with two time constants: a time constant of 1.5 years with weight 0.3 and one of 13 years with weight 0.7. Similar conclusions can be drawn from the data in USDHHS [19].

Applying time constants from smoking studies to air pollution entails of course uncertainties. For PM the similarities in pollutant composition and in the nature of the health end points may be close enough for this purpose. Röösli et al [22] have analyzed the two available intervention studies that involve PM_{10} and found a time constant of 1.1 yr for the Utah steel mill intervention [7] and 9 yr for the intervention in Dublin county [9]; these values are consistent with those from smoking if one notes that the duration of the Utah intervention was only about one year, to short to allow the determination of longer time constants, whereas the change in Dublin was permanent but the study period of Clancy et al covered only six years. For other pollutants such as O_3 and SO_2 the estimation of time constants is more problematic.

At this point I use a model with a single time constant, for the purpose of illustration. For a permanent step decrease Δc of the concentration the LE gain is

$\Delta L(t) = - k\, \Delta c\, \tau\, [1 - \exp(-t/\tau)]$ with t = time after decrease . (23)

The ultimate gain, for $t \to \infty$, is

$$\Delta L_\infty = - k \Delta c \tau \quad . \tag{24}$$

One could include an age dependence in $\Delta L(t)$ and k, although the available data do not show any significant variation with age [26].

Since some of the repair probably does not begin immediately, some of the LE gain is delayed relative to the model of Eq.23. A more realistic model would include a distribution $p(\lambda)$ of different lags λ between exposure and LE change, replacing Eq.23 by

$$\Delta L(t) = - k \Delta c \tau \int_0^t d\lambda \, p(\lambda) [1 - \exp(-(t-\lambda)/\tau)] \quad . \tag{25}$$

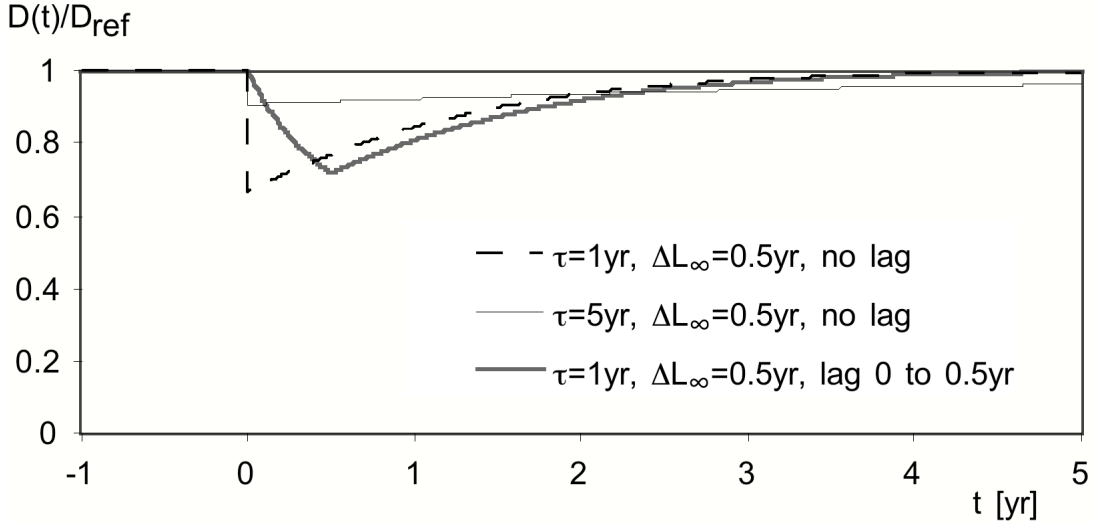
3.4. Possible Outcomes

Results are plotted in Fig.4, for three models. For all of them D(t) drops to a minimum soon after the intervention, but then increases again, becoming almost indistinguishable from the old values after several time constants. Without lag the initial drop is abrupt and has magnitude

$$D(0)/D_{ref}(0) = 1/(1 + \Delta L'(0)) = 1/(1 - k \Delta c) \quad \text{if no lag,} \tag{26}$$

regardless of the number of time constants in the model. With a distribution of lags the drop is gradual, as shown by the thick gray line in Fig.4 for which a uniform distribution of lags from 0 to 0.5 yr has been assumed arbitrarily. The area between the curve and the line $D(t)/D_{ref} = 1$ is equal to ΔL_∞.

Fig.4. Plot of deaths per time D(t), before and after intervention, for a stationary population. Results are shown for model with one time constant τ and $\Delta L_\infty = 0.5$ yr.



4. Discussion

4.1. Relation between Time Series and Cohort Studies

Even though the designs of cohort and time series studies are very different, in particular with regard to the accounting for characteristics of individuals, the results should be consistent to the extent that the end point is comparable. That time series and cohort studies have a common ground has also been shown by Burnett et al [11], formulated in terms of relative

risk (hazard function). Since the models of Sections 3.3 and 3.4 yield the entire time dependence of the mortality after a change in exposure, they imply a relation between the results of TS and cohort studies.

In these models the frail pool is implicit: it consists of the individuals who are going to die in the near future and whose deaths would be advanced by a pollution peak to the days following the peak. The LE change in these equations expresses the total effect of pollution on a stationary population, without distinguishing between acute effects from recent exposure and chronic effects from past exposure.

If the models are also valid for acute effects, they can be applied to a TS of fluctuations because it does not matter whether concentrations increase or decrease: the models are linear and the exposure for each new day is added to the previous exposures. The concentrations are always positive, whether increasing or decreasing. The effects are symmetric between increases and decreases. A single peak of duration t is equivalent to the superposition of a permanent increase and a permanent decrease of equal magnitude t later. The change in mortality that would be found in a time series during the first day (or days) after a pollution peak is the change during the first day (or days, up to t) in Fig.4.

As an example consider the model of Eq.25 with one time constant τ and a distribution $p(\lambda)$ of lags, applied to the entire population. With the approximations already made in Section 3.1 for the relation between $\Delta RR(t)$ and $\Delta L'(t)$ for short times t one obtains

$$\Delta RR(t)/\Delta c = k\, P(t) \qquad (27)$$

with

$$P(t) = \int_0^t d\lambda\, p(\lambda) \exp(-(t-\lambda)/\tau) \quad . \qquad (28)$$

With the TS result of $\Delta RR(0)/\Delta c$ = 2.1E-03 per 10 $\mu g/m^3$ PM_{10}, Eq.14, this fixes the relation between k and P(t) at t = 1 day

$$k = 2.1E\text{-}03/P(1day) \text{ per } 10\ \mu g/m^3\ PM_{10} \quad . \qquad (29)$$

On the other hand, combining Eqs.17 and 24 for the LE loss ΔL_∞, one obtains

$$k\,\tau = 0.23 \text{ yr per } 10\ \mu g/m^3 \text{ of } PM_{10}. \qquad (30)$$

Assuming τ around 10 yr one finds k=0.023 per 10 $\mu g/m^3$. Thus the two estimates of k agree if P(1day) = 0.0021/0.023 = 0.09, i.e. if only 9% of the repair begins during the first day. Of course, the epidemiological estimates are quite uncertain, and the model for repair is speculative and crude, especially if it contains only one time constant. Nonetheless it is encouraging that the two estimates of k are compatible.

4.2. Contribution of Acute Mortality to LE Loss from Chronic Exposure

The LE loss of Eq.14 is the acute mortality, i.e. the mortality during the first day of a one-day of exposure. For health impact assessments of pollutants for which only TS results are available, one needs to evaluate the acute impacts of successive one-day exposures. That is

not simply the product of the one-day impact times the exposure duration because past exposures are reduced by the repair capacity of the body. The LE loss of Eq.14 cannot be used directly because it is for a single peak.

Let us split the LE change of Eq.25 into an acute contribution ΔL_{ac} plus the rest, the acute term being the effect of each day's exposure during that same day. Assuming a one-time constant model for the acute term one finds, analogous to the derivation of Eq.24, that the cumulative change resulting from an infinite series of one day exposures to Δc is

$$\Delta L_{ac}(\infty) = - k_{ac} \Delta c \tau_{ac} \quad . \tag{31}$$

Since the change $\Delta L(1\ day) = \Delta RR(0) * 1\ day$ (see Eq.14) from a single day is entirely due to acute effects, we can set k_{ac} equal to k P(t) of Eq.27 and obtain

$$\Delta L_{ac}(\infty) = \Delta L(1\ day) * \tau_{ac}/1\ day \quad . \tag{32}$$

For acute effects a time constant around 1.5 year is plausible because it corresponds to time constants for short term cardiovascular benefits found in smoking cessation studies [21]. That implies $- \Delta L_{ac}(\infty) = 0.0021$ days * 365 * 1.5 = 1.2 days, a little more than 1% of the total acute + long term $- \Delta L_{\infty} = 92$ days of Eq.17.

In previous publications a different approach to estimate the LE loss due to acute mortality has been used by the ExternE project series [3], namely calculating a number of deaths as product of baseline mortality rate and ΔRR and multiplying it by assuming 6 months as LE loss per death. Whereas the resulting ratio of acute over total LE loss for PM_{10} was also about 1%, the method is not correct for several reasons:

- the total number of attributable deaths is not known as explained in Section 3.2;
- the LE loss per death is not known;
- the calculation does not take into account the effect of repair because it simply multiplies one-day impact by exposure duration.

Thus number of air pollution deaths, which was shown [4] to be meaningless for cohort studies (total air pollution mortality) is meaningless even for acute mortality. The approach of Eq.32 has the advantage of starting from a solid basis, namely the LE loss due to a single pollution peak; of course, it is also problematic because it needs to invoke a repair model.

There are question marks about the models that I have assumed, quite apart from the number of time constants and the parameter values. In particular, the triggering of deaths among frail individuals during a pollution peak (via heart attacks that can shorten the life of a few individuals by a large amount) is different from the accumulation of damage among the general population (small incremental LE loss for many individuals). So the repair model may not be correct for all acute effects, and the symmetry between increases and decreases of exposure may be only approximate. In that case the model(s) for LE change as function of exposure would have to be modified by an explicit model for the frail pool.

5. Conclusions

By formulating the analysis of air pollution mortality in terms of LE (life expectancy) rather than mortality risk, one obtains a unified framework for time series studies, intervention studies and cohort studies. TS studies measure the instantaneous time derivative of LE

changes due to pollution. One of the advantages of this approach is that it yields as rigorous model-independent result the LE change after a pollution peak or after an intervention as an integral of the observed mortality rates. However, the estimation of the number of deaths attributable to air pollution is problematic and so is the LE loss per air pollution death.

The relation between the results of the different study types depends on the processes by which the body repairs air pollution damage. Using plausible models for the repair processes, one finds that the mortality rates change most strongly in the initial period after the intervention, thereafter returning to a level close to the original, even though the population has obtained a permanent LE gain. The time scale depends on the time constant(s) of the repair processes. Unfortunately not enough is known about repair processes at the present time to allow more specific conclusions.

With the assumed repair models one finds that the results of TS studies are consistent with the ultimate LE change due to a permanent exposure change, as determined by cohort studies. This raises the interesting possibility of using repair models to estimate the LE gain achievable by a permanent reduction in O_3 exposure, a pollutant for which a significant effect has been identified so far only by TS and not by cohort studies.

Abbreviations and symbols

c = concentration of pollutant;
Δc = concentration change;
D = death rate of population or population segment, absolute number [deaths/time];
k = proportionality constant for relation between Δc and ΔL;
LE = life expectancy;
$L(x_0)$ = remaining life expectancy (survival time);
ΔL = change in life expectancy [yr/person], positive for a gain;
N = population size;
RR = relative risk;
$S(x_0,x)$ = survival function = fraction of birth cohort of initial age x_0 that survives to age x;
t = time;
TS = time series
w_i = weighting factors of different time constant in repair model;
x = age;
λ = lag time of repair model;
μ = mortality rate = death rate/population size [deaths/time per person];
τ = time constant of repair model;

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Appendix A. Relation between age-specific mortality and life expectancy

The survival function $S_\mu(x_0, x)$ is determined as the solution of the differential equation

$$dS_\mu(x_0,x) = - S_\mu(x_0,x)\ \mu(x)\ dx \quad , \tag{A.1}$$

with the boundary condition $S_\mu(x_0,x_0) = 1$. The solution is

$$S_\mu(x_0,x) = \exp[- \int_{x_0}^{x} \mu(x')\ dx'] \quad . \tag{A.2}$$

Since the probability of a cohort member to survive to age x and die between x and x+Δx is $S_\mu(x_0,x)\ \mu(x)\ \Delta x$, the remaining life expectancy $L(x_0)$, also known as expected survival time, of this cohort is obtained by integrating the age x times this probability over the entire cohort

$$L(x_0) = \int_{x_0}^{\infty} x\ S_\mu(x_0,x)\ \mu(x)\ dx \quad . \tag{A.3}$$

Using Eq.A1 one sees that $L(x_0)$ is the area under the survival function, bounded by the x-axis and the y-axis at $x=x_0$. Integrating by parts one obtains

$$L(x_0) = \int_{x_0}^{\infty} S_\mu(x_0,x)\ dx \quad . \tag{A.4}$$

If μ(x) is given, $S_\mu(x_0,x)$ and $L(x_0)$ are uniquely determined. Vice versa, by the following steps one can show that $L(x_0)$ determines μ(x). The derivative of $L(x_0)$ is

$$\frac{dL(x_0)}{dx_0} = -S_\mu(x_0,x_0) + \int_{x_0}^{\infty} \frac{\partial S_\mu(x_0,x)}{dx_0}\,dx \quad , \tag{A.5}$$

and with Eq.A1 this becomes

$$\frac{dL(x_0)}{dx_0} = -1 + \int_{x_0}^{\infty} \mu(x_0)\ S_\mu(x_0,x)\,dx = -1 + \mu(x_0)\ L(x_0) \quad , \tag{A.6}$$

from which one obtains μ(x) as an explicit function of L(x).

$$\mu(x_0) = \left[1 + \frac{dL(x_0)}{dx_0}\right] / L(x_0) \quad . \tag{A.7}$$

Appendix B. Change due to Intervention, by Age Group

The arguments of Section 2.4 can also be used for a group of a specified initial age, either a birth cohort that has age x_0 at the time of the intervention or a "constant age segment", i.e. a population segment the age of which is held fixed. In the case of the birth cohort the death rate $D_{ref}(x_0,t)$ in the absence of the intervention also changes with time, and one needs to consider the relation between $D(x_0,t)$ and $D_{ref}(x_0,t)$. Generalizing Fig.3 to a situation where $D_{ref}(x_0,t)$ varies with time, one readily finds

$$D(x_0,t+\Delta L(x_0,t)) = D_{ref}(x_0,t)/(1 + \Delta L'(x_0,t)) \quad \text{for } t > 0 \tag{B.1}$$

(now $\Delta L'(x_0,t)$ designates the partial derivative of $\Delta L(x_0,t)$ with respect to t). The size of a birth cohort is equal to the birth rate times the fraction $S_\mu(0,x,t)$ that survives to age x

$$S_\mu(0,x,t) = \exp[-\int_0^x \mu(x',t)\, dx'] \qquad \text{with } x = x_0 + t. \tag{B.2}$$

Therefore the age-specific mortality rate and the relative risk RR(x,t) are determined by

$$RR(x,t) = \mu(x,t)/\mu_{ref}(x,t) = [D(x,t)/D_{ref}(x,t)]/[S_\mu(0,x,t)/S_{ref}(0,x,t)] \quad . \tag{B.3}$$

This is an integral equation since $S_\mu(0,x,t)$ involves an integral of $\mu(x,t)$. However, as first approximation one can set

$$\mu(x,t)/\mu_{ref}(x,t) \approx D(x,t)/D_{ref}(x,t) \tag{B.4}$$

for the small changes encountered in practice. Then one could improve the approximation by iterations, if desired. Thus the second approximation involves inserting $\mu(x,t) = \mu_{ref}(x,t)$ $D(x,t)/D_{ref}(x,t)$ into Eq.B.3 and using it to calculate an improved estimate of $S_\mu(0,x,t)$. That the corrections are very small can easily be verified by comparing $S_{ref}(0,x,t)$ with $S_\mu(0,x,t)$ in the limit of very large t when $S_\mu(0,x,t)$ approaches the steady state limit corresponding to the ultimate LE gain ΔL_∞. As an example let us take a relative risk of 1.06 for a concentration change of 10 $\mu g/m^3$ of $PM_{2.5}$ [12, for the average concentration 1979-2000, in their Table 2]. It implies an ultimate LE gain of 0.4 yr for a permanent decrease of $PM_{2.5}$ by 10 $\mu g/m^3$. One finds that the corresponding difference between $S_{ref}(0,x,t)$ and $S_\mu(0,x,t)$ is at most a small fraction of a percent for ages below 50. Around 70 to 80 the relative difference becomes larger, up to a few percent, but even that implies only a small correction for the difference between $\mu(x,t)/\mu_{ref}(x,t)$ and $D(x,t)/D_{ref}(x,t)$, a correction that could be taken into account adequately by one iteration if necessary.

Appendix C. Repair model with several time constants

Processes with different time constants can be incorporated by making the replacement

$$\exp[-(t-t')/\tau)] \rightarrow \sum_i w_i \exp[-(t-t')/\tau_i)] \qquad \text{with } \sum_i w_i = 1 \quad . \tag{C.1}$$

in the equations of Sections 3 and 4. Leksell & Rabl [13] reviewed the studies of ex-smokers, especially the one by Doll et al [15], one of the most comprehensive long term study of smokers and ex-smokers. They found that the recovery can be approximated quite well by an exponential decay model with two time constants: a time constant of 1.5 years with weight 0.3 and one of 13 years with weight 0.7. With this model the LE gain $\Delta L(t)$ after the cessation of smoking is

$$\Delta L(t) = -\Delta L_\infty \{1 - [w_1 \tau_1 \exp(-t/\tau_1) + w_2 \tau_2 \exp(-t/\tau_2)]/(w_1 \tau_1 + w_2 \tau_2)\} \tag{C.2}$$

where $w_1 = 0.7$, $\tau_1 = 13$ yr, $w_2 = 0.3$, $\tau_2 = 1.5$ yr, and ΔL_∞ is the ultimate gain.