On Keiding’s Equation and its relation to differential equations about prevalence and incidence in chronic disease epidemiology

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Abstract

We study the relation between the age-specific prevalence, incidence and mortality in an illness-death model consisting of the three states Healthy, Ill, Dead. The dependency on three different time scales (age, calendar time, disease duration) is considered. It is shown that Keiding’s equation published in 1991 is a generalisation of the solution of Brunet and Struchiner’s partial differential equation from 1999. In a special case, we propose a particularly simple estimate of the incidence from prevalence data.

1 Background

Keiding reviewed the relations between the incidence and prevalence of a chronic disease based on an illness-death model [7]. The illness-death model consists of the three states Healthy, Ill and Dead (Figure 1). The transition rates $i, m_0,$ and $m_1$ between the states may depend on the time scales calendar time ($t$), age ($a$), and the rate $m_1$ may additionally depend on the duration of the disease ($d$). As we are dealing with chronic diseases, there is no transition from the state Ill to Healthy. Let $S(t, a)$ denote the number of persons aged $a, a \geq 0$ at time $t$ in the state Healthy. Similarly, $C(t, a, d)$ denotes the number of persons aged $a$ at $t$ who are diseased for $d, d \geq 0$ time units. The notation is chosen for historical reasons, $S$ and $C$ stand for susceptibles and cases, respectively.

In epidemiology, it is common to consider the age-specific prevalence

$$p(t, a) = \frac{C^*(t, a)}{C^*(t, a) + S(t, a)}.$$
Healthy \( \xrightarrow{i(t,a)} \) Ill
\( \xrightarrow{m_0(t,a)} \) Dead
\( \xrightarrow{m_1(t,a,d)} \) Dead

Figure 1: Illness-death model. The transition rates \( i \) and \( m_0 \) depend on calendar time \( t \) and age \( a \). The rate \( m_1 \) additionally depends on the duration \( d \).

where \( C^*(t,a) = \int_0^a C(t,a,\delta) \, d\delta \) denotes the number of diseased persons aged \( a \) at time \( t \), irrespective of the duration \( d \). Keiding gave following expression for the prevalence odds [7, p. 379]:

\[
\frac{p(t,a)}{1 - p(t,a)} = \frac{\int_0^a \mathcal{M}_{t,a}(y) \, i(t - a + y, y) \, e^{-\int_0^y m_1(t - a + \tau, \tau - y) \, d\tau} \, dy}{\mathcal{M}_{t,a}(a)}
\]

with

\[
\mathcal{M}_{t,a}(y) = \exp \left( -\int_0^y m_0(t - a + \tau, \tau) + i(t - a + \tau, \tau) \, d\tau \right).
\]

From Equation (1) the following Proposition can be deduced.

**Proposition 1.** For the age-specific prevalence \( p(t,a) \) it holds

\[
p(t,a) = \frac{\int_0^a i(t - \delta, a - \delta) \, \mathcal{M}_{t,a}(a - \delta) \, e^{-M_1(t,a,\delta)} \, d\delta}{\mathcal{M}_{t,a}(a) + \int_0^a i(t - \delta, a - \delta) \, \mathcal{M}_{t,a}(a - \delta) \, e^{-M_1(t,a,\delta)} \, d\delta},
\]

where

\[
M_1(t,a,d) := \int_0^d m_1(t - d + \tau, a - d + \tau, \tau) \, d\tau.
\]

**Proof.** Solving Equation (1) for \( p(t,a) \) and re-parametrising the path of integration yields Eq. (2).

Keiding has not presented a proof of Equation (1). In this article, we will give a proof and relate Equation (2) to two partial differential equations (PDEs) published a few years after Keiding’s pivotal work in 1991.
2 Partial differential equations

In this section, we will formulate PDEs for $S(t, a)$ and $C(t, a, d)$ based on the model in Figure 1. The only assumptions are

- All newborns are disease-free at time of birth (i.e., $C^*(t, 0) = 0$ for all $t$.)
- There is no migration into or from the states Healthy and Ill.
- The rates $i, m_0$ and $m_1$ are smooth, i.e. partially differentiable with continuous derivatives.

For the number $S$ of susceptibles we obtain following PDE:

$$ \partial_t + \partial_a S(t, a) = -(m_0(t, a) + i(t, a)) S(t, a) $$

$$ S(t-a, 0) = S_0(t-a). $$

Here $S_0(t-a) = S(t-a, 0)$ denotes the number of (healthy) newborns at time $t-a$. The notation $\partial_x$ means the partial derivative for $x, x \in \{t, a\}$. Equation (3) together with the initial condition $S_0(t-a) = S(t-a, 0)$ is a Cauchy problem which has a unique solution (the rates $m_0$ and $i$ are smooth) [9]. This solution of the Cauchy problem is given in Eq. (4).

$$ S(t, a) = S_0(t-a) \exp \left( - \int_0^a m_0(t-a+\tau, \tau) + i(t-a+\tau, \tau) \, d\tau \right). $$

The calculation of the number $C$ of cases will be a bit more difficult, because at any time $t$ and at any age $a$ the current disease duration $d$ plays an important role. As there is no migration, the number $C(t, a, d)$ is described by the following equations:

$$ C(t, a, d) = C(t-d, a-d, 0) \exp \left( - \int_0^d m_1(t-d+\tau, a-d+\tau, \tau) \, d\tau \right) $$

$$ = i(t-d, a-d) S(t-d, a-d) e^{-\int_0^d m_1(t-d+\tau, a-d+\tau, \tau) \, d\tau}. $$

$C(t, a, d)$ is a solution of another Cauchy problem. The associated PDE is

$$ (\partial_t + \partial_a + \partial_d) C(t, a, d) = -C(t, a, d) \, m_1(t, a, d), $$

and the initial condition is $C(t, a, 0) = i(t, a) S(t, a)$ for all $t, a$.  

Proof. It holds
\[
\partial_x C(t, a, d) = \partial_x i(t - d, a - d) S(t - d, a - d) \exp \{-M_1(t, a, d)\} \\
+ i(t - d, a - d) \partial_x S(t - d, a - d) \exp \{-M_1(t, a, d)\} \\
- i(t - d, a - d) S(t - d, a - d) \exp \{-M_1(t, a, d)\} \times \\
\partial_x M_1(t, a, d)
\]

and
\[
\partial_d C(t, a, d) = - (\partial_t + \partial_a) i(t - d, a - d) S(t - d, a - d) \exp \{-M_1(t, a, d)\} \\
- i(t - d, a - d) (\partial_t + \partial_a) S(t - d, a - d) \exp \{-M_1(t, a, d)\} \\
- i(t - d, a - d) S(t - d, a - d) \exp \{-M_1(t, a, d)\} \times \\
\partial_d M_1(t, a, d).
\]

This implies
\[
(\partial_t + \partial_a + \partial_d) C(t, a, d) = - C(t, a, d) (\partial_t + \partial_a + \partial_d) M_1(t, a, d).
\]

For \( x \in \{t, a\} \) it is
\[
\partial_x M_1(t, a, d) = \int_0^d \partial_x m_1(t - d + \tau, a - d + \tau, \tau) \, d\tau.
\]

Furthermore, we find that
\[
\partial_d M_1(t, a, d) = - \int_0^d (\partial_t + \partial_a) m_1(t - d + \tau, a - d + \tau, \tau) \, d\tau + m_1(t, a, d).
\]

With the smoothness constraint, this proves that \( C(t, a, d) \) is the unique solution of the Cauchy problem.

We are interested in the overall number \( C^*(t, a) \):
\[
C^*(t, a) = \int_0^a C(t, a, \delta) \, d\delta
\]
\[
= \int_0^a i(t - \delta, a - \delta) S(t - \delta, a - \delta) e^{-\int_0^\delta m_1(t-\delta+t, a-\delta+t, \tau) \, d\tau} \, d\delta \quad (5)
\]

By inserting (4) and (5) into the definition of \( p(t, a) \), we obtain Equation (2).

As described above, Equation (2) be transformed into Equation (1), which proves Keiding’s Equation.
The advantage of the Equations (2) and (1) is that for given incidence $i(t, a)$ and mortality rates $m_0(t, a)$ and $m_1(t, a, d)$, the age-specific prevalence can be calculated for all times $t$ and ages $a \geq 0$. By this, we may estimate the impact of health related interventions with an appropriate treatment of the involved time scales. Unfortunately, the theory suggested by Keiding has rarely been used in epidemiology, public health, or health economics. For instance, instead of treating time as a continuous variable, discrete time steps are preferred, which may impose a considerable discretisation error (for an example of a discretisation error of more than 100%, see [1]). In the article [5], the effect of a health related intervention is estimated by treating time continuously.

As a byproduct from Equation (2) we may conclude:

**Remark 1.** The prevalence $p(t, a)$ is independent from the number of newborns $S_0$.

### 3 Independence from the duration of the disease

In case the mortality $m_1$ of the diseased persons is independent from the duration $d$, the number of cases $C^*(t, a)$ is a solution of the following PDE:

\[
(\partial_t + \partial_a) \gamma(t, a) = -m_1(t, a) \gamma(t, a) + i(t, a) S(t, a).
\]

**Proof.** Together with the initial condition $\gamma(t - a, 0) = 0$ the PDE (6) has
the solution
\[
\gamma(t, a) = e^{-\int_0^a m_1(t-a+\alpha, \alpha) \, d\alpha} \left\{ \gamma(t - a, 0) + \int_0^a i(t - a + \alpha, \alpha) S(t - a + \alpha, \alpha) e^{-\int_0^\alpha m_1(t-a+\tau, \tau) \, d\tau} \, d\alpha \right\}
\]
\[
= \int_0^a i(t - a + \alpha, \alpha) S(t - a + \alpha, \alpha) e^{-\int_0^\alpha m_1(t-a+\tau, \tau) \, d\tau} \, d\alpha
\]
\[
= \int_0^a i(t - \delta, a - \delta) S(t - \delta, a - \delta) e^{-\int_0^{a-\delta} m_1(t-a+\tau, \tau) \, d\tau} \, d\delta
\]
\[
= \int_0^a i(t - \delta, a - \delta) S(t - \delta, a - \delta) e^{-\int_0^{\delta} m_1(t-\delta+\tau, a-\delta+\tau) \, d\tau} \, d\delta.
\]

By comparison with Eq. (5) we see that \( C^*(t, a) \) is the solution of the PDE.

If we insert (3) and (6) into the definition of \( p(t, a) \), we may deduce following PDE (1):

\[
(\partial_t + \partial_a) p = (1 - p) \left( i - p \left( m_1 - m_0 \right) \right).
\]

Similarly, we obtain following PDE for the prevalence odds \( \pi(t, a) = \frac{p(t, a)}{1-p(t, a)} \) of Brunet and Struchiner [5], which is equivalent to Eq. (7):

\[
(\partial_t + \partial_a) \pi = i - \pi \left( m_1 - m_0 - i \right).
\]

In contrast to the PDE (7), the PDE (8) has the advantage of being linear. Thus, its solution is straightforward and allows a handy simplification of Eq. (2) (see [3, Eq. (1)]).

We conclude this section with the observation that Keiding’s Equation (1) is a generalisation of the solution of both PDEs (7) and (8).

4 Incidence being independent from calendar time

An important application of the theory in epidemiology is the question if incidence rate can be recovered from observed prevalence data. This question
has already been mentioned in 1934 [8] and has been studied in [4] with test data. Now it is shown that in the special case of incidence being independent from calendar time \(i(t, a) = i(a)\) the dependence of \(m_1\) on the duration \(d\) does not have to be known to estimate the incidence. This has the advantage that a possible duration dependency in \(m_1\) may be unknown.

Starting from (4) we find

\[
I(t, a) := \int_0^a i(t - a + \tau, \tau) d\tau = \ln \frac{S_0(t - a)}{S(t, a)} - M_0(t, a)
\]

\[
= \ln S_0(t - a) - \ln S(t, a) - M_0(t, a)
\]

\[
= \ln S_0(t - a) - \ln \left(1 - p(t, a)\right) - \ln N(t, a) - M_0(t, a)
\]

with

\[
M_0(t, a) := \int_0^a m_0(t - a + \tau, \tau) d\tau.
\]

The number \(N(t, a)\) denotes the amount of persons aged \(a\) at \(t\) who are alive \((N = S + C)\). If \(i\) is independent from \(t\), it holds

\[
\partial_a I(t, a) = i(a) \quad \text{for all } t.
\]

Hence, we may deduce following representation of the age-specific incidence:

\[
(9) \quad i(a) = \partial_a \left( \ln S_0(t - a) - \ln \left(1 - p(t, a)\right) - \ln N(t, a) - M_0(t, a) \right).
\]

This is an amazing result, because the occurring variables \(S_0\) and \(N\) are well known from demography. Assumed that the mortality \(m_0\) can also be surveyed, the possibly complex \(m_1(t, a, d)\) does not have to be known for an estimate of the incidence in case of a given age-specific prevalence \(p(t, a)\).

Remark 2. Many epidemiological studies examine the mortality \(m_1\) of the diseased instead of the mortality \(m_0\) of the non-diseased. Equation (9) suggests a paradoxic study design: Instead of following up on mortality of the diseased persons, the healthy persons are of primary interest.

5 Examples

5.1 General case

In this subsection the age-specific prevalence \(p(t, a)\) for a hypothetical chronic disease is calculated using Equation (2). We assume that \(t, a\) and \(d\) are

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counted in units “years” with \( t, a, d \geq 0 \). Mortality \( m_0 \) is assumed to be of Gompertz-Makeham type,

\[
m_0(t, a) = \exp(-10.7 + 0.1 a) (1 - 0.002)^t,
\]

and the incidence is given by

\[
i(t, a) = \left(\frac{a-30}{3000}\right) (1 - 0.003)^t.
\]

The mortality \( m_1 \) of the diseased is assumed to be the product of \( m_0 \) and relative mortality \( R(d) = (0.2 d - 1)^2 + 1 \):

\[
m_1(t, a, d) = R(d) m_0(t, a).
\]

The integrals \( M \) and \( M_1 \) are calculated analytically, which is possible here. The integral from 0 to \( a \) in the numerator and denominator in (2) are calculated by Romberg’s rule, which allows an a-priori prescribed accuracy.

Figure 2 shows the resulting age-specific prevalences at \( t = 0, 50, \) and 100 (in years). The three age profiles have a similar qualitative behaviour: After onset of the disease for \( a \geq 30 \), the prevalence increases sharply with age and until the seventh decade of life. All three curves reach their maximum at the age of about 80 (years) and then decrease slightly.
Figure 2: Age-specific prevalences in the example in the years $t = 0, 50,$ and 100.
5.2 Time-independent incidence

If we leave out the term $(1 - 0.003)^t$ in Eq. (10), we can estimate $i = i(a)$ from $p$ surveyed in year $t = 100$ via Eq. (9). The partial derivative $\partial_a$ has been approximated by a finite difference. Figure 3 show the results. Visually, there is a nearly perfect agreement between the theoretical and the estimated incidence.

Figure 3: Age-specific incidence in year $t = 100$. The solid line shows the theoretical incidence rate $i(a) = \frac{(a-30)_+}{3000}$. The points represent the estimated values using Equation (9).

Additionally, we set up a population with a birth rate of 5000 persons per year in 60 consecutive years $(0, \ldots, 59)$. Events in the illness-death model (diagnosis, death with or without the disease) are simulated by a discrete event simulation as described in [2]. In the year $t = 100$, we mimic a cross-section to estimate the prevalence $p(100,a)$. As above, the incidence is estimated by Eq. (9) and approximating $\partial_a$ by a finite difference. Figure 4 shows the
results. In contrast to Figure 3, the incidence cannot be estimated exactly with is due to the random error in the prevalence \( p(100, a) \).

Figure 4: Age-specific incidence in year \( t = 100 \). The solid line shows the theoretical incidence rate \( i(a) = \frac{(a - 30)^+}{3000} \). The points represent the estimated values using Equation (9) and the simulated prevalence.
6 Conclusion

This article combines the results of Keiding [7], Brunet and Struchiner [6], and Brinks and Landwehr [1, 3]. We have found that Keiding gave an analytical expression for the age-specific prevalence in the most general case of the illness-death model, i.e. with involvement of all time scales (age, calendar time, and duration). Keiding presented this expression eight years before Brunet and Struchiner published their linear partial differential equation without duration dependency. Brinks and Landwehr extend the work by Keiding and Brunet and Struchiner by allowing migration and remission [1]. Even in the case with duration dependency, the age-specific prevalence can be related to the transition rates in the illness-death model by a scalar partial differential equation. Details can be found in [4].

In addition, we have proposed a new way of estimating the incidence from a cross-sectional prevalence study where it is not necessary to survey the possibly complex duration dependency of $m_1$. In this paradoxic study design, the mortality of the healthy ($m_0$) needs to be known instead of the mortality of the diseased ($m_1$). The proposed method was demonstrated by an example of a hypothetical chronic disease.

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