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Ageing populations and childhood infections: the potential impact on epidemic patterns and morbidity

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SUMMARY

Background

Population decline, arising from below replacement fertility and possibly giving rise to substantial changes in age distribution, is a feature of many industrialised developed countries; Italy is the most notable European example. The potential influence of this phenomenon on prevalence of chronic non-infectious disease is well known, but little attention to date has been paid to the impact on severe disease due to childhood infections in those cases where control is insufficient to achieve elimination.

Methods

A transmission dynamics model incorporating realistic demography is used to investigate the possible impact of population decline and ageing and suboptimal vaccination uptake on the age distribution of incidence of measles infection and of consequent mortality. Data from Italy is used to parameterise the model.

Results

Declining fertility in the absence of vaccination is shown to reduce per capita incidence of infection but also to increase average and upper quartile ages at infection. The effect is substantially enhanced by significantly suboptimal vaccination uptake, when disease-induced mortality has, for a period, the potential to exceed that in the absence of vaccination.

Conclusions

Although a substantially increased burden from chronic non-infectious disease has frequently been proposed as a consequence of population decline, there is also potential for an increase in morbidity and mortality from measles and other childhood infectious diseases, particularly where vaccine uptake is substantially below the optimum. Rubella is highlighted as a particular cause for concern. This work also has implications for less developed countries.

Keywords: population decline, fertility, childhood infections, measles, rubella, vaccination coverage, mathematical model, Italy

Introduction

As is well recognised, the widespread fall in fertility observed in many so-called 'industrialised developed countries' (IDC's) and the consequent decline and ageing of their populations (1) presages increased prevalence of chronic non-infectious diseases (e.g. (2)). To date, however, it appears that little regard has been paid to the impact of this phenomenon (often termed the 'second demographic transition' (3)) upon incidence of childhood infectious diseases and corresponding morbidity.

It has been argued (4) that the drop in fertility associated with the 'first demographic transition' from rapidly growing to approximately constant population size was associated with decreased mortality from childhood infections as a result of a consequential increase in the average age at infection. At first sight, therefore, it may seem strange to consider an ageing population as a potential cause for concern in relation to such infections. However it should be recalled that historic average ages at infection and the consequent acquisition of the description 'childhood infectious diseases', resulted from interactions at the time between demography, the epidemiology or ecology of these infections, and their inducement of lasting immunity following recovery (5). The present onset of a period of significant demographic change in IDC's and other countries has the potential to strongly influence these interactions and warrants further investigation.

For a specific disease the age-related pattern of per capita incidence of infection among susceptible individuals (i.e. the force of infection (FOI)), may vary over time and is strongly influenced by patterns of contact between age groups and by

population age distribution(5). Using the example of measles in Italy, the question addressed here is to what extent the age distribution of infection is influenced by the process of population ageing, an important issue because of substantial changes in patterns of measles morbidity and mortality with age (Figure 1). Although measles is considered here, the conclusions apply with similar force to other childhood infections, mutatis mutandis.

While there is a safe and very effective vaccine against measles, very high vaccination rates are required to achieve elimination, and to date many countries, including Italy, have fallen far short of such a target (6). By reducing annual per capita risk of infection, the introduction of vaccination is itself expected to increase average age at infection (5), although where vaccine uptake is sufficiently high to achieve elimination the effect is, of course, transient.

Of all the IDC's, Italy is the country with the most dramatic decline in fertility and potentially most rapidly ageing population (Figure 2) (other examples are Spain and some Central and Eastern European countries (3)), and in this sense serves as a laboratory for considering the epidemiological effects of these processes. Here we investigate the potential influence of these phenomena on age at infection using a transmission dynamics model with age structure (5) which is capable of realistic representation of Italian demography. We demonstrate, both in the particular case of Italy and more generally, that the potential effect on the age distribution of infection is quite dramatic with consequent significant increases in morbidity and mortality. It is anticipated that similar, more or less dramatic, effects would be shown for other infections, with or without the presence of vaccination programmes. Additionally,

important effects resulting from changing demography may also be expected to be observed in so-called 'developing' or 'less developed countries' (LDC's).

Materials & Methods

Data

Italian measles notification data (Figure 3) provided a standard against which to measure the model's ability to capture Italian measles epidemiology, and pre-vaccination age-related incidence data were used to estimate the force of infection according to age group. Because there is a substantial degree of under-reporting of measles cases in Italy, data corrected for under-reporting (Williams & Manfredi, Unpublished Observations) was used. Yearly age-related fertility rates from 1950 to 1996 were provided by the Italian National Institute of Statistics (ISTAT) together with the 1950 Italian population age distribution which provided the starting point for model simulations (Figure 4). Since 1996 fertility rates have remained quite stable so for projection into the future it was assumed that they remained at 1996 levels. To distinguish between effects particular to the Italian demographic environment, and those which may be generalised, hypothetical population data was also used, characterised by an initially flat, or Type I, age-distribution. In this latter population fertility rates were either kept at replacement level throughout or at replacement for the first 30 years followed by decay over the ensuing 40 years to constant below replacement levels (Figure 2c); for this generalised population, fertility rates were uniform across age-groups at all time points. ISTAT data for the period 1970-1980 were used to derive age-related mortality rates constant though time, a reasonably plausible representation of mortality over the simulation period.

Vaccination

In part as a result of being classified within the Italian public health system simply as 'Recommended' rather than 'Compulsory', the extent of data on measles vaccination coverage in Italy is quite limited (7) although strenuous attempts are presently being made to improve this record (Salmaso, S, personal communication). Here a plausible vaccination profile, reconstructed from the limited available data, has been used (Figure 5) in the knowledge that significant errors in this estimate are unlikely to affect the general conclusions drawn from this work. This cohort vaccination profile, starting in 1976, was applied at age 1.5 years to both the Italian and generalised model populations assuming 95% efficacy and 6 months mean maternal antibody duration. For future years it was assumed vaccination continued at 1997 levels. Other model simulations were also carried out assuming a) a high-level of vaccination had been achieved from 1997 onwards (increasing by 5% each year to 95%), and b) no vaccination had been given at any time (i.e. 0% coverage for all years).

Model

A standard age structured deterministic compartmental measles model was used (5)(Figure 6), modified to allow incorporation of realistic demography in terms of initial age-distribution, age-related fertility rates, and age-related mortality (in the model, all remaining by age 75 then die). The model reproduced well the observed numbers of births in Italy since 1950 (Figure 2); Table 1 specifies the age-related contact patterns (the 'Who acquires infection from whom', or WAIFW, matrix) and FOI used in the model.

(Table 1 here)

Results

Figure 7 shows model results in terms of incidence of infection for both Italian (Figure 7a) and generalised populations (Figure 7b) in the cases of 'moderate' (i.e. estimated) and 'high' vaccination profiles and also the scenario with no vaccination. The model outputs shown here for 'moderate' vaccination in Italy (Figure 7a) correspond broadly to the corrected historic incidence data (Figure 3) in terms of magnitude, timing and shape. The results for the generalised population (Figure 7b) also bear strong similarities to the 'Italian' results if the additional 'noise' is ignored (a result of loss of damping after replacement of age-related fertility with uniform rates and substitution of an initial uniform age distribution)(5). In both cases, as predicted by theory (5), the introduction of vaccination generates an increase in inter-epidemic period . If vaccination continues at moderate levels the decline in incidence ceases, followed in later years by a significant increase, although more noticeable in the case of the 'Italian' population. With the 'high' vaccination profile, incidence rapidly declines to negligible levels. In the complete absence of vaccination, in both populations, there is still significant decline in per capita incidence to an approximately constant lower level. This effect arises from the interaction between the change in age distribution, caused by population decline, with the moderation in FOI with age. However these results, aggregated over age, do not make clear how experience of infection changes with age under these scenarios.

Figure 8a and 8b show, for the 'Italian' population, how proportions of young school-aged children and adults remaining susceptible to infection change through time under assumptions of no vaccination and continuing 'moderate' vaccination. In all cases proportion susceptible increases through time. In the case of young children (Figure 8a), vaccination reduces the demographically driven increase in proportion

susceptible. For adults (Figure 8b) the effect is reversed with vaccination increasing the susceptible proportion, and overall the relative increase in susceptibility is much greater for both adult scenarios (these effects are broadly similar for the generalised population and so are not shown). The extent of the impact of demographic change on this phenomenon can be seen for adults in Figure 8c in which the same vaccination scenarios are applied but with constant population size: here the increase in susceptibility with 'moderate' vaccination is some four or five times less.

If the combined impact of demographic change and 'moderate' vaccination on the age distribution of cases is considered a more worrying picture emerges. Figure 9a suggests that in the absence of any vaccination the upper quartile age of cases in the 'Italian' population over the next 25 years would rise from around 8 or 9 years to about 13 or 14 years. At historic 'moderate ' vaccination levels, Figure 9b suggests that the median age of cases may have already increased from around 5 years to about 10 years (recently published data gives some support to this observation (8)) and would reach about 18 years of age after another 25 years has elapsed; corresponding upper quartile ages are approximately 7 years, 17 years and 35 years of age with these measures continuing to increase substantially in the ensuing period (a similar pattern is seen for the generalised population, albeit with slightly smaller age increases). These results can be contrasted with those in Figure 9c showing that with constant population size (i.e. replacement fertility) the effect of 'moderate' vaccination on these measures is minimal.

Morbidity and mortality from measles infection is strongly age-related, and by combining this age-related risk of mortality (Figure 1) with the projected age-

distribution of cases a snapshot can be constructed of possible future patterns of mortality under scenarios of no vaccination and the sub-optimal 'moderate' vaccination (Figure 10). This important result suggests that although incidence is much lower under the 'moderate' vaccination scenario and initially accompanied by a decline in mortality and morbidity, there is the potential for mortality and morbidity to substantially increase in the ensuing years and indeed, for a period, possibly to levels in excess of those under the 'no vaccination' scenario. Fewer deaths are occurring at younger ages but these are more than compensated by the increase in deaths of mature adults

Although the 'high' vaccination scenario of Figure 7 is shown rapidly to achieve control, the attainment of such high levels of vaccination in such a small space of time is notoriously difficult. Until optimal cohort vaccination cover is achieved, an additional approach to control is supplementary with 'catch up' or campaign vaccination (9). Figure 11 shows, for the purposes of illustration, two examples of the potential impact on per capita incidence of combining vaccination campaigns with 'moderate' cohort vaccination. In the first, a single campaign reaching 90% of susceptibles up to age 20 has a rapid impact but the slow build-up in susceptibles following this provides the potential for very large breakthrough epidemics to occur at extended intervals. In the second. a more modest programme reaching 20% of those who remain susceptible up to age 20 but repeated every 4 years, allows a breakthrough epidemic after 6 years or so, but thereafter results in effective control.

Discussion

Much attention has been paid to the transmission dynamics of measles over the past 20 years (e.g. (10), (11), (12), (13) among many others). Nevertheless it is believed that this is the first published work to address the issue of the effect on measles dynamics of predicted population decline in the 'developed' world.

Demographically there are potentially two distinct phases to this decline. The first during which the age distribution of the population becomes skewed increasingly towards higher ages, and the second when a stable age distribution has been achieved but the population continues to decline. The present work has considered the first of these. It may be that at some stage fertility recovers to stabilise population numbers at a lower level, or indeed to bring about a growing population once more (14); in both cases a further change in age distribution will result. All these changes impact upon the dynamics of infection.

Such considerations also have a bearing on the dynamics of infection in 'developing' countries (which may well also experience vaccine uptake substantially below the optimum). As is well known, most such countries are still experiencing their 'first demographic transition' from a growing population to a stable stationary population size; this will also result in a change in age distribution (15), implying a consequent impact on transmission dynamics over the same time scale. Moreover it has recently been argued (16) that this first transition may now be relatively quickly followed by a further transition to population decline, mirroring that described above, with further consequences for measles dynamics, and those of other infections. These issues will be dealt with in more detail in a forthcoming publication.

Migration and age-related mortality are the two other key demographic processes. Patterns of mortality in the 'developed world' correspond reasonably well to the constant age-related 'Italian' rates used here, so that applying rates applicable to other European countries would not be expected to influence results significantly. However, models using mortality rates that do not change over time may not suffice in the case of the 'developing' world, where reductions in mortality arising from improvements in health care may interact in many cases with increasing premature mortality resulting from HIV/AIDS (17), so that net mortality rates may evolve in a much more complex way, necessitating more realistic representation if demographic patterns are to be mirrored satisfactorily. In contrast to mortality, the potential impact of migration on European demographic patterns is less clear, so the degree to which this may influence age distribution of measles infection is a question that warrants further research, although it would be expected that population movements would need to be quite substantial to affect this age distribution of infection unless both the age distribution of the migrants and of infection within the immigrant population were markedly different from those in the host population

The impact of demographic processes on the age distribution of infection clearly is influenced by the pattern and magnitude of trends in specific demographic measures, i.e. fertility, mortality and migration. Additionally assumptions intrinsic to a model in terms of contact patterns between age groups and the changes in FOI with age will also determine the evolution in the model of the age distribution of infection through time. Here the change in FOI with age has been estimated from data (Italy) and the contact pattern is one used elsewhere for modelling European childhood infections (e.g. (18), (5)) (the possibility remains that changes in age distribution may

themselves influence epidemiological contact patterns; while the contact pattern employed here provides a satisfactory starting point, this issue warrants further investigation). Although their magnitude may at first sight appear somewhat surprising, qualitatively speaking the projected changes in age distribution of infection described here are fully consistent with theory (5), and were preserved, albeit to a lesser degree, when these simulations were repeated with a higher FOI (not shown here) corresponding to that described in Edmunds *et al* (18). Additionally, in the context of rates of morbidity and mortality, it may be argued that, rather than a very finely divided age distribution, broad age categories such as 'new born', 'pre-school', 'primary education', 'adolescents' and 'adults' are more immediately relevant, and it is reasonable therefore to conclude that, in these terms, the results presented here are generally valid.

Continued circulation of measles infection relies on there being a sufficiently large pool of susceptibles to sustain it. Thus it is the cumulative build up of vaccine-based immunity (in combination with the level of infection-based immunity) which is important as a determinant of the age-distribution of susceptibility, and hence of infection over the longer term, rather than annual variations in uptake. Although a specific vaccination scenario has been employed here, to a greater or lesser degree, comparable results would be obtained from a wide range of vaccination profiles, subject to the proviso that they were significantly below uptake levels required to approach elimination (highly difficult to achieve though the results shown in Figure 11 confirm earlier work (e.g. (19) etc) suggesting that 'catch up' vaccination, already introduced in parts of Italy, is a feasible alternative)

While age-structured models of the type used in this work provide a reasonably satisfactory representation of epidemic trends, to achieve more precise representation suitable for informing detailed policy decisions, more sophisticated models are desirable, such as those described in the work of Babad (20), Ferguson et al (21) etc. Nevertheless it is argued that the results described above do provide a valid qualitative description of the impact of population decline on the age distribution of infection.

This work focuses on the effect of population decline and sub-optimal vaccination on the age-distribution of measles infection, and highlights the dangers of a resulting increase in measles-related morbidity and mortality. However it also constitutes a more general warning of the need not to lose sight of the implications of population decline for other infectious diseases in which mortality and morbidity increase with age. Varicella is one example (24), but rubella, in particular, stands out as posing a particular threat, with the potential for a large proportion of cases occurring in the fertile age range with a consequent substantial increase in cases of congenital rubella syndrome; the work described above suggests that this issue needs to be urgently addressed.

The onset of population decline and ageing has led, quite rightly, to an increasing emphasis on chronic non-infectious disease. However this emphasis should not be at the expense of overlooking the potential dangers posed by these processes in relation to age-related morbidity arising from infectious diseases. Such dangers must increase the urgency and importance of monitoring age-related experience of infection through seroprevalence surveys and, where vaccines do exist, of achieving and maintaining high levels of vaccination cover.

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Figure legends

Figure 1. An example of age-related measles mortality risk: the curve, combines initial exponential decay with a logistic curve and was fitted to data (diamond markers) from Black (22) (after Eichner (23))

Figure 2. a). Observed births per capita for Italy from 1950, and their forward projection to the year 2050; b). Estimated Italian age distribution for the year 2002 (source: US Bureau of the Census); c). Fertility rates used to model a hypothetical population with initially flat age distribution and with initial replacement levels of fertility decaying to constant below replacement fertility rates.

Figure 3. Annual standardised measles incidence in Italy per 100,000 for the period 1960 to 1996.

Figure 4. Age distribution of the Italian population in 1950

Figure 5. A reconstruction of the profile by year of measles vaccination uptake in Italy based upon the very limited recorded data (source: ICONA/ISTISAN).

Figure 6. Flow diagram showing the compartmental age-structured transmission dynamics model described in the text. In the model maternal antibody protection decays at a constant rate; the 'Exposed' compartment corresponds to the period of latent infection following exposure.

Figure 7. Model projections of predicted measles incidence from the year 1950 to year 2070. The figure shows measles incidence under continuation of the existing 'Moderate' vaccination profile (thick solid line), incidence assuming increasingly high rates of vaccine uptake being achieved from 1997 onwards (thick dashed line), and incidence under the assumption that no vaccination at all was undertaken throughout the period 1950-2070 (thin solid line) : a) for the model 'Italian' population incorporating Italian demography, and b) for a generalised population with declining fertility (see text).

Figure 8. The proportions of individuals remaining susceptible to measles infection under the assumptions of continuing 'moderate' vaccination (dashed line) and of no vaccination at any time during the period 1950-2070 (solid line): a) for young school-aged children in the 'Italian' model population, b) for adults in the 'Italian' model population, and c) for adults in the generalised population with constant fertility at replacement level.

Figure 9. Projected change through time of median age at measles infection (solid line), and upper (dashed line) and lower (dotted line) quartiles for age at infection under three scenarios: a) for a modelled 'Italian' population in the absence of any vaccination for the period 1950-2100, b) an 'Italian' population under the 'moderate' vaccination profile (Figure 5) representing past levels of vaccine uptake and the continuation into the future of the estimated 1997 level of uptake, and c) the same vaccine uptake as in b) but with the generalised population with replacement fertility so that it remains at constant size.

Figure 10. Model projections of possible numbers of deaths arising from measles infection in the 'Italian' model population under the 'moderate' vaccine uptake scenario (thick solid line) compared with that with no vaccination at any time during the period 1950-2075 (thin solid line).

Figure 11. An illustration of the potential impact in the case of the 'generalised' population of combining supplementary vaccination campaigns ('catch up' vaccination) targeted at a wide age range with the 'moderate' cohort vaccination scenario. The continuation of 'moderate' vaccination in the absence of any supplementary programme (thin solid line) is compared with model projections of the effect of : a) a single campaign reaching 90% of the eligible population (thick solid line), and b) an alternative campaign reaching 20% of the eligible population but repeated every 4 years (thick solid line).

Tables

a) Estimates used for force of infection (FOI) values used in the model; equivalent to the annual per capita incidence of measles infection among those remaining susceptible to infection:

Age range	FOI
0-1	0.077
2-4	0.158
5-10	0.290
11-17	0.181
18-74	0.062

b) Matrix specifying age-related contact patterns used in model, i.e. the 'Who acquires infection from whom' (WAIFW) matrix (5):

		Age range (yrs)				
		0-1	2-4	5-10	11-17	18-74
	0-1	β_1	β_1	β_1	β_1	β_1
Age	2-4	β_1	β_2	β_4	β_4	β_5
range	5-10	β_1	β_4	β_3	β_5	β_5
(yrs)	11-17	β_1	β_4	β_5	β_3	β_5
	18-74	β_5	β_5	β_5	β_5	β_5

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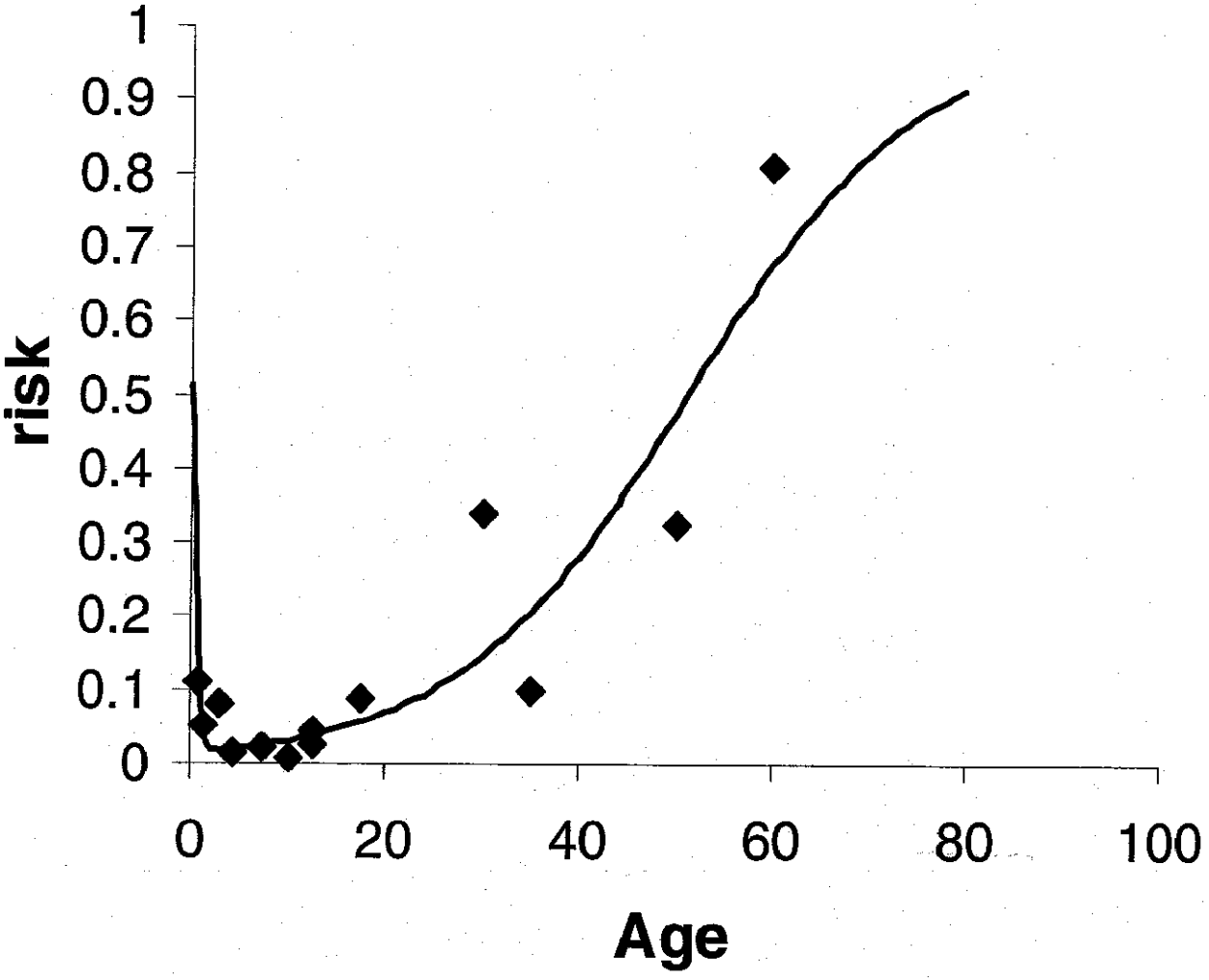


Fig 1

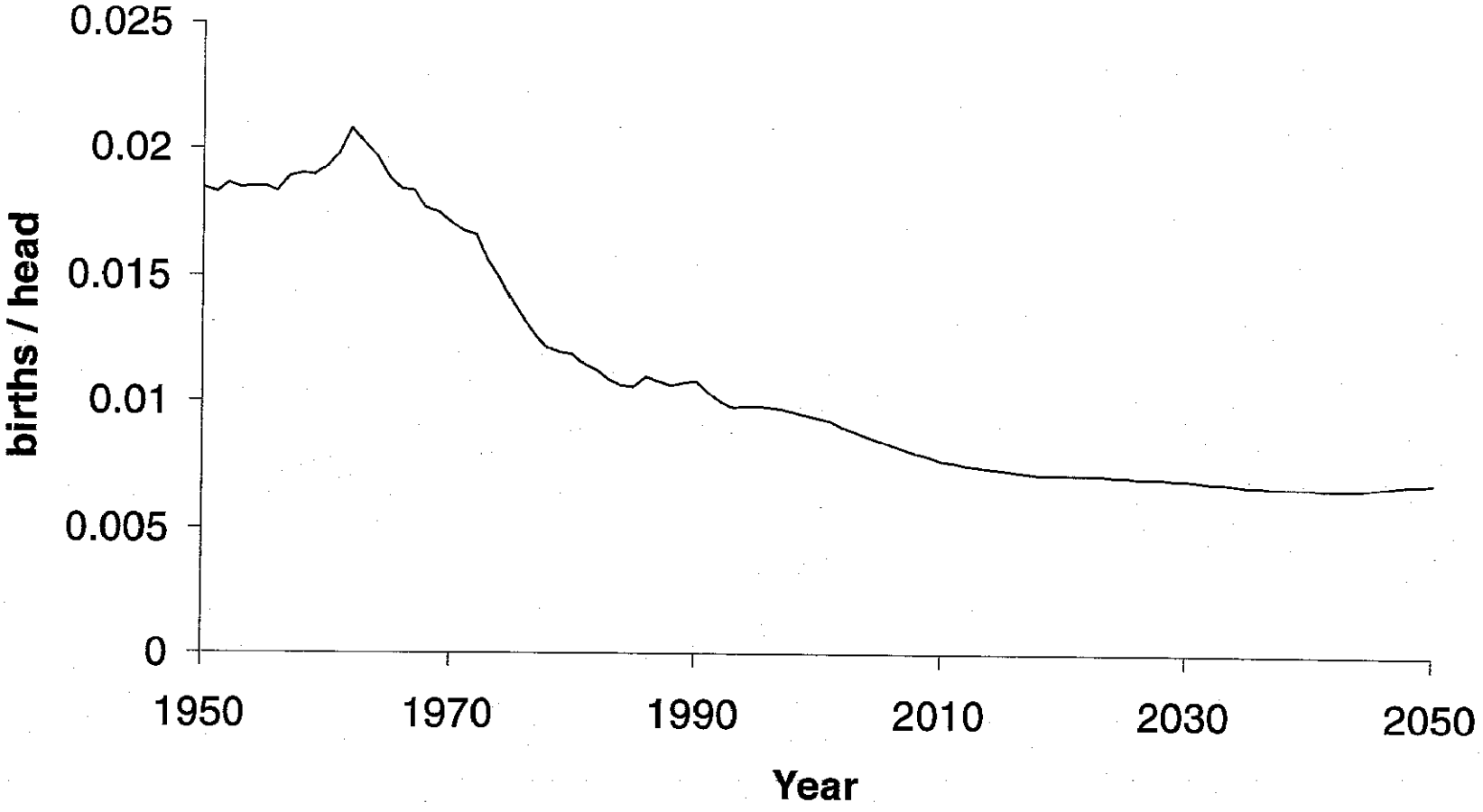

0.025
0.02
0.015
0.01
0.005
0
births / head
1950
1970
1990
2010
2030
2050
Year

Fig 2a

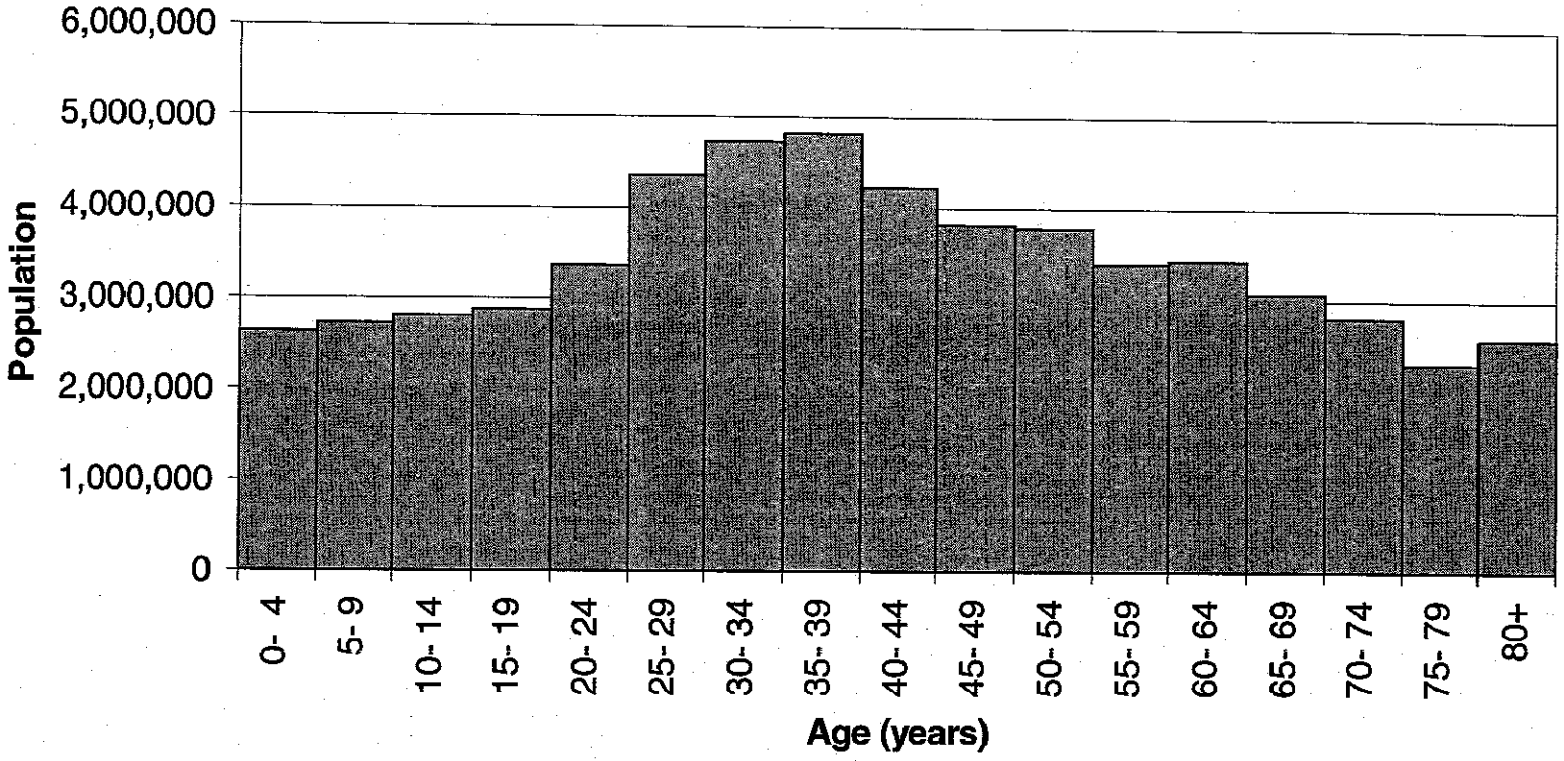
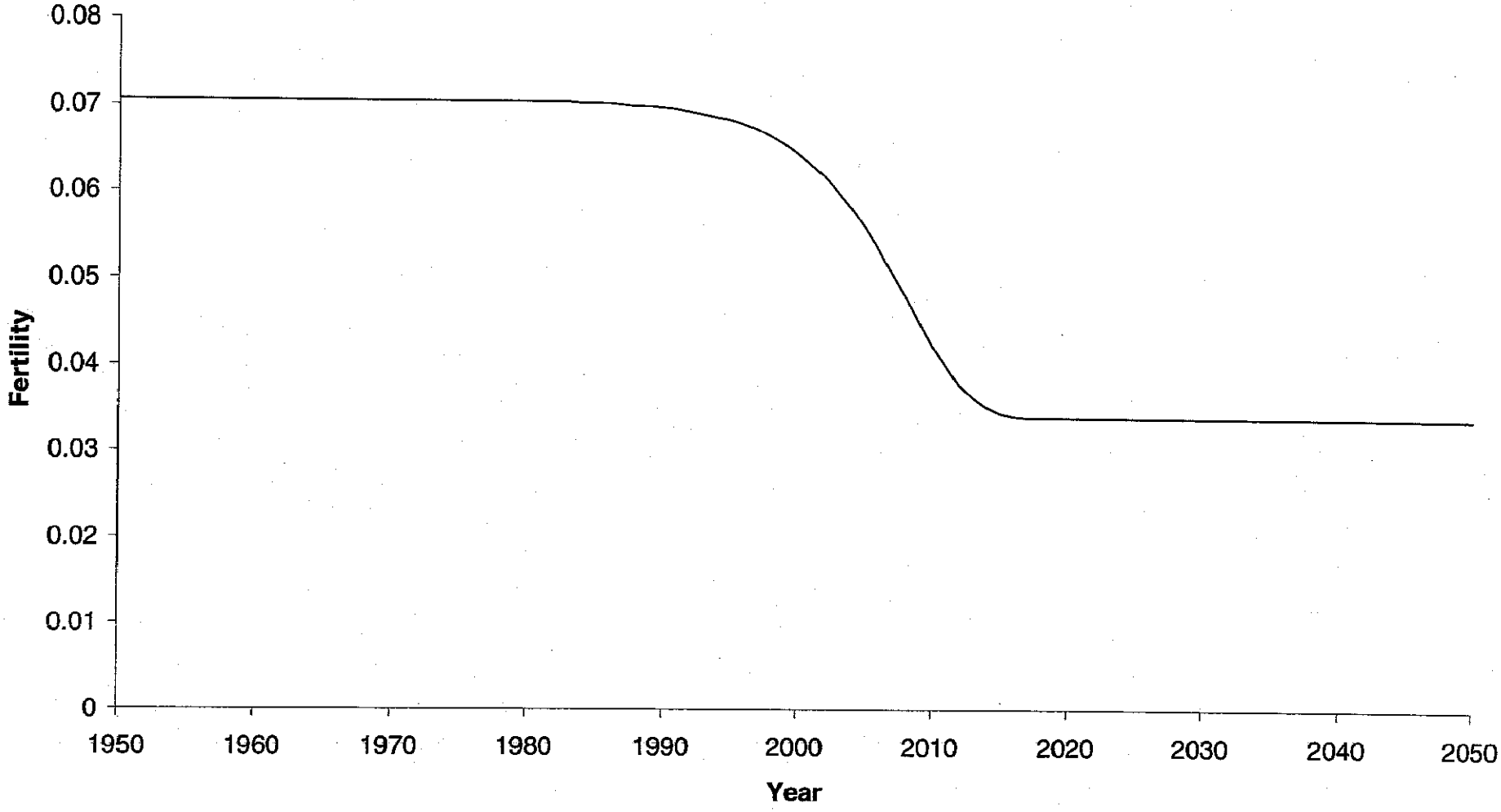

6,000,000
5,000,000
4,000,000
3,000,000
2,000,000
1,000,000
0
Population
0- 4
5- 9
10- 14
15- 19
20- 24
25- 29
30- 34
35- 39
40- 44
45- 49
50- 54
55- 59
60- 64
65- 69
70- 74
75- 79
80+
Age (years)

Fig 2b


0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Fertility
1950
1960
1970
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2010
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2040
2050
Year

Fig 2c

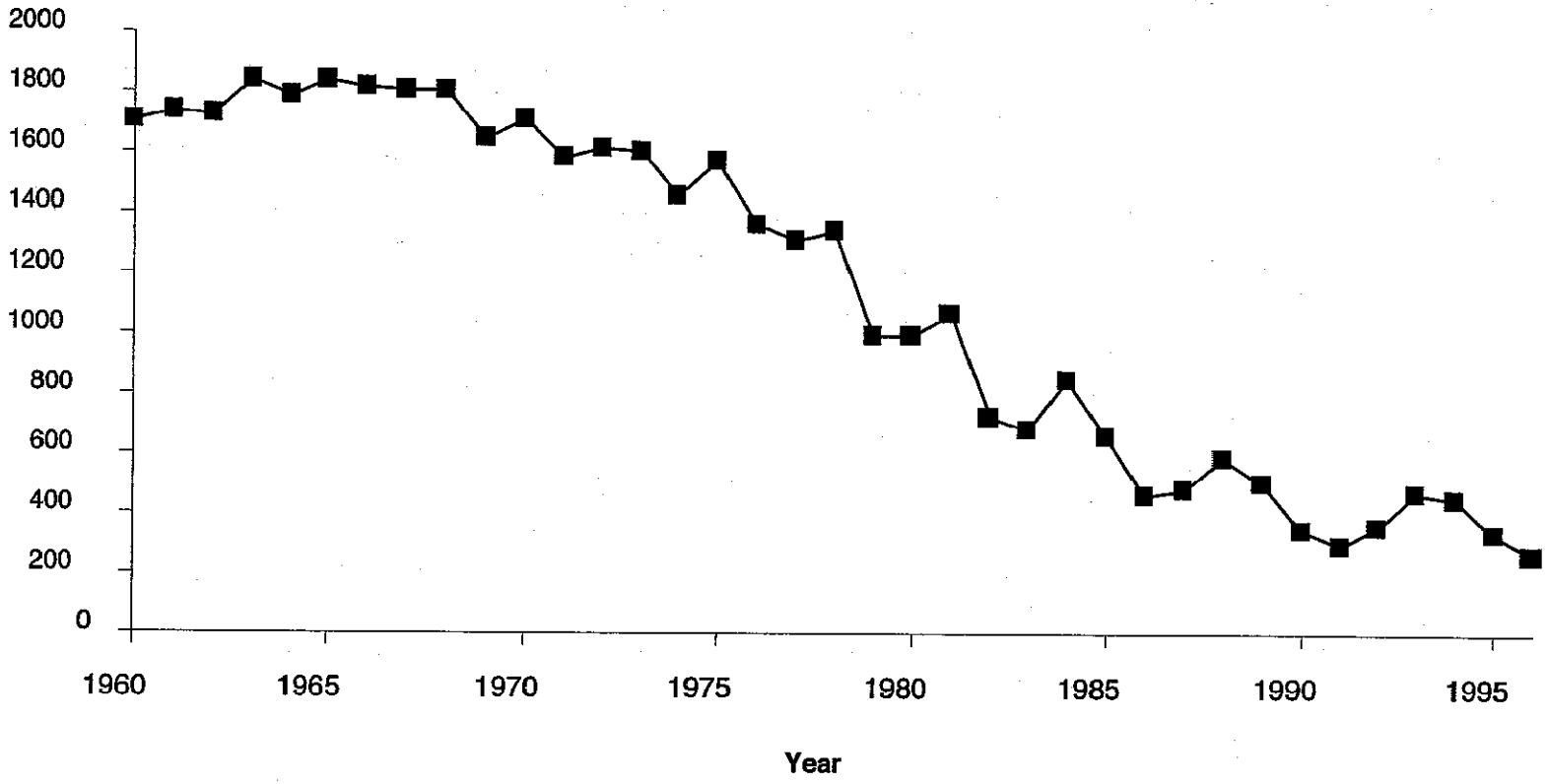
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1960
1965
1970
1975
1980
1985
1990
1995
Year

Fig 3

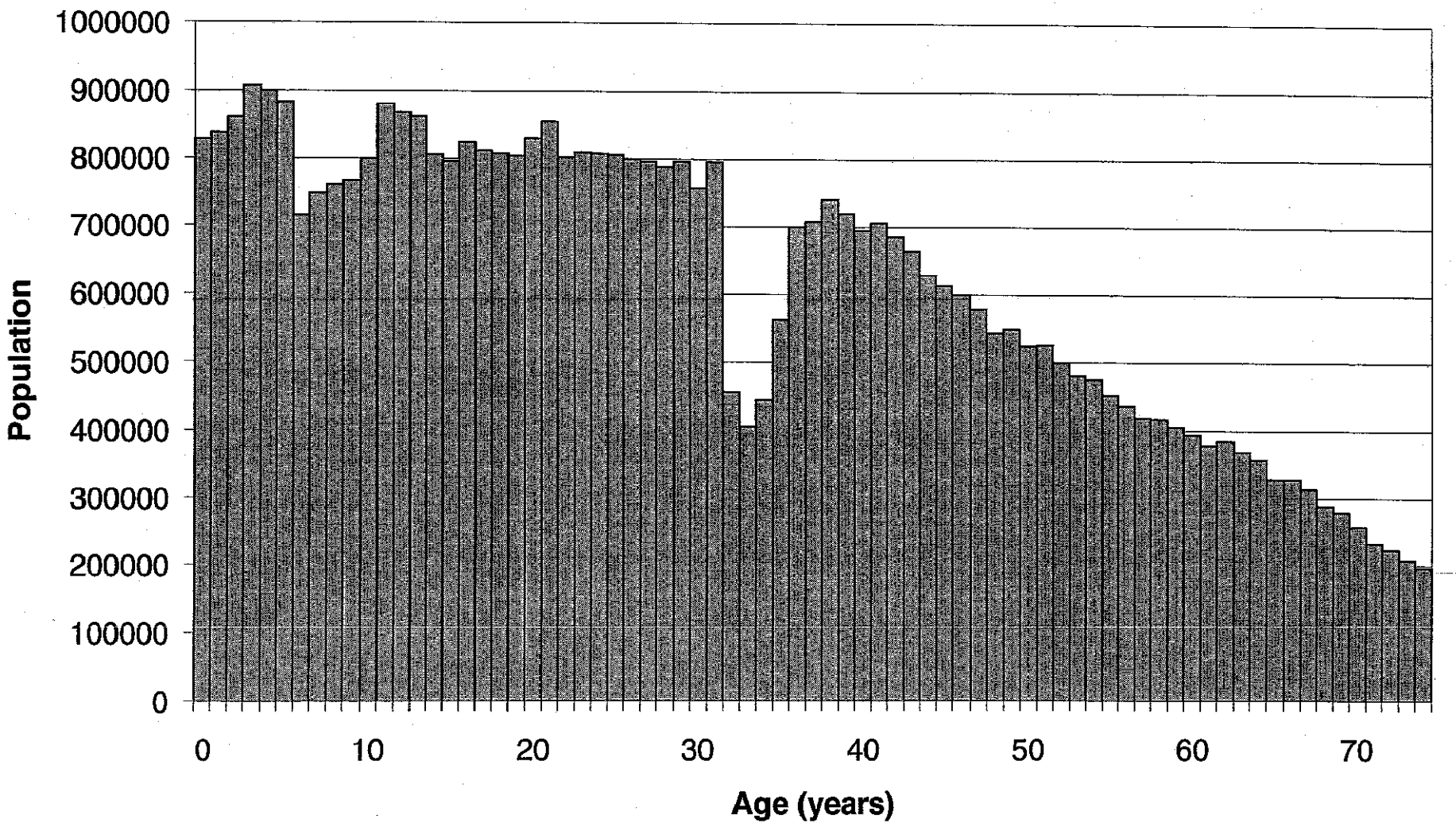
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
Population
0
10
20
30
40
50
60
70
Age (years)

Fig 4

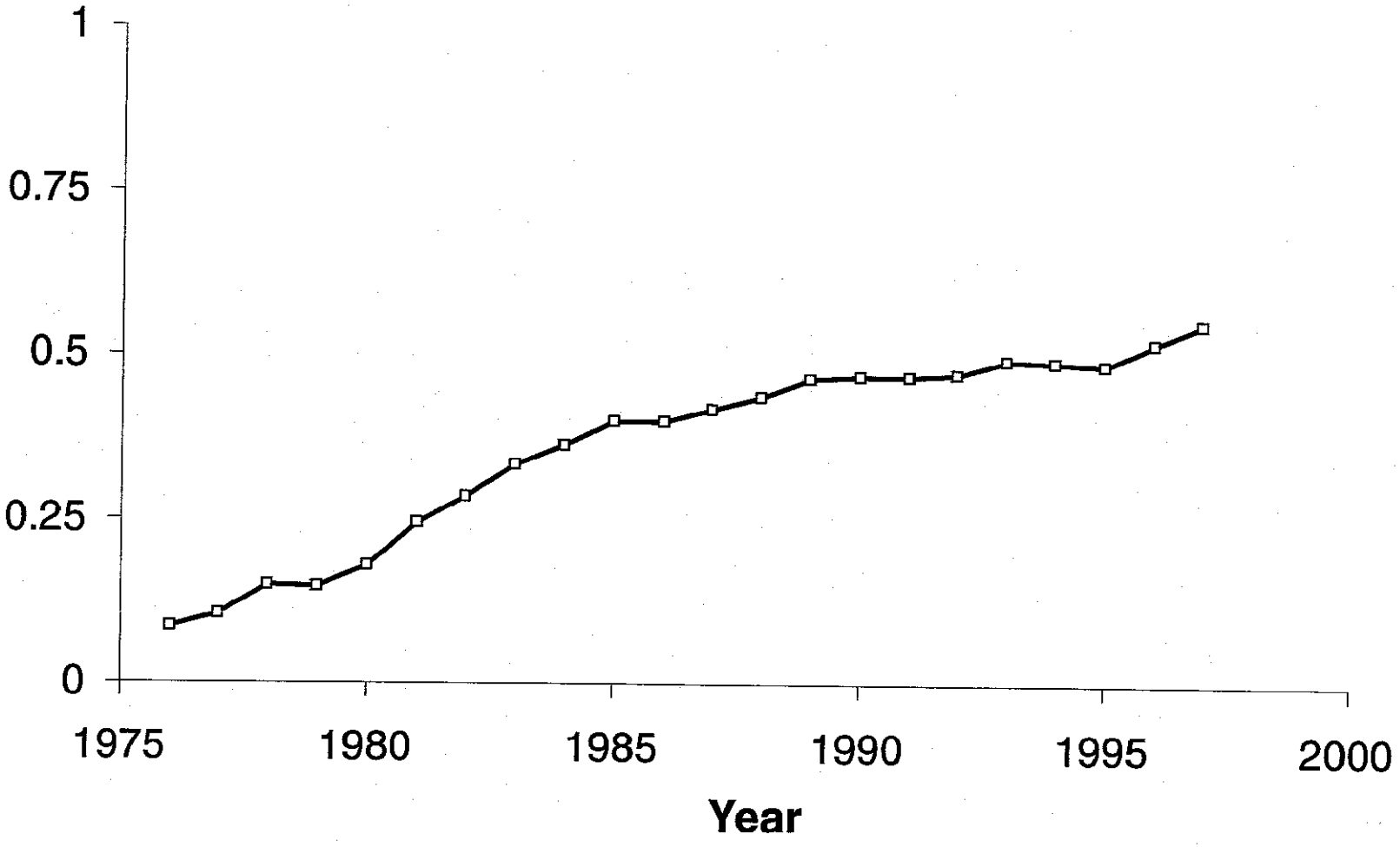

Fig 5

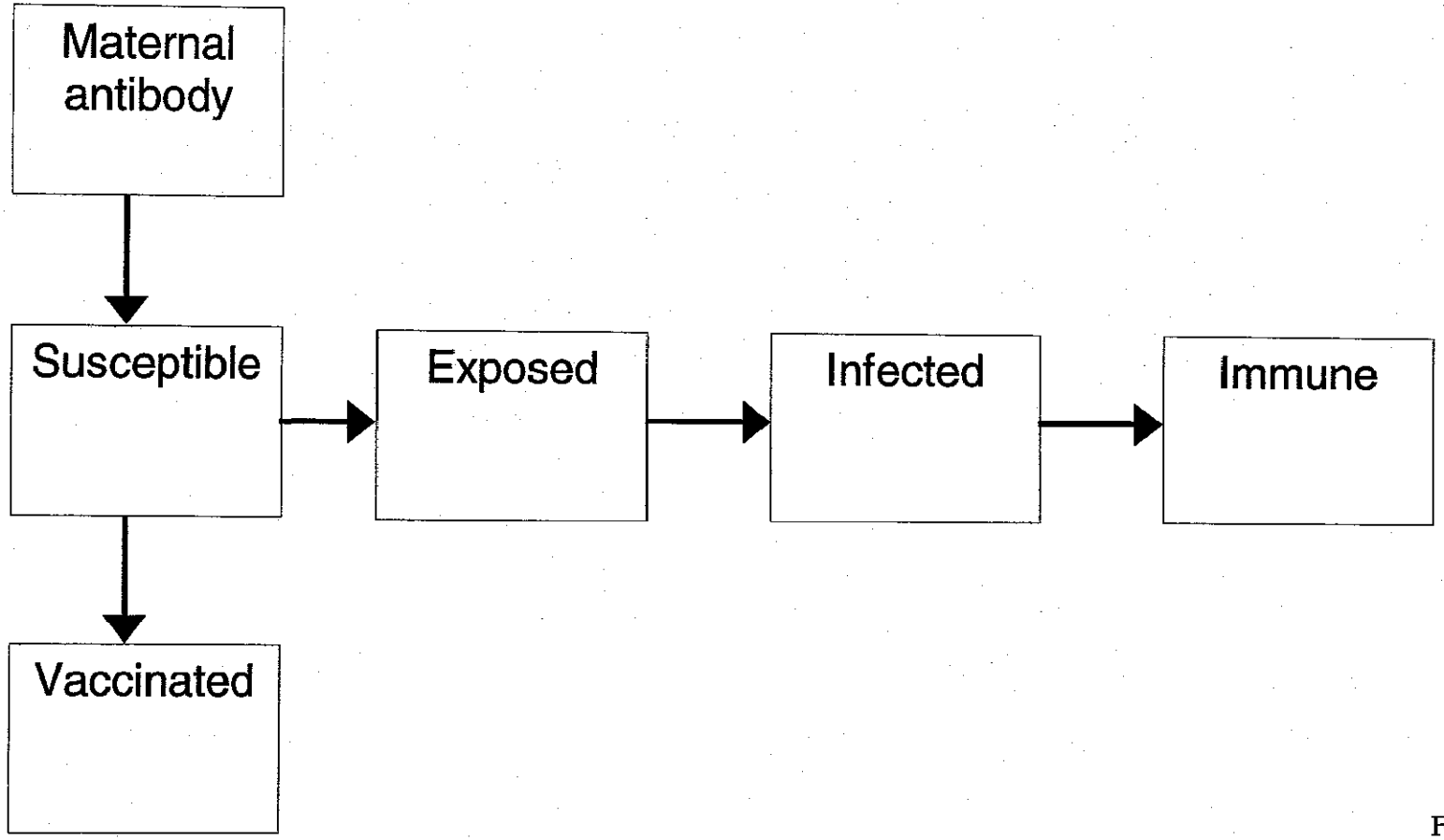
Maternal antibody
Susceptible
Exposed
Infected
Immune
Vaccinated

Fig 6

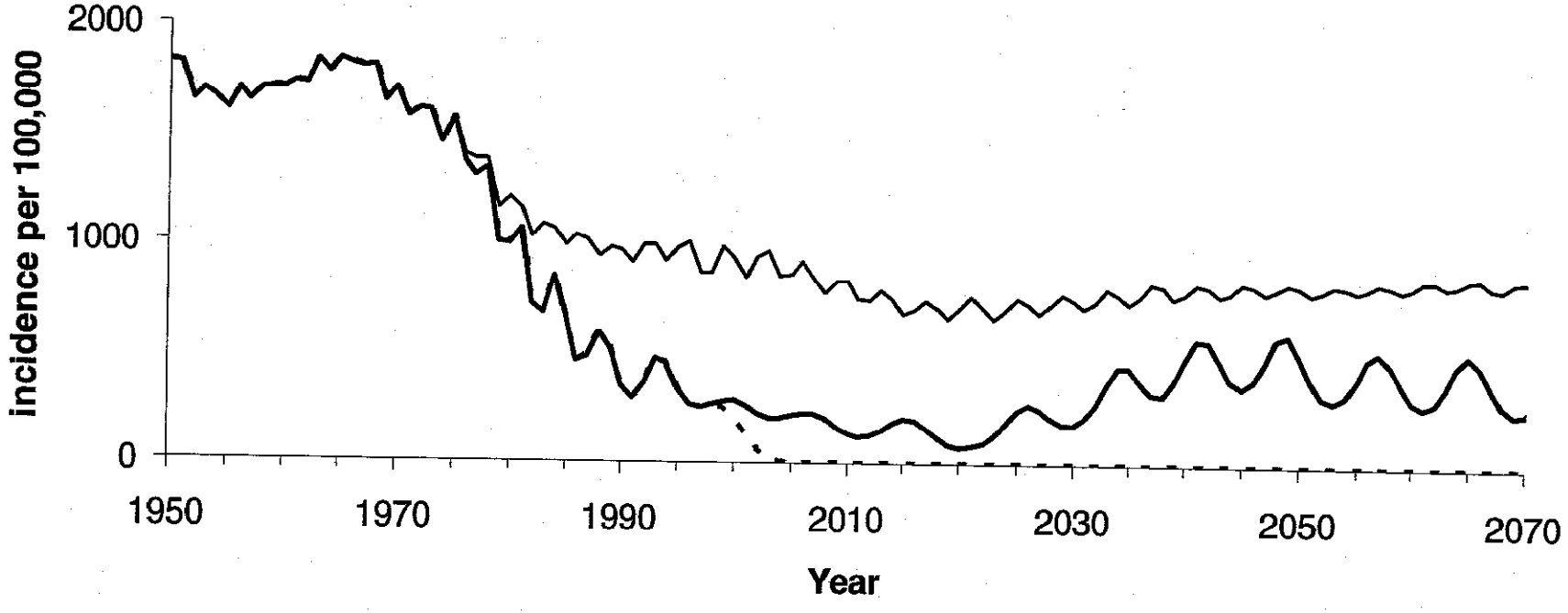
2000
1000
0
incidence per 100,000
1950
1970
1990
2010
2030
2050
2070
Year

Fig 7a

7a

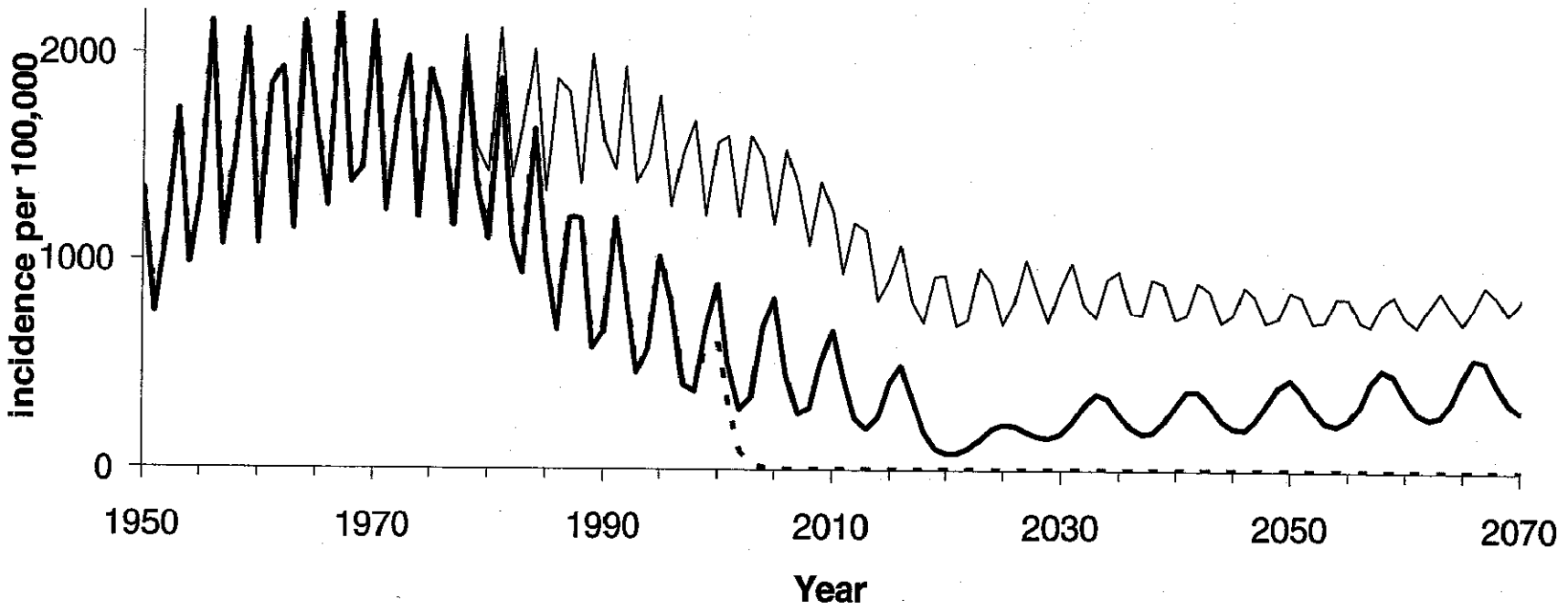
incidence per 100,000
2000
1000
0
1950
1970
1990
2010
2030
2050
2070
Year

Fig 7b

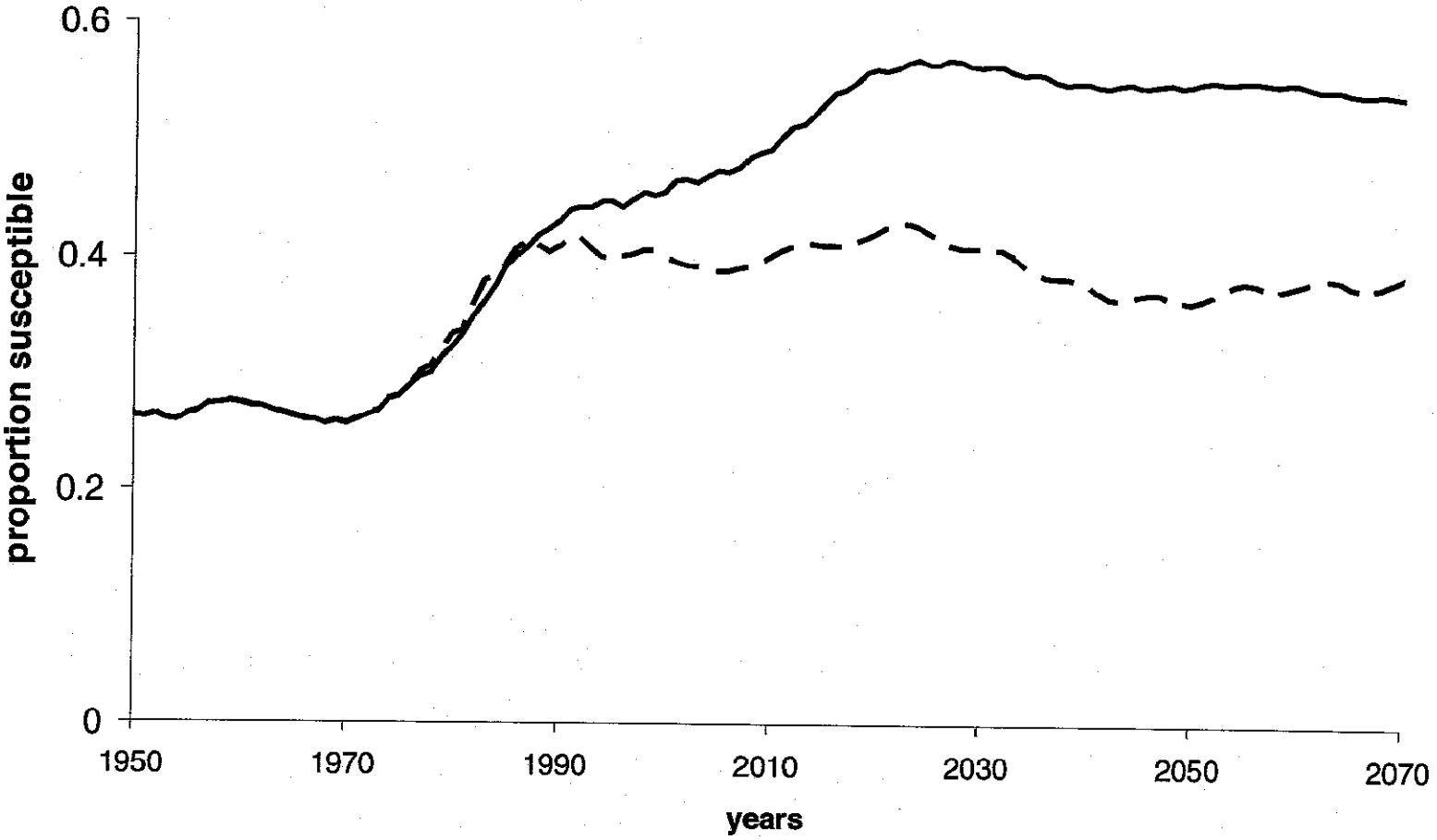
0.6
0.4
0.2
0
proportion susceptible
1950
1970
1990
2010
2030
2050
2070
years

Fig 8a

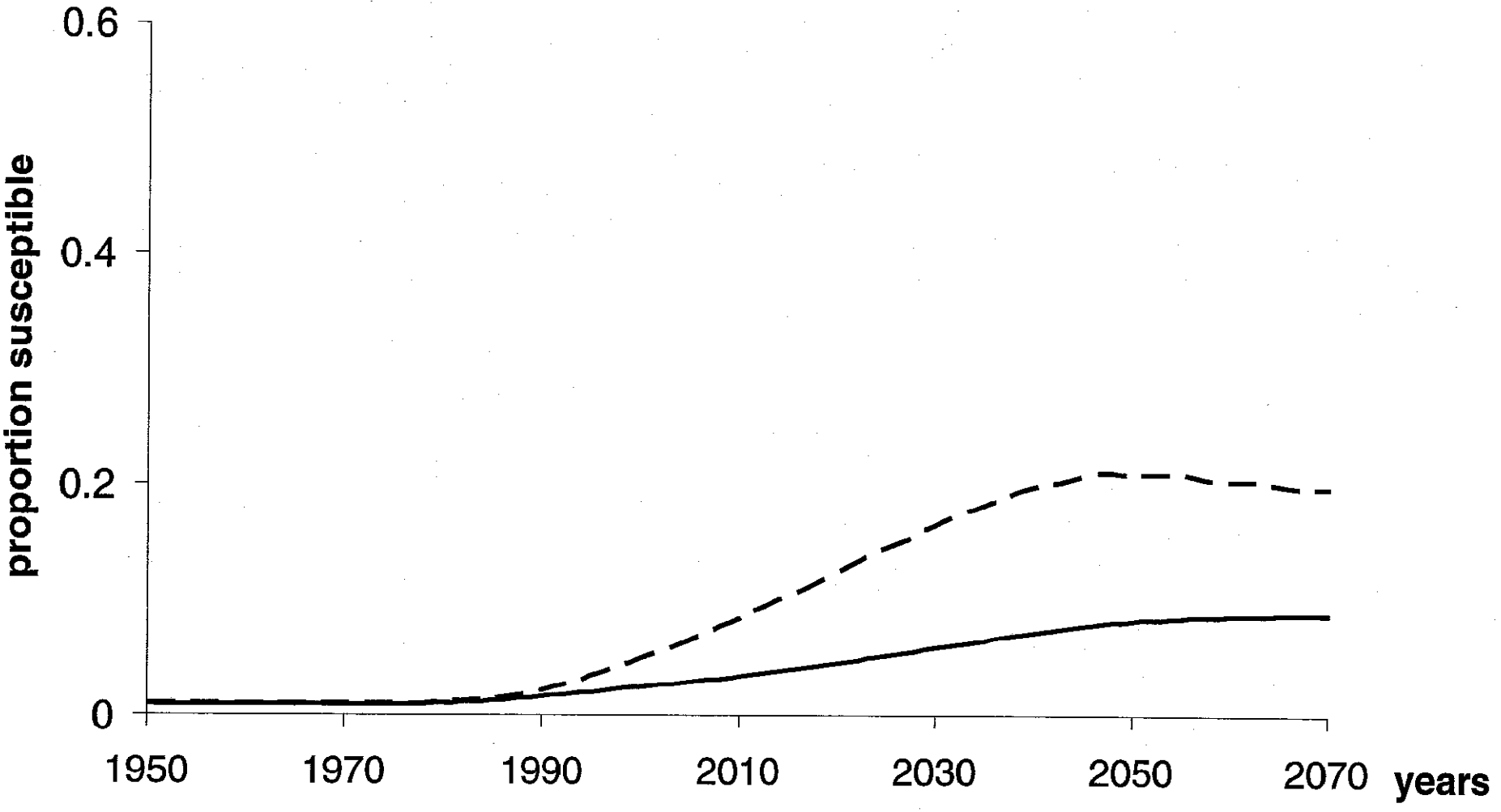
0.6
0.4
0.2
0
proportion susceptible
1950
1970
1990
2010
2030
2050
2070
years

Fig 8b

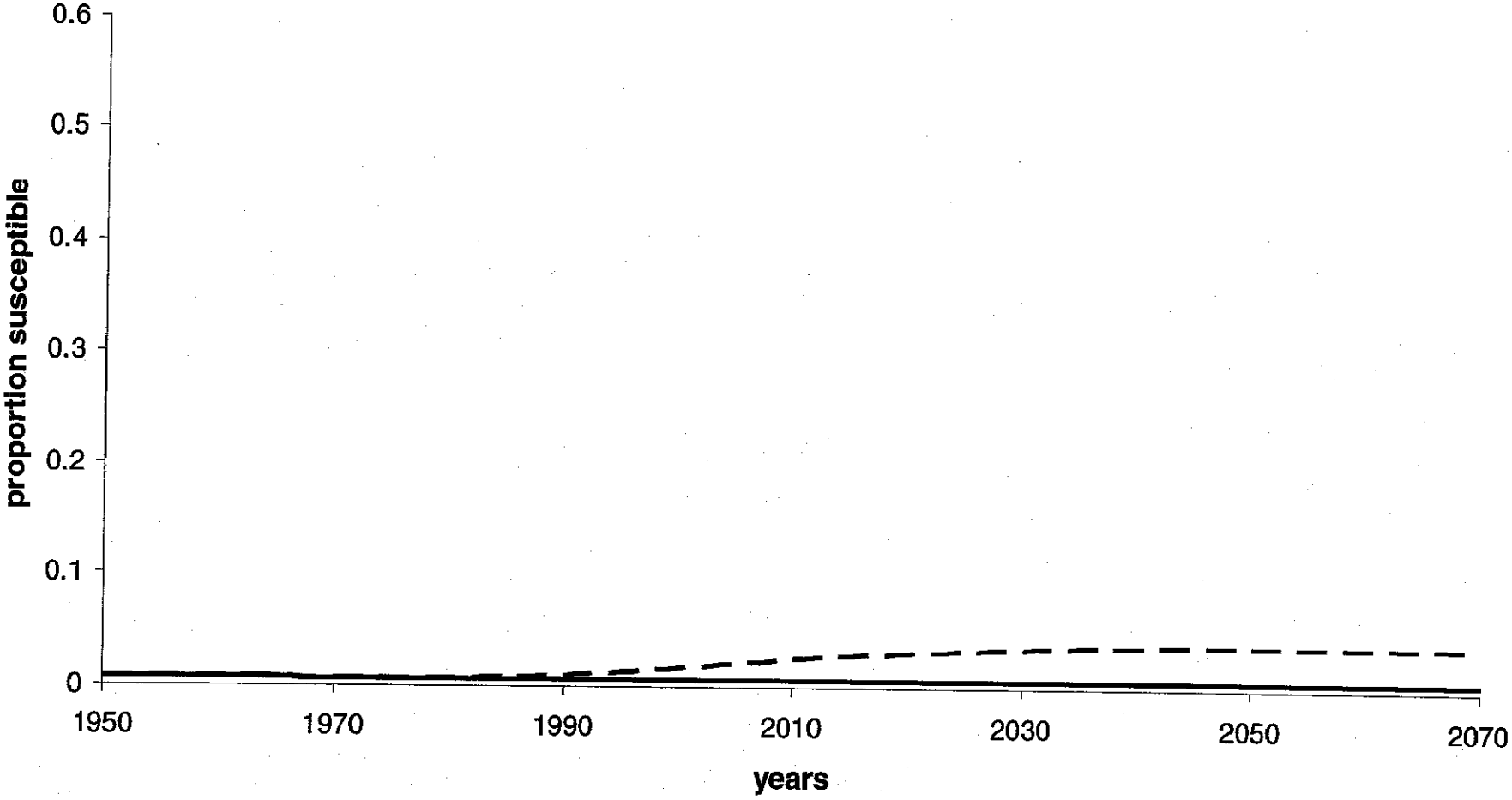
0.6
0.5
0.4
0.3
0.2
0.1
0
proportion susceptible
1950
1970
1990
2010
2030
2050
2070
years

Fig 8c

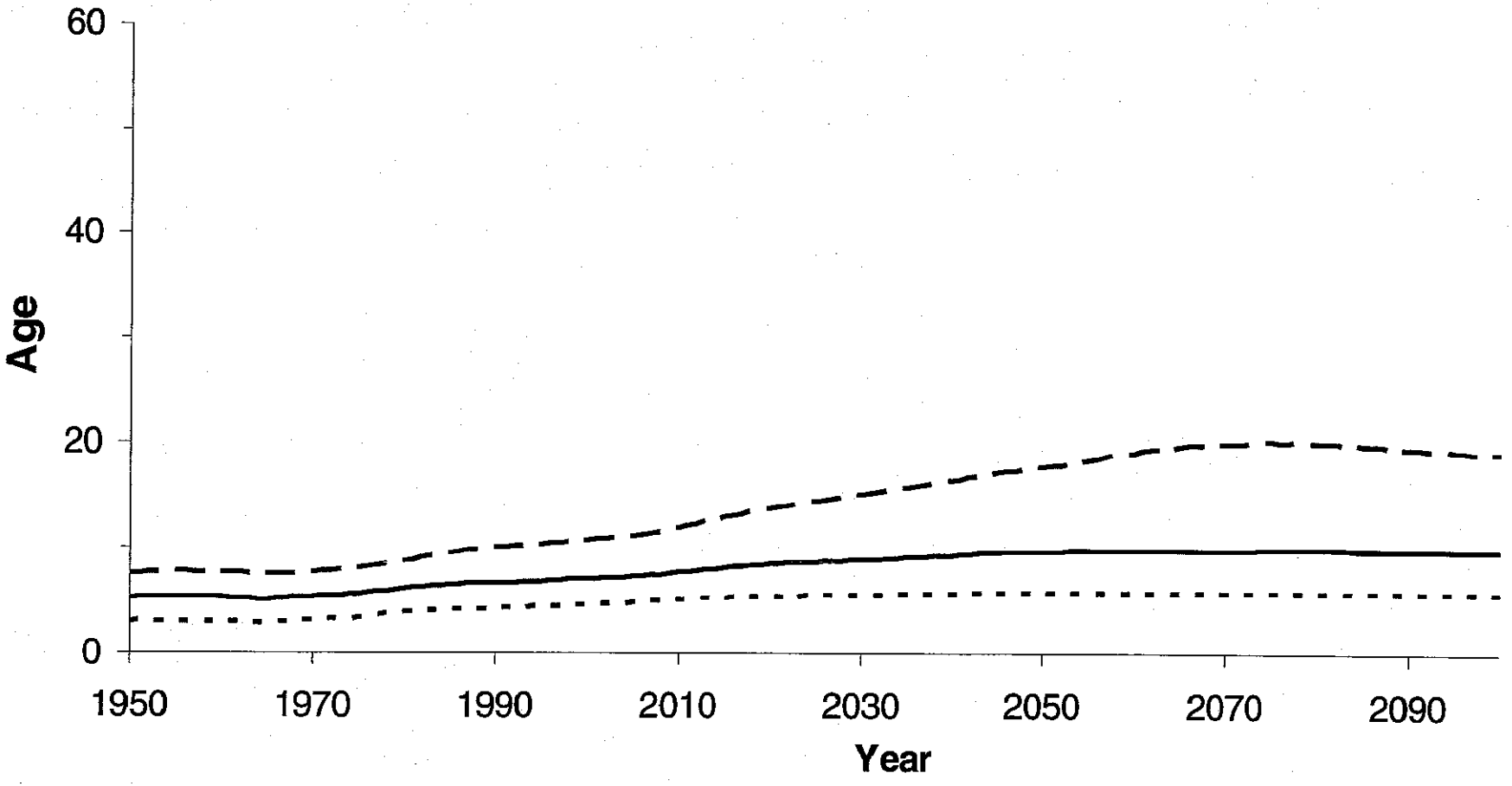

Fig 9a

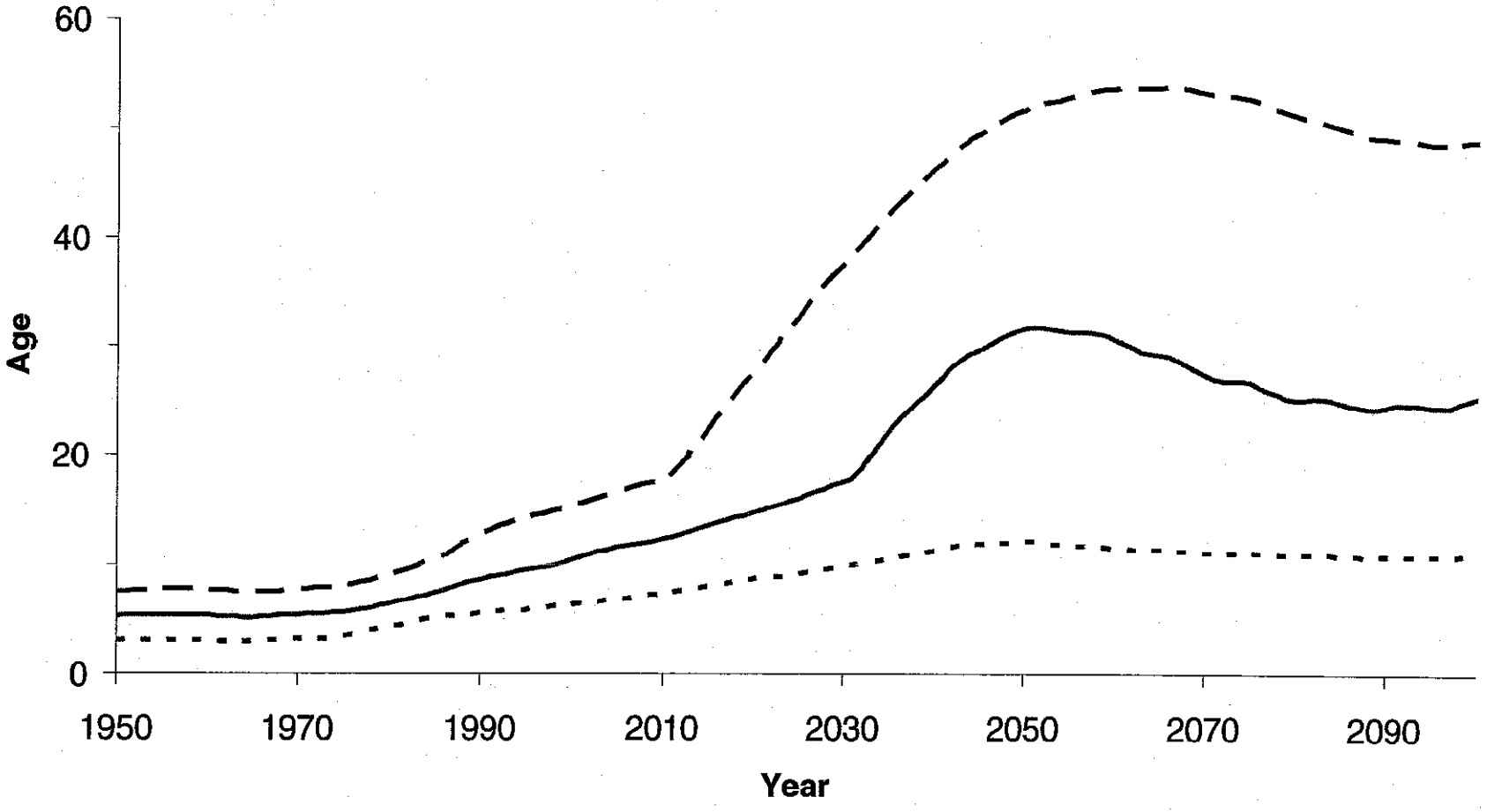

Fig 9b

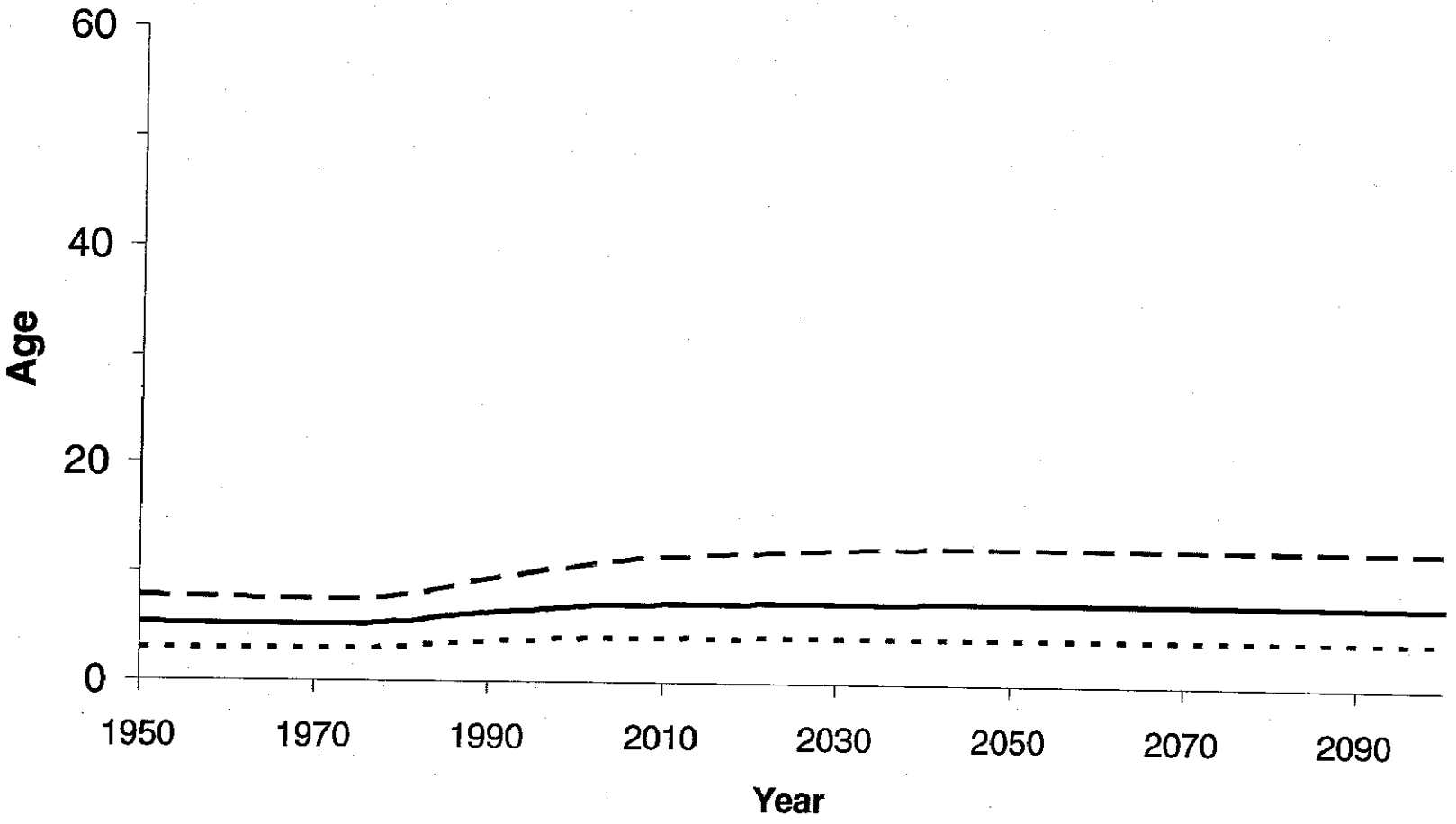

Fig 9c

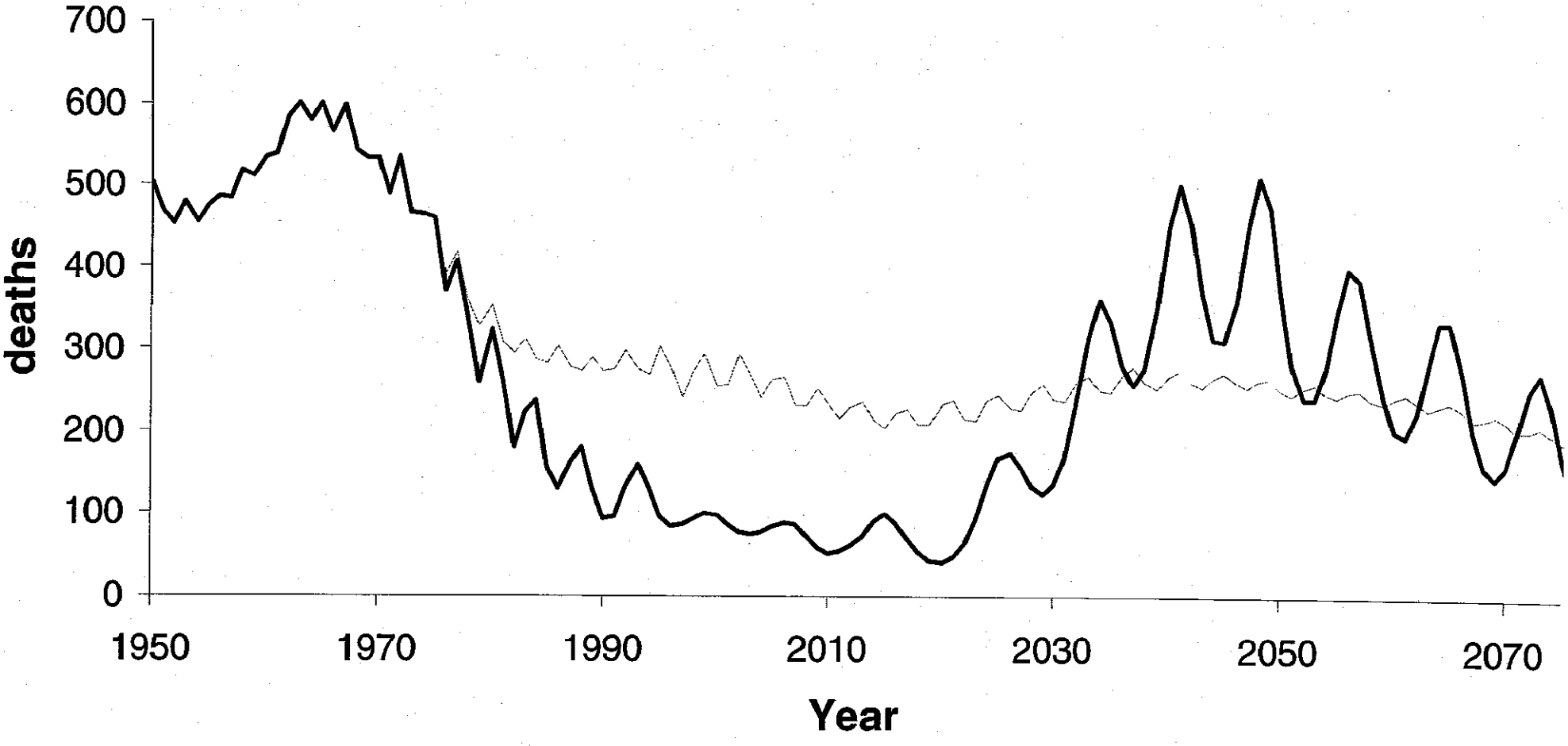
700
600
500
400
300
200
100
0
deaths
1950
1970
1990
2010
2030
2050
2070
Year

Fig 10

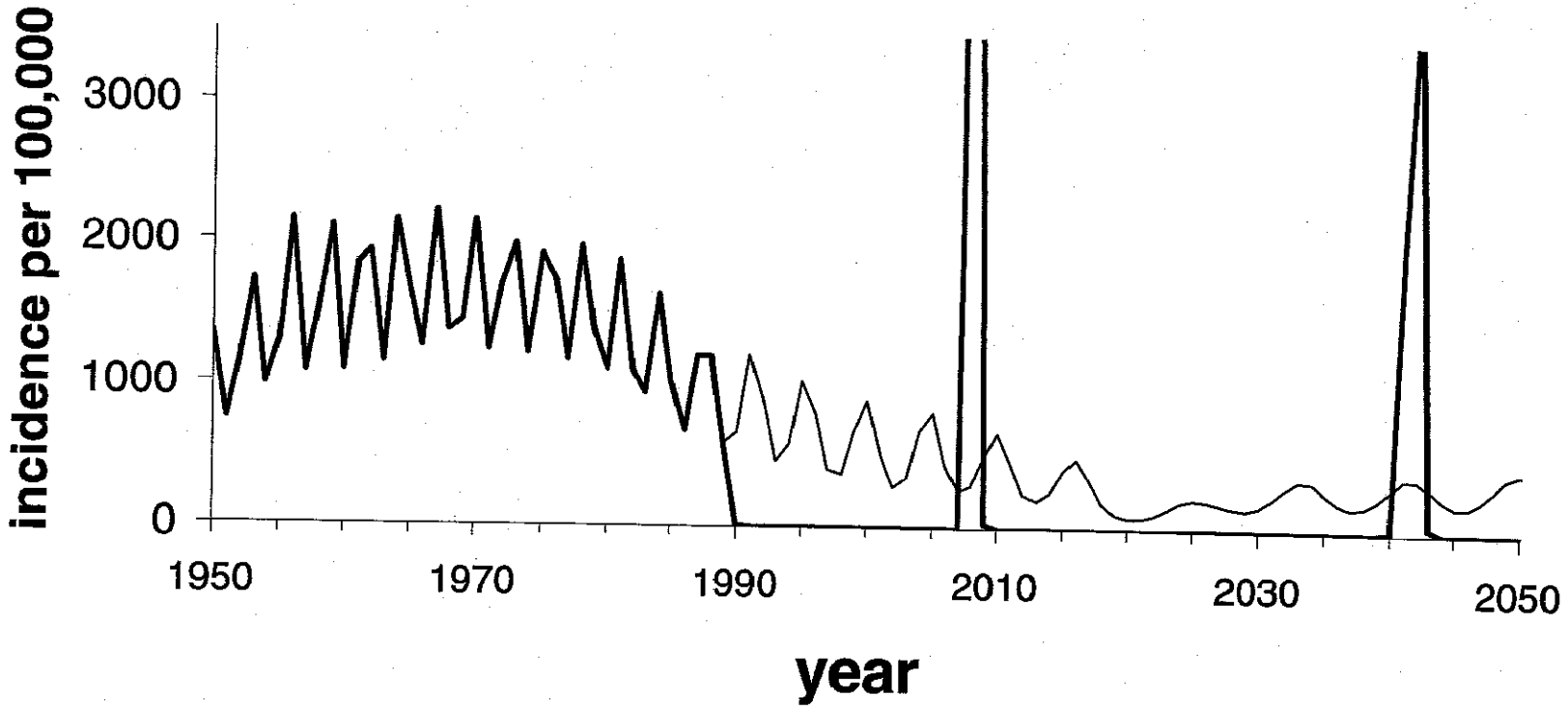
incidence per 100,000
3000
2000
1000
0
1950
1970
1990
2010
2030
2050
year

Figure 11a