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War-time evacuation and mortality from childhood leukaemia in England and Wales in 1945-9

L J Kinlen, S M John

Abstract

Objective—To discover whether the war-time government evacuation of children from London and other population centres to rural districts was associated with any increase in childhood leukaemia.

Design—Observational study of mortality from leukaemia among the childhood population of England and Wales in relation to the unique population movements during the second world war. The 476 rural districts of England and Wales were ranked according to the ratio of government evacuees (two thirds of them children) to local children in September 1941. The districts were divided into three categories, each with similar numbers of children in 1947 but with different ratios of evacuees to local children ("low," "intermediate," "high"). Mortality from childhood leukaemia was examined in these three rural categories in 1945-9. Urban areas were also examined according to their exposure to evacuees.

Setting—Local authority areas of England and Wales.

Subjects—Children aged under 15.

Results—47% excess of leukaemia at ages 0-14 years occurred in 1945-9 in the rural "high" category for evacuees relative to the "low" category, with a significant trend across the three categories. There were increases in both the 0-4 and 5-14 year age groups, but these were larger in the older age group. Rates 25% lower than average occurred in rural areas with few evacuees.

Conclusion—These findings suggest that war-time evacuation increased the incidence of childhood leukaemia in rural areas and that other forms of population mixing may have contributed to the increases in past decades. Overall, they add to the appreciable evidence for an infective basis in childhood leukaemia.

Introduction

The mixing of rural and urban groups of people has been associated with significant increases in childhood leukaemia.¹⁻⁶ This is consistent with the disease having an infective basis. Such mixing is conducive to an epidemic by promoting some critical level of contacts between susceptible and infected people, people who are susceptible being more prevalent in rural areas. During the second world war the evacuation by the government of large numbers of children from London

and other population centres to safer areas produced urban-rural mixing. We therefore investigated the possible effects of such evacuation on mortality from childhood leukaemia with particular reference to the rural parts of England and Wales.

Subjects and methods

EVACUATION AND POPULATION DETAILS

Before the second world war the fear of aerial bombardment of civilians led the British government to prepare a scheme for evacuation. Under this scheme London and many towns were designated as evacuation areas, many other local authority districts being designated as "reception areas," and the remainder being declared "neutral."^{7,8} These categories applied to children and certain other special groups in the (voluntary) official scheme, and people were free to make their own arrangements to move into neutral or reception areas if they wished. Most rural districts in England and Wales were designated as reception areas for government evacuees.

The numbers of people billeted away from their home areas under the government scheme fluctuated appreciably during the war⁹ (see table I). However, only one billeting schedule could be traced in the Public Records Office. This gave the numbers of unaccompanied and accompanied children, mothers, and other evacuated adults (including teachers and helpers) present in each local authority area in September 1941 (Public Records Office, file RG26/76).

The ratio of the number of evacuated people (as given in the billeting schedule) to the number of local children (below age 15)—the "evacuee index"—in each district of England and Wales in 1941 was taken as a crude measure of the intensity of exposure of local children in each area to evacuees. The numbers of local children in each district in 1941 were estimated by adjusting those recorded in 1947⁹ by factors that related the national populations in each age group in 1941¹⁰ to those in 1947. That year (1947) was the only year between 1931 and 1951 for which age specific populations of children were known for each local authority district, the details being derived from national registration records.⁹

The availability of local population details of children by age group in 1947 was also useful because it was the central year of the study (1945-9) and therefore provided a convenient set of denominators in the mortality analyses. The relative populations of three

Cancer Research
Campaign Epidemiology
Unit, Department of Public
Health and Primary Care,
University of Oxford, The
Radcliffe Infirmary, Oxford
OX2 6HE
L J Kinlen, director
S M John, statistician

Correspondence to:
Dr Kinlen.

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groups of rural districts (after ranking them by their evacuee index (see below)) during 1945-9 may have differed from those in 1947. Because of the absence of any census in the 15 years before the 1947 figures, we made separate calculations for the later part of the study—that is, for 1947-9. In England and Wales no other three year period was so closely associated with age specific local populations from two separate censuses (or their equivalent)—namely, the national registration records of 1947 and the 1951 census. From the mean of these we derived estimates for 1949 so that leukaemia mortality analyses in 1947-9 could be based on local populations for each of these years, those for 1948 being taken as the mean of the adjacent years.

Rural districts were the local authority areas of greatest interest in this study. Altogether there were 476. Twenty^{8 11 12} (Public Records Office, file RG26/76), mainly in Kent¹² (file RG26/76), were themselves evacuated, chiefly because of the flying bomb attacks in 1944. However, many had previously received many evacuees (file RG26/76), so that their later evacuation would further have increased contacts with evacuees in the new reception areas as well as with the people of those areas, some of which were urban. These additional exposures could not be quantified so we made a notional, token allowance for them by including an increment of 0.05 in their evacuee index. In fact, this produced little change in their categories.

The 476 districts were then ranked according to the evacuee index, calculated as above. Three categories of reception rural districts were formed based on their evacuee indices in 1941—namely, “low,” “intermediate,” and “high”—but which contained as closely

as possible similar numbers of children aged 0-14 years in 1947. In addition, evacuated and non-evacuated urban areas were identified and non-evacuated urban areas grouped into the same categories used in the rural analyses in terms of the ratio of evacuees to local children.

LEUKAEMIA

We had wished to investigate the possible effects of evacuation on leukaemia mortality both during the war and in the immediate postwar years. However, no geographical tabulations are available before 1950, and individual deaths from leukaemia (or other specific cause) can be identified by the Office of Population Censuses and Surveys only from 1959, when computerisation was introduced. Details of people who had died of leukaemia in England and Wales in 1945-9 (but not earlier) had been provided by the Registrar General for another study.¹³ These records were successfully traced and their numbers found to correspond closely with published details of deaths from leukaemia in 1945-9.¹⁴ Only six death certificates were missing for the age group 0-4 years and one missing from the age group 5-14 years.

The numbers of deaths from leukaemia at ages 0-14, 0-4, and 5-14 years in each of the three rural categories were determined. These were compared with expected numbers, calculated by applying to the 1947 age specific populations⁹ of these three groups of areas the published national death rates for leukaemia in 1945-9¹⁴ based on the 1947 populations. Separate comparisons were made for 1947-9 by using the additional population data described above.

Observed and expected numbers of deaths from leukaemia were also examined in evacuated areas and in three groups of urban areas with differing proportions of evacuees, corresponding to the evacuee indices used in the analysis of rural districts. For each set of areas leukaemia mortality was also examined in 1950-3 in conjunction with the 1951 census populations.

In an attempt partially to remedy the lack of leukaemia data before 1945 we requested (with the approval of the Office of Population Censuses and Surveys) local registrars of deaths in certain counties to search their records for 1940-4 for registrations among children that mentioned leukaemia.

TABLE I—Total numbers (thousands) of people billeted in all areas of England and Wales under government evacuation scheme

Calendar year†	Unaccompanied children	Mothers and children	Other adults	Total
1939	765	426	107	1298
1940	421	57	41	519
1941	436	450	178	1064
1942	236	196	98	530
1943	137	124	61	322
1944	284	601	128	1013
1945	13	0	0	13

†All counts except for 1940 refer to September; 1940 refers to August.

TABLE II—Numbers of rural districts by evacuee index and county (evacuated rural districts shown in parentheses)

Low Intermediate High			Low Intermediate High		
Anglesey	0	1	2	Lincolnshire:	
Bedfordshire	0	0	4	Holland	2 1 0
Brecknockshire	1	2	3	Kesteven	3 1 0
Berkshire	0	4	7	Lindsey	8 1 0
Buckinghamshire	0	2	6	Merionethshire	0 0 4
Caernarvonshire	0	0	4	Monmouthshire	1 3 1
Cambridgeshire	0	0	3	Montgomeryshire	0 4 0
Cardiganshire	0	2	3	Norfolk	4 7 4
Cardmarthenshire	0	1	3	Northamptonshire	0 2 6
Cheshire	3 (1)	6	1	Northumberland	5 4 1
Cornwall	1	0	10	Nottinghamshire	3 3 0
Cumberland	3	2	2	Oxfordshire	0 0 6
Denbighshire	0	1	4	Pembrokeshire	0 1 3
Derbyshire	5	4	0	Peterborough	1 1 0
Devon	0	0	17 (1)	Radnorshire	0 0 5
Dorset	0	3	6	Rutland	1 1 1
Durham	10	0	0	Shropshire	3 3 4
Essex	3	4	4	Somerset	0 3 13
Flintshire	0	2	2	Staffordshire	6 4 0
Glamorganshire	2	2	3	East Suffolk	4 2 1
Gloucestershire*	6	6	3	West Suffolk	0 2 4
Hampshire	1	7	3	Surrey	0 2 3
Herefordshire	2	3	3	East Sussex	1 2 2
Hertfordshire	1	3	7	West Sussex	1 2 3
Huntingdonshire	0	0	4	Warwickshire	1 6 2
Isle of Ely	0	2	2	Westmorland	0 0 2
Isle of Wight	1	0	0	Wiltshire	1 9 2
Kent	8 (6)	5 (5)	4 (4)	Worcestershire	1 7 0
Lancashire	8 (2)	6	1	Yorkshire:	
Leicestershire	2	6	1	East Riding	1 1 6
				North Riding	9 9 2
				West Riding	11 5 5

*One parish in one district was evacuated.

STATISTICS

Significance levels (two sided) for relative risks were calculated based on an assumed Poisson distribution. Point estimates for relative risks were computed in the different categories of exposure to evacuees by using the observed to expected ratios. Confidence intervals were calculated by exact methods when appropriate and otherwise by using a normal approximation.

Results

In September 1941 out of a total of 1 063 700 government evacuees in England and Wales (table I), 471 864 were billeted in rural districts; 67% were children and 16% mothers accompanying their children. Three similar sized categories of reception rural districts were formed, in which the ratios of evacuees to local children were, respectively, less than 0.170:1 (low), 0.171-0.357:1 (intermediate), and 0.358:1 and over (high; up to 1.310:1). The numbers of children aged 0-14 years in 1947 in these three categories were 580 927, 583 426, and 585 855. In 1941 they contained respectively 11%, 29%, and 60% of all the evacuees in rural districts. Details of their constituent districts by county are listed in table II.

The observed and expected numbers of deaths from leukaemia at ages 0-4, 5-14, and 0-14 years in the three rural categories are shown in table III. At ages 0-14

TABLE III—Leukaemia at ages 0-4, 5-14, and 0-14 years in 1945-9 in three categories of rural districts with different proportions of evacuated people in 1941. Results expressed as observed and expected numbers of deaths and relative risk

Evacuee index	Age 0-4 years			Age 5-14 years			Age 0-14 years		
	Observed	Expected	Relative risk (95% confidence interval)	Observed	Expected	Relative risk (95% confidence interval)	Observed	Expected	Relative risk (95% relative risk)
Low	40	44.24	1.00	21	39.57	**1.00	61	83.81	*1.00
Intermediate	46	44.51	1.14 (0.75 to 1.77)	32	39.70	1.52 (0.89 to 2.77)	78	84.21	1.27 (0.91 to 1.80)
High	49	43.66	1.24 (0.82 to 1.91)	41	40.43	1.91 (1.17 to 3.45)	90	84.09	1.47 (1.07 to 2.06)*
P for trend		0.311			0.014			0.020	
Excluding evacuated rural districts			0.367			0.043			0.047
Excluding 1945			0.182			0.026			0.016

*P<0.05. **P<0.01.

TABLE IV—Leukaemia at ages 0-4, 5-14, and 0-14 years in 1947-9 in three categories of rural districts with different proportions of evacuated people in 1941. Results expressed as observed and expected numbers of deaths and relative risk

Evacuee index	Age 0-4 years			Age 5-14 years			Age 0-14 years		
	Observed	Expected	Relative risk (95% confidence interval)	Observed	Expected	Relative risk (95% confidence interval)	Observed	Expected	Relative risk (95% relative risk)
Low	23	29.74	1.00	11	24.79	1.00	34	54.53	**1.00
Intermediate	31	30.09	1.33 (0.78 to 2.37)	20	24.94	1.80 (0.91 to 4.33)	51	55.03	1.49 (0.97 to 2.36)
High	35	29.57	1.53 (0.95 to 2.71)	25	25.18	2.24 (1.17 to 5.36)*	60	54.75	1.76 (1.17 to 2.77)**

*P<0.05. **P<0.01.

TABLE V—Leukaemia at ages 0-4, 5-14, and 0-14 years in 1950-3 in three categories of rural districts with different proportions of evacuated people in 1941. Results expressed as observed and expected numbers of deaths and relative risk

Evacuee index	Age 0-4 years			Age 5-14 years			Age 0-14 years		
	Observed	Expected	Relative risk (95% confidence interval)	Observed	Expected	Relative risk (95% confidence interval)	Observed	Expected	Relative risk (95% relative risk)
Low	40	42.89	1.00	39	42.44	1.00	79	85.33	1.00
Intermediate	50	44.07	1.22 (0.81 to 1.87)	42	43.03	1.06 (0.68 to 1.66)	92	87.10	1.14 (0.85 to 1.55)
High	47	43.55	1.16 (0.76 to 1.79)	38	42.41	0.98 (0.62 to 1.53)	85	85.96	1.07 (0.79 to 1.46)
P for trend		0.508			0.913			0.680	

there was a significant increasing trend ($P=0.02$) across the three categories. In the high evacuee category there was a 47% excess of deaths relative to the low category. The excess in the high category for evacuees was most pronounced at ages 5-14 (table III). This amounted to a 90% excess relative to the low category, with a significant trend across the categories ($P=0.014$), though at ages 0-4 years there was no significant trend. These trends partly reflected the significantly lower than average death rates from childhood leukaemia in the low rural category for evacuees. The significant trends ($P<0.05$) at ages 5-14 and 0-14 years remained after exclusion of the evacuated rural districts. In these there were seven deaths at ages 0-4 years (expected 6.59) and two at 5-14 years (expected 5.73) (table III). Compared with the whole study period (table III) all the excesses were more pronounced in 1947-9 when additional population data were used, the trend at ages 0-14 years being more significant ($P=0.08$) (table IV). There was no suggestion of these trends persisting into the next period (1950-3; table V).

None of the deaths in 1945 occurred in evacuated children, for whom two addresses were required at death registration. Nor was there any suggestion from the stated place of residence of a parent that any later death in the high rural category occurred in any of the few evacuees who remained in reception areas because they had lost their parents or their homes. Excluding deaths in 1945 (23 at 0-4 years, 21 at 5-14 years) had little effect on the excesses or the trends (0-4 years, $P=0.182$; 5-14 years, $P=0.026$; 0-14 years, $P=0.016$) (table III).

Examination of leukaemia mortality in London and other evacuated areas showed no significant change at ages 0-14 or 0-4 years either in 1945-9 (table VI) or in 1950-3 (data not shown). No excess or trend was detected in non-evacuated urban areas (table VII),

when the same cut off points as in table III were used for the three categories of exposure to evacuees.

The response from local registrars who were asked to search their registers was insufficient to assess mortality from childhood leukaemia in 1940-4 in rural counties with many evacuees. However, coverage (possibly incomplete) of the rural districts of Devon, which had more evacuees than any other county, disclosed four deaths at ages 0-4 years (expected 2.45) among local children. By contrast, in the main study period (1945-9) there was no death in this age group (3.65 deaths expected; $P<0.05$) in any rural district of Devon.

Discussion

EVACUATION

The evacuation of massive numbers of children and other people away from densely populated and potentially dangerous areas in the second world war was an extraordinary undertaking. Films, publications,^{7 15} the records of mass observation, and widespread personal recollections have left vivid images of wartime evacuees from deprived urban areas sent to rural areas. However, certain details of the scale of these movements are not so well known.^{7 15}

TABLE VI—Observed and expected numbers of leukaemia deaths at ages 0-4 and 0-14 years in 1945-9 in evacuated urban and rural districts

Type of area	Age 0-4 years		Age 0-14 years	
	Observed	Expected	Observed	Expected
London	43	53.46	94	92.75
County boroughs	161	170.55	306	313.22
Other urban	73	67.54	130	122.73
Total urban	277	292.25	530	530.00

TABLE VII—Observed and expected numbers of leukaemia deaths at ages 0-4 and 0-14 years in 1945-9 in three categories of non-evacuated urban districts with different proportions of evacuated people in 1941

Evacuee index	Age 0-4 years						Age 0-14 years					
	County boroughs		Other urban		Total		County borough		Other urban		Total	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Low	47	53.23	180	159.18	227	212.41	91	98.46	318	297.37	409	395.83
Intermediate	4	4.82	30	36.49	34	41.31	8	9.20	77	69.70	85	78.90
High	5	7.20	38	37.10	43	44.30	11	13.59	69	70.39	80	83.98

In the three days before the outbreak of war in September 1939, 1.3 million people in England and Wales (two thirds of them children, some with their mothers) had been moved under government auspices from London and other target areas. Two million other people had moved themselves, and about 140 000 sick people had been turned out of hospitals in readiness for civilian casualties from air attacks. These attacks did not occur, and by the end of that year over half a million children and mothers had returned to their homes, leaving 775 000 official evacuees still in reception areas.

In mid-1940 concern about an invasion led to many children being evacuated from east coastal towns from Norfolk to Sussex. In September 1940, when the heavy bombing of London began, much of the work of dispersing mothers and children had to be repeated. By February 1941 there were 1.3 million official evacuees in England and Wales, though unlike in 1939 this had been achieved without a mass exodus. In the two years from March 1942 the numbers of evacuees (chiefly those billeted in private households) again declined substantially but in June 1944 the start of flying bomb attacks led to the evacuation of a large belt of country between London and the coast. This amounted to 307 600 mothers and children under the official scheme, making the country total over a million (table I). In addition, about 552 000 mothers, children, and others left target areas in Kent under their own arrangements.

With the decline of the flying bombs later in 1944, and despite the start of rocket attacks, return home ("drift back") was occurring on a large scale. By March 1945 the number of official evacuees had fallen from more than a million in September 1944 to 438 000, and by September only 13 000 were still away. Early in 1946 only 5200 evacuated children remained (possibly about 2300 in rural areas), mainly because they had no suitable homes to return to, and these became the responsibility of the local authority.

POSSIBLE LIMITATIONS

We would prefer to have studied childhood leukaemia in rural areas both during and just after the war in relation to some measure of the overall level of exposure to evacuees, but this was not possible. In consequence our study has certain limitations. Thus the effects on childhood leukaemia of the rural billeting of urban evacuees in 1941 (a peak year for evacuation) might be obscured by the effects of evacuees earlier or later in the war or of other population movements, on none of which have we any details for different local areas. Thus billeting details for, say, 1944 might have been more relevant to our leukaemia data for 1945-9.

It is also possible that early and intense exposure to evacuated people in some areas produced an excess of leukaemia which lasted only three or four years, as found in relation to large concentrations of national military servicemen in the early 1950s.³ If so such an excess would have been missed by our study. It may be relevant that in Devon, which received more evacuees than any other county, a search of local death registers for its rural districts in 1940-4 yielded four deaths at ages 0-4 years among local children (expected 2.45), whereas in 1945-9 Devon's rural districts did not have

a single death at these ages (3.65 deaths expected; $P < 0.05$). This contrast is reminiscent of observations in rural new towns. After a significant excess of leukaemia at these ages as the towns grew rapidly there was a deficiency of deaths, consistent with an unusually low prevalence of susceptible children as a result of the earlier epidemic.²

ACCURACY OF ANALYSIS

Our study of 1945-9 is effectively one of local children. This is both by intention and because only negligible numbers of evacuees (about 600) were left in rural reception areas in December 1947, to which the main population data relate. These evacuees—even if all were in high category districts—could make only a very small contribution to the expected numbers (< 0.07). Only in the first half of 1945 were appreciable numbers of evacuees still present in reception areas. Because these were not represented in the denominator, no evacuee who died of leukaemia could be included in the corresponding numerator. However, no death of an evacuee from leukaemia was found in 1945 (or later) in a rural district, though many such cases were found in the limited search of death registers for 1940-4. In some of these the father's occupation suggested that they were outside the government scheme.

Conceivably an evacuee to a rural area who was shortly to return home but who died of leukaemia in 1945 would have only the original (urban) address offered by the informant at death registration. If this occurred the practice would have appropriately removed the child from the rural analysis. Excluding all data for 1945, however, had no material effect on the findings (table III, footnote). There is no reason to suppose that rural districts that received most evacuated children were subject to different population changes in 1945 and 1946 from those of other rural areas. The separate analysis for 1947-9 using additional local population data gave no suggestion of any such bias.

SIGNIFICANCE OF FINDINGS

These movements of children were recognised by epidemiologists at the time as having implications for the infectious diseases of childhood.^{16,17} Similar implications exist for the hypothesis about population mixing and childhood leukaemia. Notwithstanding certain limitations, we found a significant (positive) trend in leukaemia mortality below age 15 in 1945-9 in rural areas of England and Wales with increasing proportions of government evacuees in 1941. That this trend was more pronounced at ages 5-14 than at 0-4 years, particularly in 1947-9, may reflect the declining number of preschool children (and their mothers) who were exposed to wartime evacuees.

It has been claimed that mortality from childhood leukaemia during or after the war was not affected by evacuation but merely continued the increase that had begun long before.¹⁸ Against this national death rates are inevitably insensitive to increases among indigenous rural children, given the small proportion of the country's children that they represent. In the same way, national notification rates for childhood infections that were unremarkable concealed increases

in reception areas for evacuees.^{16 17} Our findings in a subgroup of rural districts are therefore not surprising.

It would be difficult to attribute our findings to differences in diagnostic standards or death certification practices among the three groups of rural areas, so varied was their geographical composition. In particular, this would have to explain both the significantly low mortality in the category of rural districts with few evacuees during the war and the successive improvements in areas with previously more evacuees. That higher standards of medicine should exist in 1945-9 in a large number of localised areas that had previously received many evacuees does not seem likely. As shown in table II, most counties contained rural districts in each of the three groups so that often the same hospital would serve districts in each category. The absence of any such effects in urban areas is in keeping with observations after population mixing in other urban areas.¹⁻⁶ and is consistent with a lower prevalence of people who are susceptible than in rural districts, where the low population density makes for a higher prevalence.

OTHER WARTIME POPULATION MIXING

Government evacuees were not the only people with opportunities for introducing infective agents into rural areas before or during the study period. Independently of the government scheme, many better off families moved to rural areas, often where they had spent holidays. To this category also belong boarding schools that moved their site. No details are available about the numbers of "private" evacuees in different areas,⁷ but they have been estimated as about 2 million in England and Wales in 1939, more than in the official scheme (1.2 million). In Devon, which had more official evacuees in 1941 than any other county, the ratio of private to official evacuees was estimated as about 7:1 in 1939.⁷

The same applies to the major movements of government departments and of war workers to specific areas. However, compared with these the official evacuees seem more relevant to the present hypothesis. Their origin in congested areas with much paternal unemployment together with the state of their clothing and footwear, the lack of cleanliness, and the frequent infestation were in stark contrast with conditions in the reception areas. Indeed, these unrequested glimpses of widespread conditions of life in other parts of Britain shocked public opinion and widened consciousness of social inequalities.⁷ These differences are relevant to this study as surrogates for important requirements for an epidemic—namely, a source of infection coupled with enough susceptible people.

Servicemen and women returning from the war are another large group that may be relevant to our findings. Concentration of servicemen in rural areas in a subsequent period of national military service was associated with local increases in childhood leukaemia.³ But the association between childhood leukaemia mortality and the proportion of evacuees in an earlier period cannot be explained just by "mixing" by these men. Their numbers would have been no greater in areas which had received many evacuees than in rural areas with few. The relative excess and the positive trend, however, were more pronounced in 1947-9 than in 1945-6, so some contribution by servicemen is possible. It may be relevant that in a study of the oil industry in northern Scotland there was evidence of combined mixing effects influencing childhood leukaemia.⁵

EXTENT OF MIXING BY EVACUEES

Basic to this study is the presumption that evacuation resulted in appreciable mixing between evacuees and local children, though there is no means of

Epidemiological implications

- The large scale mixing of urban and rural groups of people must increase contacts between susceptible and infected people, susceptible people being more prevalent in rural areas
- A series of studies of such situations have found associated increases of childhood leukaemia
- The evacuation by the government of large numbers of children in the second world war from London and large towns is another such situation, and a 47% increased mortality from childhood leukaemia was found by this study in the rural areas that received the largest numbers of evacuees
- The findings add further support for an infective basis in childhood leukaemia

determining its scale. This question was raised by Stocks in relation to his wartime studies of childhood infections and was considered complex.¹⁶ It would be unwarranted to assume that evacuation invariably resulted in mixing, at least to any great degree. Because of the drift back tendency many evacuated people—particularly those billeted in private houses—did not spend long periods away from their home areas. Also, some government evacuees whose schools kept their identity in the new areas remained separate from local children. Many evacuees quickly returned home. Nevertheless, it is inescapable that direct and indirect contacts occurred between the evacuated and local people, particularly out of school. Adults are also relevant in view of the evidence that both servicemen³ and oil industry workers⁵ may influence the incidence of childhood leukaemia in rural areas.

OTHER IMPLICATIONS

The period 1945-9 covered by this study is notable in that it is the earliest calendar period in which mortality from childhood leukaemia can be examined in rural parts of England and Wales, though only the "low" category represented rural areas without substantial changes recently affecting their childhood population. Interestingly, therefore, in that period mortality from childhood leukaemia was almost 30% lower in the rural low category than in England and Wales as a whole ($P < 0.05$) (table III). This suggests that in earlier periods rural districts more generally may have had lower rates than urban areas. The increases in childhood leukaemia mortality earlier this century up to the 1950s in part probably reflected improvements in diagnosis that were in turn helped by the declining mortality from the infectious diseases that had often masked the leukaemic state.¹⁹ This study implies that population mixing may also have contributed to these increases. More strongly, it suggests that war-time evacuation brought mortality from childhood leukaemia in many rural areas into line with that in urban areas of England and Wales.

Overall the findings add to the appreciable evidence from studies of population mixing for an infective basis in childhood leukaemia.¹⁻⁶

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Apolipoprotein e4 allele and cognitive decline in elderly men

Edith J M Feskens, Louis M Havekes, Sandra Kalmijn, Peter de Knijff, Lenore J Launer, Daan Kromhout

Abstract

Objectives—To determine whether polymorphism of apolipoprotein E—notably, the e4 allele—predicts cognitive deterioration in the general population.

Design—Population based cohort investigated in 1990 and in 1993.

Setting—Zutphen, the Netherlands.

Subjects—Representative cohort of 538 Dutch men aged 70-89 at baseline.

Main outcome measures—Cognitive function assessed by mini mental state examination, change in cognitive function and incidence of impaired cognitive function at three years.

Results—The baseline prevalence of impaired cognitive function (mini mental state examination score ≤ 25) was higher among carriers of the e4 allele compared with men without the allele (41.0% (55) v 31.1% (122) $P=0.03$), and this result was still valid after adjustment for age, occupation, smoking, alcohol use, and cardiovascular diseases. The decline in cognitive function at three years was largest in men homozygous for e4 (-2.4 points), intermediate in those heterozygous for e4 (-0.7 points), and lowest in men without e4 (-0.1 points), and it was independent of other risk factors ($P=0.02$). The risk of developing impaired cognitive function during follow up was significantly increased in allele carriers compared with non-carriers (27.6% (16/58) v 15.5% (32/207)). The adjusted odds ratio was 2.87 (95% confidence interval 1.29 to 6.42). Twenty two per cent of the risk of developing impaired cognitive function in this population may be attributable to the e4 allele.

Conclusions—The apolipoprotein e4 allele predisposes to cognitive decline in a general population of elderly men.

Introduction

Cognitive performance is an important indicator of health and functioning in elderly people and is, as such, of increasing importance in our aging society. Cognitive decline can be regarded as a marker of a dementing process, and current knowledge of the aetiology of dementia may point at potential risk factors for reduced cognitive function with aging.

The genetic heterogeneity of apolipoprotein E may have a functional role in the pathogenesis of both late

and early onset familial Alzheimer's disease.^{1,2} Apolipoprotein E is a plasma protein involved in the metabolism of cholesterol and triglycerides. It is present in particles such as chylomicrons, very low density lipoprotein and their remnants, and high density lipoprotein. It serves as ligand for receptor mediated uptake of these lipoproteins in the liver and other organs.³ It is a polymorphic protein with e2, e3, and e4 as common isoforms. The gene is localised on the long arm of chromosome 19.^{4,5} Several studies have shown that apolipoprotein E polymorphism affects plasma concentrations of lipid and lipoprotein,^{6,8} and the e4 isoform was found to be associated with an increased risk of premature coronary heart disease.^{6,9}

Apolipoprotein E is also involved in the regenerative response of injured nerve tissue, and it is present in amyloid plaques of various amyloid forming diseases.^{1,10} Linkage between markers in the apolipoprotein E gene region and late onset familial Alzheimer's disease has been reported.¹¹ Recently, it has been shown that the prevalence of the e4 allele is increased in subjects with late onset familial and sporadic Alzheimer's disease,¹²⁻¹⁵ as well as in early onset cases.^{2,16} In addition, increased prevalence of the e4 allele was reported from patients with vascular dementia.¹⁷

It is not yet clear to what extent apolipoprotein E affects overall cognitive performance, and population based studies are currently lacking. Because of its potential role in atherosclerosis and vascular dementia as well as in Alzheimer's disease we hypothesised that the e4 allele is a risk factor for cognitive dysfunction, and we investigated this issue in a three year longitudinal study of a population based cohort of elderly men in the Netherlands.

Subjects and methods

SUBJECTS

The Zutphen elderly study is a longitudinal investigation of risk factors for chronic diseases in elderly men carried out in Zutphen, a town in the eastern part of the Netherlands.¹⁸ It represents a continuation of the Zutphen study, the Dutch contribution to the seven countries study.¹⁹ In 1985, 555 men of the original cohort born between 1900 and 1920 were still alive and were invited for new examinations together with an additional random sample of 711 men of the same age group (65-84 years). In 1985, 939 men (response rate

Department of Chronic Diseases and Environmental Epidemiology, National Institute of Public Health and Environmental Protection, PO Box 1, 3720 BA Bilthoven, Netherlands
Edith J M Feskens, senior researcher
Sandra Kalmijn, research fellow
Lenore J Launer, researcher
Daan Kromhout, professor

TNO-Institute of Preventive Health Research PG-TNO, Gaubius Laboratory, Leiden, Netherlands
Louis M Havekes, senior researcher
Peter de Knijff, researcher

Department of Epidemiology and Biostatistics, Rotterdam Medical School, Netherlands
Sandra Kalmijn, research fellow

Correspondence to: Dr Feskens.

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