Papers

Population based study of rates of multiple pregnancies in Denmark, 1980-94

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Abstract

Objective: To study trends in multiple pregnancies not explained by changes in maternal age and parity patterns.

Design: Trends in population based figures for multiple pregnancies in Denmark studied from complete national records on parity history and vital status.

Population: 497 979 Danish women and 803 019 pregnancies, 1980-94.

Main outcome measures: National rates of multiple pregnancies, infant mortality, and stillbirths controlled for maternal age and parity. Special emphasis on primiparous women ⩾30 years of age, who are most likely to undergo fertility treatment.

Results: The national incidence of multiple pregnancies increased 1.7-fold during 1980-94, the increase primarily in 1989-94 and almost exclusively in primiparous women aged ⩾30 years, for whom the adjusted population based twinning rate increased 2.7-fold and the triplet rate 9.1-fold. During 1989-94, the adjusted yearly increase in multiple pregnancies for these women was 19% (95% confidence interval 16% to 21%) and in dizygotic twin pregnancies 25% (21% to 28%). The proportion of multiple births among infant deaths in primiparous women ⩾30 years increased from 11.5% to 26.9% during the study period. The total infant mortality, however, did not increase for these women because of a simultaneous significant decrease in infant mortality among singletons.

Conclusions: A relatively small group of women has drastically changed the overall national rates of multiple pregnancies. The introduction of new treatments to enhance fertility has probably caused these changes and has also affected the otherwise decreasing trend in infant mortality. Consequently, the resources, both economical and otherwise, associated with these treatments go well beyond those invested in specific fertility enhancing treatments.

Introduction

The rates of multiple pregnancies have varied considerably during this century. These fluctuations have predominantly been explained by changes in maternal age and parity.[1] New risk factors for multiple pregnancies have appeared with the introduction of hormonal induction of ovulation and advanced reproduction techniques.[2-5] Such regimens may result in multiple pregnancies in about a quarter of the births.[5] Despite the relatively small proportion of a population who undergo treatment to enhance fertility, their substantially increased risks of multiple pregnancies could have considerable impact on the national rates.

We took advantage of the population based national registers in Denmark to study trends in rates of multiple pregnancy that were not explained by changes in maternal age and parity patterns. Furthermore, we analysed to what extent changes in these rates influenced the national rates for stillbirths and infant mortality.

Subjects and methods

Data from the Danish Civil Registration System were used to obtain complete family histories. All liveborn children and new residents in Denmark are recorded in this register and ascribed a unique 10 digit personal identification number (the person number). Individual information is kept under the person number in all national registers, which enables high quality linkages between the different registers. The registration system was established on 1 April 1968, when all people who were alive and resident in Denmark were registered. It includes various data such as date of birth, sex, vital status, and information on parents. On the basis of this system we established a database that contains close to complete information on parity for all women born in Denmark who gave birth during the study period (January 1980 to September 1994). For this particular study, we added information from the Danish National Birth Registry on all stillborn children (born after 28 completed weeks of pregnancy) born during the period 1978-93. Data on stillbirths were not available for 1994. In this study a pregnancy was defined as a delivery. In order to identify multiple pregnancies we looked for children (live and stillborn) born to the same mother within two days (on each side of midnight). All children were assigned a number that indicated whether they were singleton, twin, triplet, quadruplet, or quintuplet. The mothers were assigned a parity number for each delivery.

Weinberg's differential rule was used to estimate the number of dizygotic and monozygotic twin pairs—that is, the number of dizygotic twin pairs was calculated as twice the number of opposite sexed twin

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Table 1 Distribution of all pregnancies (deliveries) in Danish women from January 1980 to September 1994

Year	All pregnancies	Twin pregnancies (per 100 pregnancies)	Triplet pregnancies (per 10 000 pregnancies)	Higher order pregnancies	All multiple pregnancies (per 100 pregnancies)
1980	54 449	557 (1.02)	6 (1.11)	0	563 (1.03)
1981	50 435	508 (1.01)	8 (1.59)	0	516 (1.02)
1982	50 204	513 (1.02)	6 (1.20)	0	519 (1.03)
1983	48 374	514 (1.06)	8 (1.65)	1	523 (1.08)
1984	49 111	558 (1.14)	6 (1.22)	0	564 (1.15)
1985	50 931	576 (1.13)	6 (1.18)	0	582 (1.14)
1986	51 991	562 (1.08)	10 (1.92)	0	572 (1.10)
1987	52 455	592 (1.13)	6 (1.14)	0	598 (1.14)
1988	54 631	630 (1.15)	11 (2.01)	1	642 (1.18)
1989	56 652	661 (1.17)	19 (3.35)	0	680 (1.20)
1990	58 401	668 (1.14)	17 (2.91)	2	687 (1.18)
1991	58 376	787 (1.35)	21 (3.60)	1	809 (1.39)
1992	60 969	850 (1.40)	28 (4.60)	1	879 (1.44)
1993	59 987	942 (1.57)	26 (4.33)	2	970 (1.62)
1994*	46 053	771 (1.67)	28 (6.08)	1	800 (1.74)
Total	803 019	9689 (1.21)	206 (2.57)	9†	9904 (1.23)

*Only first three quarters of 1994 are included. Stillbirths were not available in 1994.
†One quintuplet and eight quadruplet pregnancies.

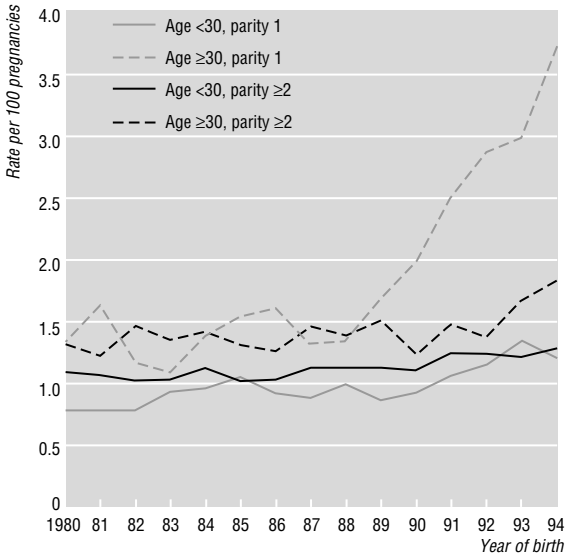

Fig 1 Twinning rates for Danish women from January 1980 to September 1994 by age of mother and parity

pairs and the number of monozygotic pairs was calculated as the total number of twin pairs minus the estimated number of dizygotic pairs.[6]

Adjustment for changes in maternal age and parity was done with a log-linear binomial regression model[7] with the SAS procedure PROC GENMOD.[8] Adjustment for parity was based on a categorisation into three groups (1, 2, and ≥3 para) and adjustment for maternal age on a categorisation into six age groups (<20, 20-24, 25-29, 30-34, 35-39, and ≥40 years) for multiple pregnancies and twin pregnancies overall, while for dizygotic and monozygotic twin pregnancies and for triplet pregnancies the adjustment was into four age groups (<25, 25-29, 30-34, and ≥35 years) because of smaller numbers.

Analyses of infant deaths (liveborn children dead within one year of birth) were performed only for children born during 1980-92 as data on deaths were not available for the whole year of 1994.

Results

Multiple pregnancies

During January 1980 to September 1994 we recorded 803 019 pregnancies (deliveries) (table 1) among 497 979 women. Of these, 9904 (1.23%) were multiple pregnancies. There were 9689 (1.21 per 100 pregnancies) twin pregnancies, 206 (2.57 per 10 000 pregnancies) triplet pregnancies, eight quadruplet pregnancies, and one quintuplet pregnancy. During 1980-94, the mean age of the mother at first birth rose from 24.2 to 26.8 years and the mean age at second and later deliveries rose from 28.4 to 30.2 years. Overall, 38.7% of all deliveries occurred in primiparous women below 30 years of age and 7.4% in primiparous women ≥30 years. In comparison, 29.2% of all deliveries were recorded in multiparous women below 30 years of age and 24.7% in multiparous mothers ≥30 years. The proportion of women who had their first baby when they were aged ≥30 years rose from 4.9% in 1980 to 10.3% in 1994.

The crude rate of multiple pregnancies increased from 1.03 per 100 pregnancies in 1980 to 1.18 in 1988 and increased further to 1.74 in 1994 (table 1). The crude twinning rate increased from 1.02 per 100 pregnancies in 1980 to 1.15 in 1988 and reached 1.67 in 1994 (table 1). Figure 1 illustrates the calendar effect on twinning rates by parity and maternal age. Table 2 shows changes in the twinning rates adjusted for maternal age and parity. For primiparous women ≥30 years of age there was a 2.7-fold (95% confidence interval 2.3 to 3.2) adjusted increase in the twinning rate from the period 1980-8 to 1994, corresponding to a yearly increase of 18% (15% to 20%) from 1989 to 1994. Primiparous women <30 years of age, multiparous women <30 years, and multiparous women ≥30 years experienced adjusted increases in the twinning rates of 1.3 (1.1 to 1.5), 1.2 (1.0 to 1.4), and 1.3 (1.2 to 1.5), respectively.

Triplet pregnancies showed a similar but more pronounced pattern (table 2). The crude triplet rate

Table 2 Changes in twinning and triplet rates during 1989-94 by age of mother and parity. Values are rate ratios adjusted for age and parity (95% confidence intervals)

	Twin pregnancies				Triplet pregnancies			
	Parity 1		Parity ≥2		Parity 1		Parity ≥2	
Year	<30 Years	≥30 Years	<30 Years	≥30 Years	<30 Years	≥30 Years	<30 Years	≥ 30 Years
1989-90	0.96 (0.86 to 1.07)	1.34 (1.12 to 1.59)	1.03 (0.91 to 1.15)	1.01 (0.90 to 1.13)	1.75 (0.86 to 3.58)	7.58 (2.94 to 19.54)	0.61 (0.18 to 2.03)	1.61 (0.65 to 3.94)
1991-2	1.17 (1.06 to 1.30)	1.94 (1.67 to 2.25)	1.14 (1.02 to 1.27)	1.05 (0.94 to 1.16)	2.16 (1.11 to 4.20)	9.73 (3.94 to 24.98)	0.39 (0.09 to 1.66)	2.26 (1.04 to 4.93)
1993-4*	1.35 (1.22 to 1.50)	2.39 (2.07 to 2.75)	1.14 (1.01 to 1.28)	1.28 (1.16 to 1.41)	2.18 (1.09 to 4.39)	10.30 (4.19 to 25.29)	0.89 (0.31 to 2.60)	3.21 (1.57 to 6.56)
1994* only	1.27 (1.09 to 1.48)	2.68 (2.25 to 3.19)	1.17 (0.99 to 1.38)	1.34 (1.18 to 1.53)	2.11 (0.80 to 5.55)	9.09 (3.24 to 25.53)	1.58 (0.47 to 5.28)	5.27 (2.42 to 11.48)

1980-8 was used as reference for all groups.
*Only first three quarters of 1994 are included. Data on stillbirths were not available in 1994.

increased from 1.44 per 10 000 pregnancies during 1980-8 to 6.08 per 10 000 pregnancies in 1994 (table 1). For primiparous women ≥30 years of age the adjusted increase was 9.1-fold (3.2 to 25.5) from 1980-8 to 1994, while there was little change in the triplet rate for multiparous women <30 years (table 2, fig 2).

The crude dizygotic twinning rate increased from 0.57 in 1980 to 1.29 per 100 pregnancies in 1994 and the monozygotic twinning rates remained stable at 0.45 and 0.38 per 100 pregnancies during the same period. Among primiparous women ≥30 years of age the adjusted dizygotic rate increased 4.0-fold (3.3 to 4.9) from 1980-8 to 1994 (table 3), with an adjusted yearly increase of 25% (21% to 28%) from 1989 to 1994. For primiparous women <30 years of age the adjusted increase in the dizygotic twinning rate in 1994 compared with 1980-8 was 1.8-fold (1.5 to 2.1). The corresponding increase for multiparous women was 1.4 (1.1 to 1.7) and 1.7 (1.5 to 2.0) for women <30 years and ≥30 years, respectively. None of the adjusted monozygotic twinning rates increased during 1989-94 for any of these four groups of women (data not shown).

Table 3 Changes in rate of dizygotic twinning* during 1989-94 by age of mother and parity. Values are rate ratios adjusted for age and parity (95% confidence intervals)

	Parity 1		Parity ≥2	
Year	<30 Years	≥30 Years	<30 Years	≥30 Years
1989-90	1.19 (1.02 to 1.37)	1.58 (1.27 to 1.96)	1.08 (0.94 to 1.25)	1.06 (0.92 to 1.21)
1991-2	1.30 (1.13 to 1.50)	2.58 (2.16 to 3.09)	1.19 (1.04 to 1.37)	1.21 (1.06 to 1.37)
1993-4†	1.95 (1.72 to 2.23)	3.32 (2.80 to 3.93)	1.23 (1.06 to 1.42)	1.54 (1.38 to 1.73)
1994† only	1.76 (1.46 to 2.12)	4.00 (3.28 to 4.88)	1.36 (1.11 to 1.66)	1.72 (1.48 to 2.00)

1980-8 was used as reference for all groups.
*Monozygotic twinning rates remained stable.
†Only first three quarters of 1994 are included. Data on stillbirths were not available in 1994.

Death rates

The overall stillbirth rate was 0.46 and 0.47 per 100 children born during the periods 1980-8 and 1989-93, respectively. The rates among singletons were 0.42 and 0.43 per 100, among twins 2.24 and 2.00 per 100, and among triplets 6.67 and 5.04 per 100, respectively. None of the stillbirth rates differed significantly between the two periods.

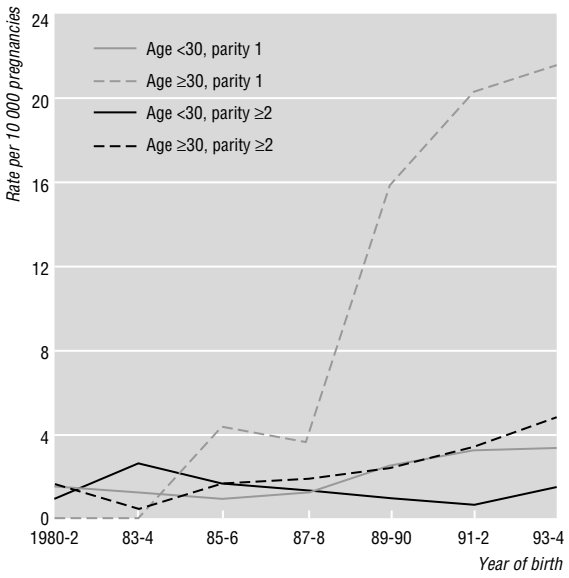

Fig 2 Triplet rates for Danish women from January 1980 to September 1994 by age of mother and parity

In primiparous women ≥30 years of age the proportion of multiple births among stillborn children increased 1.4-fold (0.8 to 2.3) from 1980-8 to 1989-93 (table 4). The total rate of stillbirths in primiparous women ≥30 years, however, was the same (0.59 per 100 born children) in both periods.

There was a 0.95-fold (0.89 to 1.00) adjusted decrease in the overall infant mortality from 1980-8 to 1989-92, which fell from 0.79 to 0.72 per 100 liveborn children. The infant mortality for singletons decreased 0.93-fold (0.88 to 0.99) from 0.72 to 0.65 per 100, while there was a non-significant decrease in the rate for twins from 3.82 to 3.34 per 100 and for triplets from 10.58 to 8.33 per 100.

In primiparous women ≥30 years of age the proportion of multiple births among infant deaths increased 2.3-fold (1.4 to 3.7) for children born during 1989-92 compared with 1980-8 (table 4). Among all livebirths in this group of women, however, there was a 0.90-fold (0.72 to 1.11) adjusted decrease in the total infant mortality over time. This was due to a 0.76-fold (0.59 to 0.97) adjusted decrease in the infant mortality among singletons from 1980-8 to 1989-92.

Discussion

Maternal age and parity patterns fluctuate over time and significantly influence the rate of multiple pregnancies. The existence in Denmark of such complete national registers enabled us to study trends in rates of multiple pregnancy that were adjusted for such confounding effects. This is in contrast with previ-

Table 4 Percentages (proportions) of multiple births among stillbirths and infant deaths by age of mother, parity, and period with adjusted relative increase in proportion of multiple births among stillbirths (from 1980-8 to 1989-93) and infant deaths (from 1980-8 to 1989-92)

	Stillbirths*			Infant deaths†		
Age and parity group	1980-8	1989-93	Adjusted relative increase (95% CI)‡	1980-8	1989-92	Adjusted relative increase (95% CI)‡
Parity 1:						
<30 Years	10.1 (93/919)	9.0 (50/555)	0.86 (0.61 to 1.19)	11.6 (170/1461)	11.8 (75/636)	0.98 (0.76 to 1.27)
≥30 Years	12.9 (22/170)	19.4 (31/160)	1.39 (0.84 to 2.30)	11.5 (24/208)	26.9 (36/134)	2.31 (1.44 to 3.70)
Parity ≥2:						
<30 Years	11.2 (67/599)	13.2 (41/311)	1.22 (0.85 to 1.76)	10.2 (127/1251)	8.3 (42/505)	0.81 (0.58 to 1.13)
≥30 Years	11.6 (56/484)	13.4 (52/388)	1.10 (0.77 to 1.56)	9.7 (75/772)	14.8 (63/427)	1.51 (1.11 to 2.06)
Total	11.0 (238/2172)	12.3 (174/1414)	1.07 (0.89 to 1.29)	10.7 (396/3692)	12.7 (216/1702)	1.15 (0.98 to 1.34)

*Fetal deaths after at least 28 completed weeks of pregnancy.
†Liveborn children dead within one year of birth.
‡Adjusted for changes in maternal age and parity between the two periods.

ous studies that have either lacked this possibility or have only to some extent been able to distinguish between these factors.[1 9-11] In the Netherlands a 1.3-fold increase was reported in the twinning rate and a 2.7-fold increase in the triplet rate from 1975 to 1989. "Natural" causes for the increase, such as increasing age of childbearing, could, however, not be ruled out in that study.[9] In white Americans in the United States there was a 1.3-fold increase in the ratio of twins among liveborn children from 1980 to 1992.[10] In the same population a 2.1-fold increase was reported in the rate of triplet and higher order multiple births from 1972-4 to 1985-9, which, adjusted for maternal age, amounted to a 1.8-fold increase, an increase that was seen particularly in women ≥30 years of age.[11] The impact of parity on the increasing rates in the United States, however, could not be determined in either of these studies.[10 11]

We found a considerable increase in the national rates for multiple pregnancies in Denmark during 1980-94 that could not be explained by changes in maternal age and parity. This increase was primarily observed during the most recent period of 1989-94 and in particular for primiparous women ≥30 years of age. In this group of older women, the adjusted increase in the twinning rate was 2.7-fold and in the triplet rate as much as 9.1-fold during 1994 compared with the rates of 1980-8. The increase in the twinning rate was exclusively observed for dizygotic twin pregnancies and in particular among primiparous women ≥30 years of age who experienced a 4.0-fold adjusted increase during 1989-94.

Key messages

- National rates of multiple pregnancies have risen from 1.0% to 1.7% during 1980-94 in Denmark; this rise was most pronounced in recent years
- Multiple pregnancy rates changed particularly among primiparous women ≥30 years of age, where the adjusted twinning rate increased threefold and triplet rate ninefold during 1989-94
- The dramatic increase in the twinning rate seems to be restricted to dizygotic twin pregnancies
- These changes are believed to be associated with the increasing use of treatments to enhance fertility

Effect of fertility treatment

Our ability to adjust for the confounding effect of maternal age and parity implies that the observed increase represents a realistic figure for the absolute increase attributable to other causes. The increases in the national multiple pregnancy rates seem closely related to the increasing use of ovulation induction and advanced reproduction techniques that may result in multiple pregnancy in about a quarter of births, ranging from a low of 7-9% for clomiphene citrate to a high of 25-40% for human menopausal gonadotropins and advanced reproduction techniques.[2-5 12] A study of births after in vitro fertilisation reported 97% of the women to be primiparous with a mean maternal age of 32 years and a rate of multiple pregnancy of 22%.[13] Our finding of a dramatic increase in the multiple pregnancy rate mainly among older primiparous women strongly supports the link to fertility enhancing treatment.

In Denmark the first child from in vitro fertilisation was born in the beginning of the 1980s. It was only after the mid-1980s, however, that this treatment became common practice. The number of clinics performing in vitro fertilisation and other advanced reproduction techniques went from one in the mid-1980s to six in the beginning of 1990[14] and at least 12 in 1993.[15] In 1993 it was estimated that 800-1000 children had been born as a result of in vitro fertilisation in Denmark since the introduction of this treatment,[15] and in 1994, 2929 women received treatment with advanced reproduction techniques.[16] Although there are no exact figures available for Denmark concerning the use of induction of ovulation as a treatment to enhance fertility, there has been a definite increase in its use in recent years.[17] Reduction procedures in multiple pregnancies have been applied in Denmark only in exceptional situations. To reduce the increase in multiple pregnancies caused by fertility enhancing treatment, however, in 1993 the Danish National Board of Health recommended that only two and never more than three oocytes or embryos should be transferred per treatment cycle, and when hormonal induction of ovulation is the only treatment a final ovulatory trigger should be given only if there are no more than three follicles ≥17 mm.[17]

It is generally accepted that most of the variation in the twinning rate worldwide is due to variation in the dizygotic rate and that monozygotic rates are fairly constant.[18] Ovulation induction[19] and in vitro fertilisation[20] have, however, been reported to increase slightly the incidence of monozygotic twinning. Nevertheless, the results of our study would suggest that the effect on the monozygotic twinning rate is unimportant on a national scale and that the primary impact is an increasing dizygotic twinning rate. The validity of Weinberg's rule to estimate the number of monozygotic and dizygotic twins has been debated.[21-23] It is, however, generally adopted by researchers all over the world, and it seems unlikely that the debated uncertainties should invalidate the overall interpretation of our findings.

Infant mortality

It is noteworthy that changed treatment regimens for a relatively small group of women have so drastically changed the overall national rates of multiple pregnancies. We also found a particular impact on infant deaths, in which the proportion of multiple births increased more than 2-fold from 11.5% to 26.9% for primiparous women ≥30 years of age. The total infant mortality, however, did not increase for this group of women because of a significant decrease in the infant mortality among singletons during the same period. Overall, this suggests that the introduction of new fertility enhancing treatments has retarded the otherwise decreasing national trends of infant mortality in Denmark. Multiple births are also known to be associated with higher risks of complications such as premature birth, low birth weight, and increased morbidity.[11 24] Consequently, the resources, both economically[25 26] and otherwise, associated with infer-

tility treatment go well beyond those invested in the specific procedures.[27]

We may be only in the beginning of a new pattern for multiple pregnancies as the rate has increased each year in the 1990s. It should be noted that the mortality data presented here pertain only to the first years of this new trend. With longer follow up and an increasing proportion of multiple births, it may well turn out that the births related to fertility treatment have a greater impact on the national mortality rates. It seems essential that the trends in multiple pregnancies and infant mortality are monitored in future years to detect unwarranted consequences of these treatments.

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Conflict of interest: None.

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Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients

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Abstract

Objective: To measure the prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and determine risk factors and associations with postdysenteric symptoms.
Design: Postal questionnaire.
Setting: Nottingham Health Authority.
Subjects: 544 people with microbiologically confirmed bacterial gastroenteritis between July 1994 and December 1994.
Main outcome measures: Prevalence of gastrointestinal symptoms and relative risks for development of the irritable bowel syndrome and self reported altered bowel habit.
Results: A quarter of subjects reported persistence of altered bowel habit six months after an episode of infective gastroenteritis. Increasing duration of diarrhoea, younger age, and female sex increased this risk, whereas vomiting as part of the illness reduced the risk. One in 14 developed the irritable bowel syndrome with an increased risk seen in women (relative risk 3.4; 95% confidence interval 1.2 to 9.8) and with duration of diarrhoea (6.5; 1.3 to 34 for 15-21 days).
Conclusions: Persistence of bowel symptoms commonly occurs after bacterial gastroenteritis and is responsible for considerable morbidity and health care costs.

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Introduction

As social patterns of eating change episodes of food poisoning continue to rise, with campylobacter accounting for 40 750 and salmonella for 30 800 laboratory confirmed cases each year in the United

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Bowel questionnaire

1 Do you suffer from abdominal pain?
2 Do you pass loose or watery stools (motions)?
3 Does your bowel habit vary from day to day?
4 Do you have to strain to open your bowels?
5 Do you rush to the toilet to open your bowels?
6 After opening your bowels do you ever feel the need to go the the toilet again?
7 Do you pass slime or mucus when opening your bowels?
8 Do you feel bloated or that your abdomen is swollen after eating a meal?
9 Do you have to loosen your clothing after eating a meal?

All of the above questions were followed by "If yes, on how many days a week"

Kingdom.[1] Although these episodes are usually brief, self limiting illnesses, the long term effects have rarely been analysed in detail. Functional bowel diseases, particularly the subgroup known as the irritable bowel syndrome, have by contrast been subjected to much study because of their great clinical importance, accounting as they do for up to 40% of outpatient gastroenterological consultations. About a fifth of such patients describe an acute onset of symptoms, often with diarrhoea, vomiting, and fever, which has been taken to indicate an infectious origin. Several series have suggested that this particular group differs from other sufferers in several characteristics, including less psychiatric morbidity and better overall prognosis, most improving over a five year period.[2 3] A recent study of 38 patients with salmonella enteritis reported that 12 still had bowel dysfunction a year after the acute infection despite documented clearance of the organism.[4]

We examined the prevalence and severity of bowel symptoms in a much larger, unselected group of patients who suffered from infectious gastroenteritis and were notified to Nottingham Health Authority.

Subjects and methods

The notifications records of Nottingham Health Authority were used to identify 544 people who had a laboratory confirmed diagnosis of a bacterial gastrointestinal pathogen notified during the period July 1994 to December 1994 among residents within the authority. The laboratory routinely informs the public health department of all positive isolates from faecal specimens.

A questionnaire was designed and piloted before the survey to assess patients' understanding. It included questions on the episode of food poisoning six months before, their bowel habit a year ago (six months before the food poisoning), and the same questions about their current bowel habit, together with questions about their general health, diet, medical history, allergies, and whether they had sought medical attention after their episode of food poisoning. The questionnaire asked specifically how many days a week they experienced a range of symptoms (see box) and whether they experienced a variable bowel habit. A diagnosis from the questionnaires of the irritable bowel syndrome was made separately by two experienced clinicians with the modified Rome criteria. Interobserver agreement was excellent, and in only two cases was there need for a consensus diagnosis. The first questionnaire was sent to the address given at the time of notification and a reminder sent one month later. A prepaid envelope was enclosed.

Modified Rome criteria for the irritable bowel syndrome

Abdominal pain relieved by defecation or associated with change in frequency or consistency of stool and
Irregular pattern of defecation for at least two days a week (three or more of the following):
- Altered stool frequency
- Altered stool form (hard/loose)
- Altered stool passage (straining/urgency/sense of incomplete evacuation)
- Mucus per rectum
- Bloating or feeling of abdominal distension

Statistics—Data were entered on an Epi-Info database, which was also used for the analysis of 2×2 tables. All other statistical analyses were undertaken by using SPSS for Windows, version 6.1. The individual significance of risk factors for predicting self reported change in bowel habit and development of the irritable bowel syndrome by the Rome criteria (excluding those who already had it) was determined by using multiple logistic regression analyses in two separate models.

Results

A total of 386 questionnaires were returned, a further six patients had died and nine envelopes were returned by the post office, making an overall response rate of 72%. Table 1 shows the age, sex, and microbiological diagnosis for the patients in the notifications database and those who returned the questionnaires. People over the age of 30 had a significantly better response rate ($P < 0.001$). No difference was seen by sex or infecting organism.

Although the median duration of diarrhoea was 7 days, this varied widely from 1-90 days with an interquartile range of 5-14 days. Severity of disability also varied widely with 318 (73%) reporting time off work or regular duties such as housework and 168 (39%) reporting more than 7 days' incapacity. At the more severe end of the spectrum, 90 (21%) reported more than 6 kg weight loss while 49 (11%) required admission to hospital. One of these patients died from salmonella

Table 1 Details of subjects questioned about gastroenteritis

Detail	All notified cases	No (%) who returned questionnaire
Sex:		
Men	259	175 (68)
Women	285	211 (74)
Age (years)*:		
18-29	180	107 (59)
30-44	143	106 (74)
45-59	132	98 (74)
⩾60	89	75 (84)
Organism:		
Campylobacter	349	251 (72)
Salmonella	166	117 (70)
Shigella	29	18 (62)
Total	544	386 (71)

*P<0.001.

infection, and one patient with colonic perforation required a laparotomy and a period in intensive care.

At six months we found 90 (25%) subjects reported persistently altered bowel habits compared with before the illness. The symptoms listed in table 2 indicate that for most this was a change towards looser stools and more frequent and urgent defecation. There were also features suggesting rectal irritability, such as needing to return to the toilet soon after defecation and having to rush to the toilet. By using the modified Rome criteria[5] 20 had pre-existing irritable bowel syndrome and 23 developed new irritable bowel syndrome after infection.

The duration of diarrhoea was an important predictor of altered bowel habit (table 3), with a relative risk of 3.5 in those with diarrhoea lasting more than 22 days compared with those with diarrhoea for less than a week. Female sex was also a significant independent risk factor for altered bowel habit with a relative risk of 2.9 (1.6 to 5.1). Older subjects had a lower relative risk for persistent symptoms after we controlled for sex and length of initial episode of diarrhoea. Although all subjects suffered from diarrhoea, the pattern of associated symptoms also seemed significant as those with vomiting had a lower risk of developing persistent symptoms (relative risk 0.5; 0.3 to 0.9).

Twenty subjects seemed to have had the irritable bowel syndrome before the bout of food poisoning, 17 had persistent symptoms while three seemed to have improved at six months. There were no significant differences in changes in bowel habit in these 20 patients compared with the rest of the group.

We then considered the more restricted group of 23 subjects who developed the irritable bowel syndrome as defined by our modified Rome criteria[5] when we questioned them six months after their infection. Significant risks factors were female sex (relative risk 3.4; 1.2 to 9.8) and duration of diarrhoea (6.5; 1.3 to 34) for those with diarrhoea lasting 15-21 days; the risk was even greater for those whose symptoms lasted more than three weeks (table 4).

There were no differences in change of bowel habit or development of the irritable bowel syndrome by bacterial species.

Table 2 Mean number of days each week with symptoms six months before and six months after gastroenteritis in people who reported altered bowel habit

Symptom	Mean days/week (median)		P value (Wilcoxon matched pairs)
	Before illness	After illness	
Abdominal pain	0.7 (0)	1.7 (0)	0.0009
Loose or watery stools	0.8 (0)	2.4 (2)	<0.0001
Hard or lumpy stools	1.6 (1)	1.4 (1)	0.9
Straining	1.0 (0)	1.0 (0)	0.5
Rushing to toilet	0.7 (0)	1.8 (1)	<0.0001
Reopening bowels	0.7 (0)	1.9 (1)	<0.0001
Slime or mucus	0.43 (0)	1.1 (0)	0.002
Bloated abdomen	1.3 (0)	2.7 (2)	<0.0001
Loosening clothing	0.8 (0)	1.8 (0)	<0.0001

Table 3 Relative risks for predictors of self reported changes in bowel habits after gastroenteritis

Factor	Altered bowel habit (n = 90)	No alteration (n = 267)	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI)
Duration of diarrhoea (days):				
0-7	17	93	1.0	1.0
8-14	35	80	1.97 (1.2 to 3.3)	1.67 (0.9 to 3.3)
15-21	19	25	2.83 (1.6 to 4.9)	2.43 (1.1 to 5.5)
⩾22	9	22	1.88 (0.9 to 3.8)	3.45 (1.5 to 8.0)
Sex:				
Men	29	134	1.0	1.0
Women	61	133	1.77 (1.2 to 2.6)	2.86 (1.6 to 5.1)
Vomiting as part of original illness:				
No	66	172	1.0	1.0
Yes	24	93	0.7 (0.5 to 1.0)	0.47 (0.3 to 0.9)
Age (years):				
19-29	31	63	1.0	1.0
30-44	23	72	0.84 (0.6 to 1.3)	1.75 (1.1 to 2.7)
45-59	28	72	0.73 (0.5 to 1.1)	0.51 (0.3 to 0.9)
⩾60	8	60	0.46 (0.2 to 0.9)	0.36 (0.1 to 0.9)

Table 4 Relative risks for development of the irritable bowel syndrome in people after gastroenteritis

Factor	Onset of syndrome after illness (n = 23)	No syndrome (n = 324)	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI)
Sex:				
Men	6	153	1.0	1.0
Women	17	171	2.54 (1.01 to 5.9)	3.39 (1.2 to 9.8)
Duration of diarrhoea (days):				
0-7	2	104	1.0	1.0
8-14	7	123	2.85 (0.6 to 13.5)	2.94 (0.6 to 15)
15-21	7	44	7.27 (1.6 to 34)	6.46 (1.3 to 34)
⩾22	7	38	8.24 (1.89 to 38)	11.37 (2.2 to 58)

Discussion

Prevalence of symptoms

This survey clearly shows that bacterial food poisoning is not only a serious cause of acute illness in a community but is also responsible for considerable ongoing disability. Six months after a documented episode of bacterial food poisoning about one quarter reported persistently altered bowel habit, a figure in keeping with the results from a smaller series of patients with salmonella enteritis.[4] While a few (eight) were pleased to be relieved from lifelong constipation, most described more frequent and inconveniently urgent defecation. In 5% these were sufficiently troublesome to have merited further investigations, including referral to a medical outpatients clinic. It is noteworthy that only a few (7%) met the Rome criteria for new irritable bowel syndrome, while a quarter developed loose, urgent defecation, which we prefer to call "postdysenteric bowel disturbance."

Why some patients develop this syndrome is undoubtedly multifactorial with both host and pathogen factors contributing. Previous studies of campylobacter enteritis suggest that the clinical type of illness (watery versus bloody diarrhoea) can be predicted from the invasiveness of the bacteria as assessed by in vitro testing.[6] Undoubtedly there are other pathogenic factors such as cytotoxins, which merit further study.

Risk factors and associations

The present survey has, by virtue of large numbers, enabled us to identify by logistic regression several factors that can be used to predict who will develop ongoing symptoms. Host factors are female sex (relative risk 2.9) and advancing years, which seem to provide a modest degree of protection. Factors that may be related to either pathogen or host include prolonged duration of the initial illness (3.5) and vomiting as part of the initial illness, which seems to be protective. When it comes to consider the smaller group meeting

Key messages

- Bacterial gastroenteritis (food poisoning) is an important and common cause of morbidity in the community
- Bowel habit remains altered six months after bacterial gastroenteritis in a quarter of infected people
- About one in 14 of cases develop classic irritable bowel syndrome
- Severity of illness and female sex predict prolonged bowel disturbance

the Rome criteria for the irritable bowel syndrome, only female sex and duration of initial illness remain significant risk factors.

The association of persistent bowel dysfunction with markers of initial severity of illness is perhaps not surprising. The more severe episodes are likely to be associated with deeper penetration of the organism and hence more severe mucosal inflammation and disruption to both epithelium and mucosal nerves,[7 8] which would be predicted to take longer to subside. Several studies have suggested that there is a subgroup of patients with the irritable bowel syndrome who have persistently increased concentrations of inflammatory cytokines including interleukin 1,[9] which by inhibiting absorption of sodium and water could contribute to persistent diarrhoea. The slight reduction in risk of persistent bowel dysfunction associated with vomiting may be because organisms that mainly affect the upper gut are less likely to interfere with colonic function. Alternatively, vomiting may reduce the infecting dose and hence be protective.

The strong influence of female sex is less easily explained and cannot be due to women suffering more severe initial illness as these factors were controlled for in the logistic regression analysis. Notification data indicate that young men are more likely to have food poisoning,[10] but in our study young women were much more likely to suffer continuing symptoms. As shown in many other studies young men were less likely to reply to our questionnaire but people with persistent symptoms are more likely to respond. This would probably lead to an underestimate of the observed difference between men and women. Patients who submit faecal specimens may not be typical of all those with bacterial gastroenteritis. They probably include the more severe cases and those admitted to hospital, where faecal culture is routine. Even if our case series is biased it is the most extensive one available, and even if the findings apply only to this group they remain an important cause of morbidity. The age and sex distribution of our patients is similar to a large study of diarrhoea episodes in the community in the United Kingdom,[11] and this study did not report differences in any factors on the rates of submitting faecal samples. We can not exclude the possibility that people obsessed with their bowels were more likely to submit a specimen, but they would be included only if they had an infection. The prevalence of the irritable bowel syndrome before infection was 5.4% (3.4% to 8.3%), consistent with other prevalence reports in the United Kingdom.[12]

Previous studies

Other studies have similarly reported that women are more likely to develop the postdysenteric irritable bowel syndrome, in keeping with the known predominance for the irritable bowel syndrome in women generally.[4] This group also reported that patients admitted to hospital who developed the irritable bowel syndrome were more anxious, depressed, and scored higher on somatisation and neuroticism, both within a few days of admission and three months later. Although some have argued that this association of psychological features with the irritable bowel syndrome is because such patients are more likely to present themselves to a doctor,[12] it is also possible that such people are more vulnerable to the effect of infectious enteritis[13] and other as yet unknown insults that lead to the syndrome. Alternatively, they may be more likely to complain given the same level of symptoms. Animal models have shown that mental stress can impair the recovery from inflammatory colitis,[14] and similar studies in rats have also suggested that female sex does increase susceptibility to the acceleration of colonic transit by stress induced by restraint.[15]

Most of the subjects in our survey had been treated in the community and only a minority had sought hospital assistance. Our findings are thus independent of the bias towards those exhibiting "illness behaviour"[12] found in surveys based in hospital and suggest that female sex is a risk factor for the irritable bowel syndrome independent of associated illness behaviour.

Only around 5% of diarrhoeal episodes are investigated by stool culture.[11] Food poisoning is therefore much commoner than the reported figures suggest,[1] with estimated incidence rates between 1% and 10% a year. Given the high prevalence of altered bowel habit six months after bacterial food poisoning that we have demonstrated, postdysenteric bowel disturbance seems to be an important cause of total population morbidity and is worthy of further study.

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Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study

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Abstract

Objective: To evaluate putative risk factors for the development of incipient diabetic nephropathy (persistent microalbuminuria) and overt diabetic nephropathy (persistent macroalbuminuria) in patients with non-insulin dependent diabetes.
Design: Prospective, observational study of a cohort of white, non-insulin dependent diabetic patients followed for a median period of 5.8 years.
Setting: Outpatient clinic in tertiary referral centre.
Subjects: 191 patients aged under 66 years with non-insulin dependent diabetes and normoalbuminuria (urinary albumin excretion rate <30 mg/24 h) who attended the clinic during 1987.
Main outcome measures: Incipient and overt diabetic nephropathy.
Results: Fifteen patients were lost to follow up. Thirty six of the 176 remaining developed persistent microalbuminuria (30-299 mg/24 h in two out of three consecutive 24 hour urine collections) and five developed persistent macroalbuminuria ($\geq$300 mg/24 h in two out of three consecutive collections) during follow up. The five year cumulative incidence of incipient diabetic nephropathy was 23% (95% confidence interval 17% to 30%). Cox's multiple stepwise regression analysis revealed the following risk factors for the development of incipient or overt diabetic nephropathy: increased baseline log urinary albumin excretion rate (relative risk 11.1 (3.4 to 35.9); $P<0.0001$); male sex (2.6 (1.2 to 5.4); $P<0.02$); presence of retinopathy (2.4 (1.3 to 4.7); $P<0.01$); increased serum cholesterol concentration (1.4 (1.1 to 1.7); $P<0.01$); haemoglobin A_{1c} concentration (1.2 (1.0 to 1.4); $P<0.05$); and age (1.07 (1.02 to 1.12); $P<0.01$). Known duration of diabetes, body mass index, arterial blood pressure, serum creatinine concentration, pre-existing coronary heart disease, and history of smoking were not risk factors.
Conclusion: Several potentially modifiable risk factors predict the development of incipient and overt diabetic nephropathy in normoalbuminuric patients with non-insulin dependent diabetes.

Introduction

Insulin dependent and non-insulin dependent diabetic patients with so called microalbuminuria (urinary albumin excretion rate between 30 and 299 mg/24 h) have an increased risk of developing diabetic microangiopathy and macroangiopathy, and in addition they suffer from premature death compared with normoalbuminuric diabetic patients, as reviewed by Parving *et al.*[1] Diabetic patients with persistent microalbuminuria—incipient diabetic nephropathy[2]—have about 20 times the risk of developing diabetic nephropathy.[1-6] Prospective observational studies, conducted mainly in patients with insulin dependent diabetes, have identified several modifiable risk factors for the development of microalbuminuria and for progression of microalbuminuria to overt diabetic nephropathy, such as poor glycaemic control, slightly increased blood pressure, smoking, and hyperlipidaemia.[7-11] Most but not all studies in insulin dependent diabetic patients have revealed a beneficial effect of strict glycaemic control on progression of incipient to overt diabetic nephropathy.[12-14] Such data are lacking for patients with non-insulin dependent diabetes. All studies dealing with angiotensin converting enzyme inhibition in insulin dependent[15-17] and in non-insulin dependent diabetic patients[11] have reported a beneficial effect on progression of incipient to overt diabetic nephropathy (secondary prevention). Primary prevention of incipient and overt nephropathy is feasible only if the risk factors initiating the process can be identified. Unfortunately, only scant information is available about white patients with non-insulin dependent diabetes.[18]

Our prospective study lasting nearly six years was conducted to elucidate putative risk factors for the development of incipient and overt diabetic nephropathy in a cohort of normoalbuminuric white patients with non-insulin dependent diabetes.

Patients and methods

Patients

The study population was based on all 363 patients aged under 66 years with non-insulin dependent diabetes who attended the Hvidöre Hospital between 1 January and 31 December 1987. All patients were asked to collect a 24 hour urine sample for analysis of albumin excretion. We excluded 172 patients: 31 were not white, four lacked baseline urine collections, and 137 had microalbuminuria or macroalbuminuria at baseline (see fig 1). This left 191 patients who fulfilled the inclusion criteria of being white and having normoalbuminuria (urinary albumin excretion rate <30 mg/24 h) in 1987. All 191 patients were traced through the national register at the beginning of 1993. If a subject had died before 1 January 1993, the date of death was recorded and information on the cause of death was obtained from death certificates. All death certificates were reviewed independently by at least two observers, and the primary cause of death was recorded. The observation period was defined as the number of days from the date of examination in 1987 to the date of death or 1 January 1993. We also excluded 15 patients in whom only the baseline urinary albumin excretion rate was available because of loss to follow up. Thus the 176 remaining patients who

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formed the cohort in the present study had a mean of six (range 2-15) urine collections performed during follow up. These 176 patients had similar clinical baseline characteristics to those 15 patients who were lost to follow up: sex ratio (men:women) 1.3 *v* 2.0, median (range) age 55 (20-65) *v* 54 (34-64) years, known duration of diabetes 6 (1-34) *v* 5 (1-39) years, and geometric mean (range) urinary albumin excretion rate 8 (1-29) *v* 10 (3-29) mg/24 hours.

Non-insulin dependence was defined as follows: treatment by diet alone or diet combined with oral hypoglycaemic agents; insulin treatment and onset of diabetes after the age of 40 years and a body mass index above normal ($\geq$25 kg/m^2 in women, $\geq$27 kg/m^2 in men) at the time of diagnosis; or insulin treatment, normal weight, and a glucagon stimulated C peptide value $\geq$ 0.60 pmol/ml.[19] A glucagon test was performed whenever the body mass index was $<$ 25 kg/m^2 in women and $<$ 27 kg/m^2 in men at the time of diagnosis.[20]

Arterial blood pressure was measured twice in the right arm after 10 minutes' rest while the patient was in the supine position by using a Hawksley random zero sphygmomanometer (Hawksley, Sussex), recording phase I (systolic) and phase V (diastolic). All blood pressure readings were performed by one observer (MG). Arterial hypertension was defined according to the World Health Organisation criteria: systolic blood pressure $\geq$160 mm Hg or diastolic blood pressure $\geq$95 mm Hg, or both, or if antihypertensive treatment was being prescribed.

A 12 lead resting electrocardiogram was coded by using the Minnesota codes,[21] and coronary heart disease was defined as probable myocardial infarction (code 1.1-1.2) or possible myocardial ischaemia (code 1.3, 4.1-4.4, 5.1-5.3, or 7.1). Retinopathy was assessed by direct ophthalmoscopy after pupillary dilatation by one senior registrar trained in diabetes. On the basis of the description the degree of retinopathy was classified into: none, background, or proliferative. Body mass index (kg/m^2) was calculated. Present medication and history of smoking were recorded. Current smokers were defined as subjects smoking one or more cigarette, cigar, or pipe a day. Former smokers were defined as subjects who reported having stopped smoking before the baseline examination. Non-smokers were patients who described themselves as never having smoked. A positive history of smoking included current and former smokers.

Approval for the study was obtained from the ethics committee of Copenhagen county.

Laboratory measurements

Urine collection was carried out during unrestricted daily activity. If bacterial growth was found, urine collection was repeated after treatment. The urinary albumin concentration was determined by radioimmunoassay.[22] Persistent microalbuminuria was defined as a urinary albumin excretion rate of 30-299 mg/24 hours in two out of three consecutive 24 hour collections and persistent macroalbuminuria as a urinary albumin excretion rate of $\geq$300 mg/24 hours in two out of three consecutive collections.[2] The time of transition was defined as the time when the second among three measurements was above the limit.

Haemoglobin A_{1c} concentration (normal range 4.1-6.1%)[23] and serum concentrations of creatinine,[24] total cholesterol,[25] and high density lipoprotein cholesterol[26] were measured in peripheral blood.

Statistical analysis

Values are given as means (SD), medians (ranges), or percentages (95% confidence intervals). We used the unpaired *t* test to compare cross classified continuous variables and the χ^2 test to evaluate proportions when we compared baseline data in the group of patients who developed incipient or overt diabetic nephropathy with the group of patients who remained normoalbuminuric. The urinary albumin excretion rate was logarithmically transformed before statistical analysis and is presented as geometric mean and range because of its positively skewed frequency distribution. All tests were two sided.

Cox's proportional hazards multiple regression analyses[26 27] were used to examine the baseline variables predictive of progression to incipient or overt diabetic nephropathy. Results are described as relative risk (hazard ratio). The models used included those baseline variables that were found to be significantly different when we compared the two groups or that were a priori considered to be potentially important predictors of increased urinary albumin excretion rate—that is, sex, age, known duration of diabetes, body mass index, retinopathy, arterial blood pressure, hypertension, log urinary albumin excretion rate, haemoglobin A_{1c}, serum cholesterol concentration, pre-existing coronary heart disease, and smoking—and stepwise backward selection was used. Baseline urinary albumin excretion rate was logarithmically transformed because of the skewed distribution. Relative risk thus corresponds to a 10-fold increase in urinary

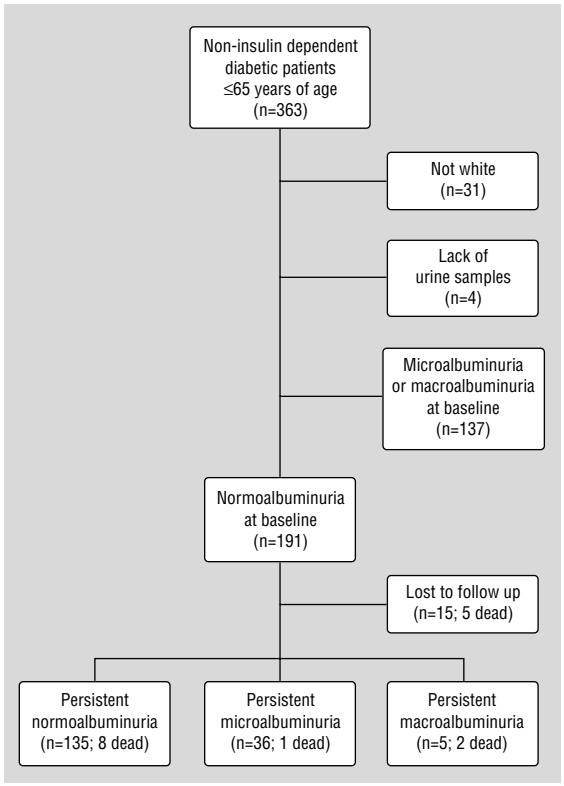

Fig 1 Flow chart of progress of all non-insulin dependent diabetic patients below 66 years of age attending Hvidöre Hospital in 1987

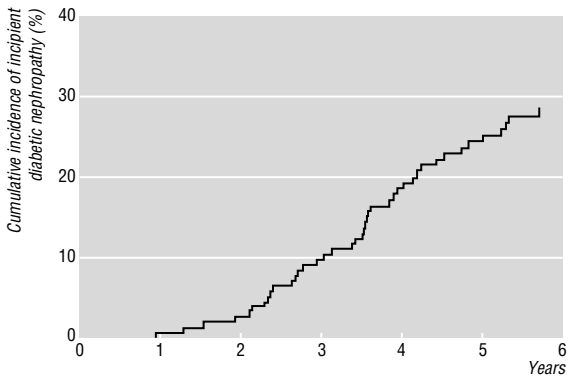

Fig 2 Cumulative incidence of incipient diabetic nephropathy according to duration of follow up in 176 non-insulin dependent diabetic patients with normoalbuminuria at baseline

albumin excretion rate. Confidence intervals were based on the normal approximation on the logarithmic scale. A P value of less than 0.05 was regarded as significant.

Results

We followed up 176 normoalbuminuric patients with non-insulin dependent diabetes for a median (range) of 5.8 (1.5-6.0) years. Thirty six (26 men) patients (20%; 95% confidence interval 15% to 27%) developed incipient diabetic nephropathy, five (three men) patients (3%; 1% to 7%) developed overt diabetic nephropathy, and 135 patients remained normoalbuminuric (fig 1). The five year cumulative incidence of incipient diabetic nephropathy was 23% (17% to 30%) (fig 2).

Sixteen patients had died: eight who remained normoalbuminuric, one who had progressed to incipient nephropathy, two who had progressed to overt nephropathy, and five who were lost to follow up (fig 1). Cardiovascular disease was the prevailing cause of death in nine patients while the seven others died from infection (such as pneumonia) or unknown causes. Renal disease was not recorded as either an underlying or contributory cause of death in any of the patients.

Table 1 shows clinical characteristics of the patients who developed raised urinary albumin excretion and those who remained normoalbuminuric. Patients who progressed to incipient or overt diabetic nephropathy were older men with poor long term glycaemic control and increased systolic blood pressure who suffered from diabetic retinopathy. Seventy six percent of patients (31/41) who progressed had retinopathy at the time of transition to microalbuminuria. The five patients who developed persistent macroalbuminuria all suffered from diabetic retinopathy at the time of transition to macroalbuminuria. The baseline urinary albumin excretion rate was significantly higher among those who progressed compared with those who remained normoalbuminuric (14 *v* 7 mg/24 h). The rate of urinary albumin excretion and concentration of haemoglobin A_{1c} were also significantly higher in the group who progressed when we adjusted for the difference in age found between the two groups. The systolic blood pressure was not significantly different between the groups when we adjusted for age. It is well known, however, that the systolic blood pressure increases with age. Forty one per cent of the patients who progressed received antihypertensive treatment, mostly a diuretic or a β blocker alone or in combination, compared with 25% of the patients who remained normoalbuminuric (P = 0.07). Serum total cholesterol concentration tended to be higher (P = 0.06) in the patients who later developed incipient or overt nephropathy. A higher prevalence of pre-existing coronary heart disease was also observed among those patients who developed incipient or overt nephropathy. Patients who progressed were comparable with respect to antidiabetic treatment, known duration of diabetes, body mass index, serum concentration of creatinine, diastolic blood pressure, prevalence of hypertension, concentration of high density lipoprotein cholesterol, and history of smoking compared with patients who remained normoalbuminuric.

The possible risk factors for development of abnormally increased urinary albumin excretion rate (>30 mg/24 h) were examined in backward stepwise Cox's multiple regression analysis. Log_{10} urinary albumin excretion rate, male sex, presence of retinopathy, serum cholesterol concentration, haemoglobin A_{1c} concentration, and age were significantly associated with development of abnormally increased urinary albumin excretion (table 2). A 10-fold increase in urinary albumin excretion rate was associated with a relative risk of 11.1 (95% confidence interval 3.4 to 35.9). A similar analysis was performed without the baseline urinary albumin excretion rate in the stepwise procedure. Again male sex, presence of retinopathy, serum cholesterol concentration, haemoglobin A_{1c}

Table 1 Baseline variables and risk factors in 176 non-insulin dependent diabetic patients according to development of diabetic nephropathy. Values are medians (ranges) unless stated otherwise

Variable	Normoalbuminuria (n=135)	Incipient/overt diabetic nephropathy (n=41)	P value
Sex (M/F) (%)	52/48	71/29	<0.05
Age (years)	54 (20-65)	56 (39-65)	<0.05
Known duration of diabetes (years)	5 (1-34)	6 (1-18)	0.7
Treatment (diet/oral hypoglycaemic agent/insulin) (%)	43/38/19	29/44/27	0.3
Mean (SD) haemoglobin A_{1c} (%)	7.6 (1.7)	8.4 (2.0)	<0.01
Body height (cm):			
Men	176 (161-192)	178 (163-190)	0.1
Women	164 (143-179)	167 (158-175)	0.4
Mean (SD) body mass index (kg/m^2)	27.9 (5.3)	27.3 (4.0)	0.5
No (%; 95% confidence interval) with retinopathy	27 (20; 14 to 28)	17 (41; 26 to 58)	<0.05
Mean (SD) serum creatinine (μmol/l)	74 (19)	77 (15)	0.3
Urinary albumin excretion rate (mg/24 h)*	7 (1-29)	12 (1-29)	<0.001
Mean (SD) systolic blood pressure (mm Hg)	143 (20)	151 (25)	<0.05
Mean (SD) diastolic blood pressure (mm Hg)	83 (11)	86 (10)	0.2
No (%; 95% confidence interval) with hypertension	51 (38; 30 to 47)	22 (54; 37 to 69)	0.1
No (%; 95% confidence interval) receiving antihypertensive treatment	34 (25; 18 to 33)	17 (41; 26 to 58)	0.07
Mean (SD) serum total cholesterol (mmol/l)	6.0 (1.4)	6.5 (1.8)	0.06
Mean (SD) serum high density lipoprotein cholesterol (mmol/l)	1.13 (0.39)	1.03 (0.46)	0.2
No (%; 95% confidence interval) with coronary heart disease†	15 (11; 7 to 18)	11 (27; 14 to 43)	<0.05
No (%; 95% confidence interval) with history of smoking	95 (70; 62 to 78)	33 (80; 65 to 91)	0.3

*Geometric mean.
†On basis of electrocardiographic Minnesota scores.

Table 2 Baseline risk factors for development of incipient or overt diabetic nephropathy in 176 patients with non-insulin dependent diabetes by means of Cox's multiple regression analysis

Variable	Relative risk (95% CI)	P value
Log urinary albumin excretion rate (factor 10)*	11.1 (3.4 to 35.9)	<0.0001
Sex (men)	2.6 (1.2 to 5.4)	<0.02
Retinopathy (0=no; 1=yes)	2.4 (1.3 to 4.7)	<0.01
Cholesterol (1 mmol/l)	1.4 (1.1 to 1.7)	<0.01
Haemoglobin A_{1c} (1%)	1.2 (1.0 to 1.4)	<0.05
Age (1 year)	1.07 (1.02 to 1.12)	<0.01

*Relative risk corresponds to 10-fold increase in variable.

concentration, and age appeared as the only significant determinants of abnormally increased urinary albumin excretion rate. The effect of baseline urinary albumin excretion rate was also analysed separately in Cox's multiple regression analysis without stepwise selection and including only the recognised risk factors—that is, sex, arterial blood pressure, haemoglobin A_{1c}, known duration of diabetes, and urinary albumin excretion rate. A 10-fold increase in baseline urinary albumin excretion rate was associated with a relative risk of 11.3 (3.3 to 38.2; $P < 0.0005$). Figure 3 indicates the relative importance of sex on the cumulative incidence of incipient diabetic nephropathy. The

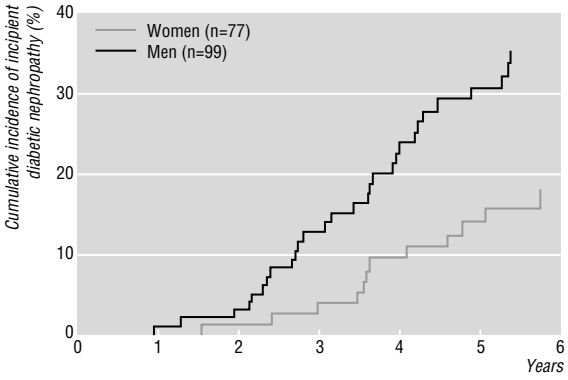

Fig 3 Cumulative incidence of incipient diabetic nephropathy with respect to sex and according to duration of follow up in 176 non-insulin dependent diabetic patients with normoalbuminuria at baseline (P<0.05)

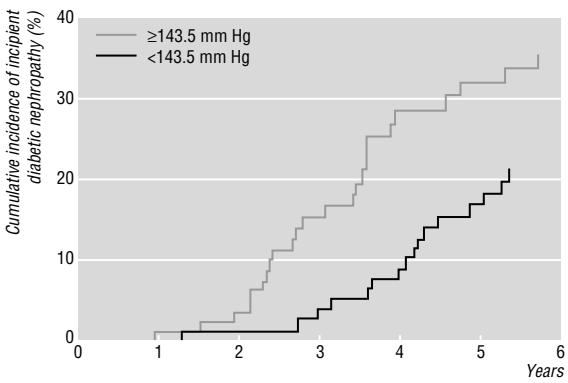

Fig 4 Cumulative incidence of incipient diabetic nephropathy with respect to median systolic blood pressure and according to duration of follow up in 176 non-insulin dependent diabetic patients with normoalbuminuria at baseline (P=0.06)

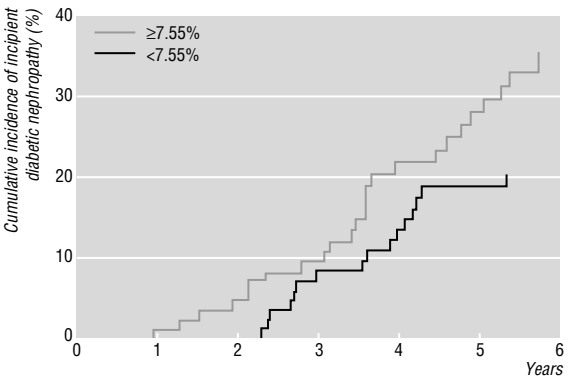

Fig 5 Cumulative incidence of incipient diabetic nephropathy with respect to median haemoglobin A_{1c} concentration and according to duration of follow up in 176 non-insulin dependent diabetic patients with normoalbuminuria at baseline (P=0.10)

relative importance of systolic blood pressure and haemoglobin A_{1c} concentration on the cumulative incidence of incipient diabetic nephropathy were calculated according to the median of the systolic blood pressure (143.5 mm Hg) (fig 4) and haemoglobin A_{1c} (7.55%) (fig 5).

Fourteen patients started antihypertensive treatment during the course of the study. Five patients were treated with angiotensin converting enzyme inhibitors, the remaining nine patients with alternative treatment. In eight of the patients we could compare the rate of change in urinary albumin excretion rate before and after the start of antihypertensive treatment; the urinary albumin excretion rate showed an average increas of 67% a year before and an average decrease of 7.7% a year after the start of antihypertensive treatment in these patients.

Discussion

Our prospective study of a cohort of normoalbuminuric white patients with non-insulin dependent diabetes revealed that 36 out of 176 developed incipient diabetic nephropathy (persistent microalbuminuria) and five overt diabetic nephropathy (persistent macroalbuminuria) during a median follow up period of 5.8 years. The five year cumulative incidence of incipient diabetic nephropathy was 23%. The major determinants of progression to incipient or overt diabetic nephropathy were identified as minimal increase of urinary albumin excretion within the normal range, poor long term glycaemic control, increased concentrations of serum cholesterol, presence of retinopathy, male sex, and older age.

We have confirmed and extended previous findings regarding the cumulative incidence of microalbuminuria in white[18] and Asian[28] non-insulin dependent patients. Normoalbuminuric Pima Indians with non-insulin dependent diabetes, however, are at an even higher risk of developing abnormally increased urinary albumin excretion (albumin:creatinine ratio ⩾30 mg/g) as the incidence of microalbuminuria was found to be 37% during a median follow up period of 4.7 years.[29]

Given the fluctuating nature of urinary albumin excretion, the use of only a single urine collection at

baseline for the classification of patients as being normoalbuminuric, microalbuminuric, or macroalbuminuric may have introduced misclassification of the patients. Only eight (6%) among the 137 patients who were excluded from the study because of the presence of microalbuminuria or macroalbuminuria at baseline, however, had reverted to persistent normoalbuminuria on basis of multiple testing during follow up.

The range of urine collections during follow up varied from two to 15. The low number of urine collections observed in some patients was mainly because of patients leaving the study early (death or moving away). The mean (SD) total number of urine collections in the 24 patients followed for under five years was 3.0 (2.4) compared with an average of 6.3 (2.0) collections in the 152 patients followed for more than five years.

A high rate of urinary albumin excretion within the normal range was found to be the most important risk factor for later development of incipient and overt nephropathy; this agrees with previous findings in non-insulin dependent[18 28] and insulin dependent diabetic patients.[7-9] This may suggest that even very low rates of urinary albumin excretion reflect the pathological process leading to diabetic nephropathy.

We found male sex to be significantly related to abnormally increased albumin excretion rates during follow up, in contrast with results from earlier studies of patients of different ethnic origin with non-insulin dependent diabetes.[18 28 29] Furthermore, the present result supports the suggestion of a more rapid progression to nephropathy in white men than in white women on the basis of our earlier observations of male predominance among macroalbuminuric patients with non-insulin dependent diabetes.[30 31]

Impact of metabolic control

Long term glycaemic control has been shown to be important with regard to the development of microvascular complications in both types of diabetes. We found that poor long term glycaemic control, indicated by the concentration of glycated haemoglobin, was an important predictor of the development of abnormally increased urinary albumin excretion, confirming data from the prospective studies in non-insulin dependent[18 29] and insulin dependent diabetic subjects.[8 9] In the study by John *et al* glycaemic control did not appear as a risk factor, but only the fasting blood glucose concentration was measured.[28] Several but not all studies in insulin dependent diabetic patients have shown beneficial effects of long term strict glycaemic control on the start and progression of microalbuminuria.[12-14 32] These findings have recently been confirmed in a selected group of insulin treated Japanese patients with non-insulin dependent diabetes.[33]

Many of the changes in plasma lipoproteins associated with renal disease are believed to be caused by renal dysfunction; hyperlipidaemia, however, may be associated with development of glomerular injury.[34] Ravid *et al* found that the concentration of cholesterol, both initially and during a five year follow up period, was positively related with the subsequent increase in urinary albumin excretion in microalbuminuric patients with non-insulin dependent diabetes.[35] In the present study the concentration of serum cholesterol was associated with an increased risk of developing incipient or overt nephropathy. Furthermore, serum cholesterol concentration was found to be related to the development of abnormally increased urinary albumin excretion rates in Pima Indians who had had diabetes for more than 10 years.[29]

Key messages

- This study found a five year cumulative incidence of incipient diabetic nephropathy (persistent microalbuminuria, urinary albumin excretion rate between 30 and 299 mg/24 h) of 23% in white patients with non-insulin dependent diabetes mellitus
- Potentially modifiable risk factors, such as increased urinary albumin excretion rate, long term poor glycaemic control, and hypercholesterolaemia predict the later development of incipient and overt diabetic nephropathy in these patients
- Elderly, non-insulin dependent diabetic men with diabetic retinopathy are at increased risk of developing incipient or overt diabetic nephropathy
- Known duration of diabetes, obesity, arterial blood pressure, serum creatinine concentration, pre-existing coronary heart disease, and history of smoking do not seem to act as risk factors

Schmitz and coworkers showed systolic blood pressure to be an independent risk factor for the relative rate of increase of the urinary albumin concentration "slope."[18] A higher mean arterial blood pressure was also a risk factor for development of an abnormally increased rate of urinary albumin excretion in the Pima Indians.[29] The same group has also reported that high blood pressure before the development of diabetes predicts microalbuminuria after the onset of non-insulin-dependent diabetes in Pima Indians.[36] Systolic blood pressure was significantly higher in those who progressed to incipient and overt diabetic nephropathy in our study. It did not, however, appear as an independent predictor of progression in the multiple Cox's regression analysis. Many patients received treatment for hypertension, potentially obscuring any role of blood pressure in the development of diabetic kidney disease. A small number of patients (five) progressed to diabetic nephropathy in the present study. We have previously demonstrated the impact of systolic blood pressure on progression of diabetic nephropathy in non-insulin dependent diabetic patients.[37] The influence of arterial blood pressure on the development of microalbuminuria in insulin dependent diabetic patients has also yielded conflicting results.[7-9]

Diabetic retinopathy supporting the diagnosis of diabetic nephropathy

The presence of diabetic retinopathy strongly suggests that diabetic nephropathy is the cause of persistent macroalbuminuria in non-insulin dependent diabetic patients.[38] In the present study patients who developed abnormally high urinary albumin excretion were significantly more likely to have retinal lesions at baseline than those who remained normoalbuminuric.

Furthermore, 76% of the patients who progressed had diabetic retinopathy at the time of transition to microalbuminuria, and the five patients who developed persistent macroalbuminuria all suffered from diabetic retinopathy at the time of transition to macroalbuminuria, supporting the diagnosis of diabetic nephropathy. A close relation between the presence of diabetic retinopathy and risk of developing an abnormally high urinary albumin excretion rate has also been reported by other workers.[7 29]

Conclusion

We have found that several potentially modifiable risk factors, such as urinary albumin excretion rate, long term poor glycaemic control, and hypercholesterolaemia predict the development of incipient and overt diabetic nephropathy in normoalbuminuric patients with non-insulin dependent diabetes.

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ONE HUNDRED YEARS AGO

A medical saint

It may interest some of our readers to learn that of the two new saints added to the Calendar by the Pope in the solemn canonisation on Ascension Day one was a member of the medical profession. Saint Antonio Maria Zacaria was born at Cremona in 1503, and studied medicine in the University of Pavia, where in due course he took his doctor's degree. He practised his profession among the poor, and died in his native town, Cremona, in 1563. Among other medical saints in the Roman Calendar besides St. Luke, the "beloved physician," may be mentioned Saints Cosmas and Damian. The former gave his name to the old College of Surgeons (Saint-Côme) in Paris. (*BMJ* 1897;ii:232.)

Regression analysis of recent changes in cardiovascular morbidity and mortality in the Netherlands

Luc Bonneux, Caspar W N Looman, Jan J Barendregt, Paul J Van der Maas

Abstract

Objectives: To test whether recent declines in mortality from coronary heart disease were associated with increased mortality from other cardiovascular diseases.
Design: Poisson regression analysis of national data on causes of death and hospital discharges.
Setting and subjects: Population of the Netherlands, 1969-93.
Main outcome measures: Annual changes in mortality from coronary heart disease, stroke, and other cardiovascular diseases and annual changes in hospital discharge rates for acute coronary events, stroke, and congestive heart failures.
Results: Patterns of cardiovascular mortality changed abruptly in 1987-93. Annual decline in mortality from coronary heart disease increased sharply for women and men: from −1.9% (95% confidence interval −2.2% to −1.6%) and −1.7% (−1.9% to −1.4%) respectively in 1979-86 to −3.1% (−3.5% to −2.6%) and −4.2% (−4.6% to −3.9%) in 1987-93. The longstanding decline in mortality from stroke levelled off: from annual change of −3.3% (−3.7% to −2.8%) and −3.2% (−3.7% to −2.8%) in 1979-86 to −0.1% (−0.7% to 0.4%) and −1.1% (−1.7% to −0.5%) in 1987-93. Mortality from other cardiovascular diseases, however, started to increase: from −2.0% (−2.4% to −1.6%) and −0.2% (−0.5% to 0.2%) in 1979-86 to 1.5% (1.0% to 2.0%) and 1.9% (1.5% to 2.3%) in 1987-93. Hospital discharge rates for acute coronary heart disease, congestive heart failure, and stroke increased during 1980-6. During 1987-93 discharge rates for stroke and coronary heart disease stabilised but rates for congestive heart failure increased.
Conclusion: Improved management of coronary heart disease seems to have reduced mortality, but some of the gains are lost to deaths from stroke and other cardiovascular diseases. The increasing numbers of patients with coronary heart disease who survive will increase demands on health services for long term care.

Introduction

In the early 1970s mortality from cardiovascular diseases started to decline in many industrialised countries.[1] Despite considerable debate, most observers would agree that reductions in risk factors, particularly smoking and hypertension, was more effective than improvements in treatments in achieving this decline in the 1970s and early 1980s.[2-7] In the mid-1980s, however, management of acute myocardial infarction was revolutionised, particularly by thrombolytic treatment, causing steep decreases in mortality from coronary heart disease.[8-10]

Coronary heart disease is not the only cardiovascular disease, however, and other cardiovascular diseases, such as stroke and congestive heart failure, share many of the same risks.[5 11 12] The improved prognosis for coronary heart disease caused by improved management should increase the number of surviving patients at high vascular risk. We present a time series analysis of Dutch nationwide statistics to illustrate the relation between mortality from coronary heart disease and other cardiovascular diseases.

Methods

Source of data

For our mortality analysis, we used the registered numbers of death by cause, age (from 25 to 84), sex, and calendar year from Statistics Netherlands.[13] We took account of only primary causes of death and considered three causes of cardiovascular related death: coronary heart disease; stroke; and all other causes, including unknown, of sudden death.[14] Table 1 shows the ICD codes (international classification of diseases) that we searched for.

The second database we used was the hospital register. This provides nationwide coverage and is complete since 1980. The register includes hospital patients' diagnosis at discharge as classified by the treating physician and codified by local staff. For every discharge, the patient's vital status is registered. Patients dying during the ambulance ride or at entry in the emergency room are not included and are considered "dead out of hospital." Again, we considered only primary diagnoses.

Statistical analysis

We estimated trends over time by Poisson regression analysis.[15] We used mid-year populations as person-years, and we specified five year age groups (categorical) and calendar year (continuous) as independent variables and mortality as a dependent variable. We analysed trends in mortality for 1969-78, 1979-86, and 1987-93 and trends from the hospital register for 1980-6 and 1987-93. We chose 1987 as the cut off point because of the apparent rupture in trend in that year.

Results

Figure 1 and table 2 show changes in mortality from cardiovascular diseases and in discharge rates from hospital for stroke, acute coronary heart events, and congestive heart failure.

For women, all cardiovascular related death rates declined from 1969 until 1986, suggesting a change in common risk factors of most cardiovascular diseases. During 1987-93, however, changes in cardiovascular related mortality levelled off, from −2.3% a year in 1969-86 to −0.7% a year in 1987-93. Mortality from coronary heart disease decreased steeply, but other vascular related death rates started to increase in 1987. Mortality from stroke levelled off after a long period of decline.

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Table 1 ICD codes used in search for changes in cardiovascular morbidity and mortality in the Netherlands during 1969-93. ICD-8 and ICD-9 (international classification of diseases, eighth and ninth revisions) used for analysis of deaths registered in Statistics Netherlands,[13] and ICD-9-CM (international classification of diseases, ninth revision, clinical modification) used for analysis of diagnosis at discharge listed in hospital register

Disease	ICD-8 (1969-78)	ICD-9 (1979-93)	ICD-9-CM (1980-93)
Cardiovascular disease	390-458, 782, 795-796	390-459, 798-799	
Coronary heart disease	410-414	410-414	
Stroke	430-438	430-438	430-438
Acute coronary events			410-411
Congestive heart failure			428-429

For men, changes in cardiovascular related mortality during 1969-78 were limited to a decline in mortality from stroke. During 1979-86 the rate of decline in cardiovascular related mortality increased, driven by declining death rates from both coronary heart disease and stroke; rates for other cardiovascular causes of death changed little. In 1987-93 mortality from coronary heart disease declined steeply, but death rates from stroke declined less steeply and death rates from other cardiovascular causes seemed to increase. These upward changes are similar to, but less clear than, those seen among women.

The hospital register showed an increase in discharge rates for acute coronary heart disease, congestive heart failure, and stroke in 1980-6. In 1987-93 the discharge rates stabilised for stroke and coronary heart disease, though rates for coronary heart disease still increased among women. The age adjusted case fatality ratio for an acute coronary event decreased from 13.6% (95% confidence interval 13.3% to 13.9%) for men and 18.4% (17.8% to 19.0%) for women in 1980-1 to 7.9% (7.7% to 8.1%) for men and 9.9% (9.5% to 10.2%) for women in 1992-3. The case fatality ratios for stroke remained constant at about 17.7% for both sexes since 1987. For congestive heart failure, both sexes showed an age dependent increase in discharges by calendar date. In more recent years, more patients were hospitalised at higher ages.

Discussion

Our study provides circumstantial evidence that the sharp drop in mortality from coronary heart disease between 1985 and 1992, the levelling off of mortality from stroke, and the increase in mortality from congestive heart failure are causally linked by the same process: the increased survival of patients with coronary heart disease. Cardiovascular diseases share many of the same risk factors, and having one disease increases the risk for others: a history of ischaemic heart disease increases the risk for other heart diseases, notably heart failure and dysrhythmia, and these increase the risks for cardiogenic stroke.[16] As the prognosis for patients with coronary heart disease improves the increasing numbers of surviving patients will increase the pool of people at high risk of other heart

Table 2 Age standardised rates (per 100 000 population) and annual percentage changes in mortality and hospital discharge rates for population of the Netherlands during 1969-93. (Data on national mortality from Statistics Netherlands[13] and data on hospital mortality and morbidity from hospital register)

	Period 1969-78		Period 1979-86*		Period 1987-93	
	Rate (SE)	Percentage change (95% CI)	Rate (SE)	Percentage change (95% CI)	Rate (SE)	Percentage change (95% CI)
Women						
National mortality from cardiovascular disease:	443 (1.1)	–2.3 (–2.5 to –2.2)	349 (0.8)	–2.3 (–2.5 to –2.1)	289 (0.7)	–0.7 (–1.0 to –0.4)
Stroke	125 (0.3)	–3.3 (–3.6 to –3.0)	90 (0.2)	–3.3 (–3.7 to –2.8)	74 (0.2)	–0.1 (–0.7 to 0.4)
Coronary heart disease	180 (0.4)	–1.0 (–1.3 to –0.8)	148 (0.4)	–1.9 (–2.2 to –1.6)	114 (0.3)	–3.1 (–3.5 to –2.6)
Other	138 (0.3)	–3.2 (–3.5 to –2.9)	111 (0.3)	–2.0 (–2.4 to –1.6)	101 (0.3)	1.5 (1.0 to 2.0)
Mortality in hospital from cardiovascular disease:			124 (0.3)	–0.7 (–1.1 to –0.2)	109 (0.3)	–1.6 (–2.0 to –1.1)
Stroke			42 (0.1)	–1.5 (–2.3 to –0.7)	36 (0.1)	0.4 (–0.4 to 1.3)
Coronary heart disease			38 (0.1)	0.2 (–0.6 to 1.0)	31 (0.1)	–5.5 (–6.3 to –4.6)
Other			44 (0.1)	–0.7 (–1.5 to 0.1)	42 (0.1)	–0.4 (–1.2 to 0.3)
Hospital discharge rate:						
Stroke			213 (0.8)	0.7 (0.3 to 1.0)	204 (0.7)	–0.0 (–0.4 to 0.3)
Acute coronary event			211 (0.8)	2.7 (2.3 to 3.1)	235 (0.8)	1.1 (0.8 to 1.5)
Congestive heart failure			141 (0.6)	2.5 (2.0 to 2.9)	160 (0.6)	1.3 (0.9 to 1.7)
Men						
National mortality from cardiovascular disease:	762 (2.4)	–0.4 (–0.6 to –0.3)	687 (2.4)	–1.5 (–1.7 to –1.3)	583 (2.1)	–1.7 (–1.9 to –1.4)
Stroke	146 (0.5)	–1.9 (–2.2 to –1.5)	117 (0.4)	–3.2 (–3.7 to –2.8)	99 (0.4)	–1.1 (–1.7 to –0.5)
Coronary heart disease	419 (1.3)	–0.1 (–0.3 to 0.1)	369 (1.3)	–1.7 (–1.9 to –1.4)	287 (1.0)	–4.2 (–4.6 to –3.9)
Other	198 (0.6)	0.0 (–0.3 to 0.3)	201 (0.7)	–0.2 (–0.5 to 0.2)	197 (0.7)	1.9 (1.5 to 2.3)
Mortality in hospital from cardiovascular disease:			238 (0.9)	–0.7 (–1.1 to –0.3)	214 (0.8)	–1.9 (–2.3 to –1.5)
Stroke			59 (0.2)	–2.2 (–3.0 to –1.4)	53 (0.2)	–0.6 (–1.4 to 0.2)
Coronary heart disease			84 (0.3)	–1.3 (–2.0 to –0.7)	65 (0.2)	–5.8 (–6.5 to –5.1)
Other			95 (0.4)	0.7 (0.1 to 1.4)	96 (0.4)	0.1 (–0.5 to 0.7)
Hospital discharge rate:						
Stroke			322 (1.1)	1.3 (0.9 to 1.6)	302 (1.0)	–0.0 (–0.4 to 0.3)
Acute coronary event			621 (1.5)	1.4 (1.1 to 1.6)	635 (1.4)	–0.4 (–0.6 to –0.2)
Congestive heart failure			229 (0.1)	3.7 (3.2 to 4.1)	281 (1.0)	1.1 (0.8 to 1.5)

*1980-6 for the hospital register data.

diseases and stroke. This will result in increasing death rates from stroke and other cardiovascular diseases.

Validity of study

The changes we observed might have been caused by changing diagnostic habits, policies for referral, or rules of classification. The validity of the Dutch register of causes of death is reasonable.[17] Any changes in coding between cardiovascular and non-cardiovascular causes of death are likely to have been small and unable to bias seriously trends over time. The possibility of misclassification between different causes of cardiovascular related death is high, but the observed patterns in both the hospital register and the mortality statistics were consistent (see table 2).

General practice registers have shown that nearly all patients suspected of having an acute myocardial infarction are hospitalised in the Netherlands.[18] Death rates both outside hospital and in hospital showed substantial reductions, which makes it unlikely that deaths outside hospital were exchanged for deaths in hospital.

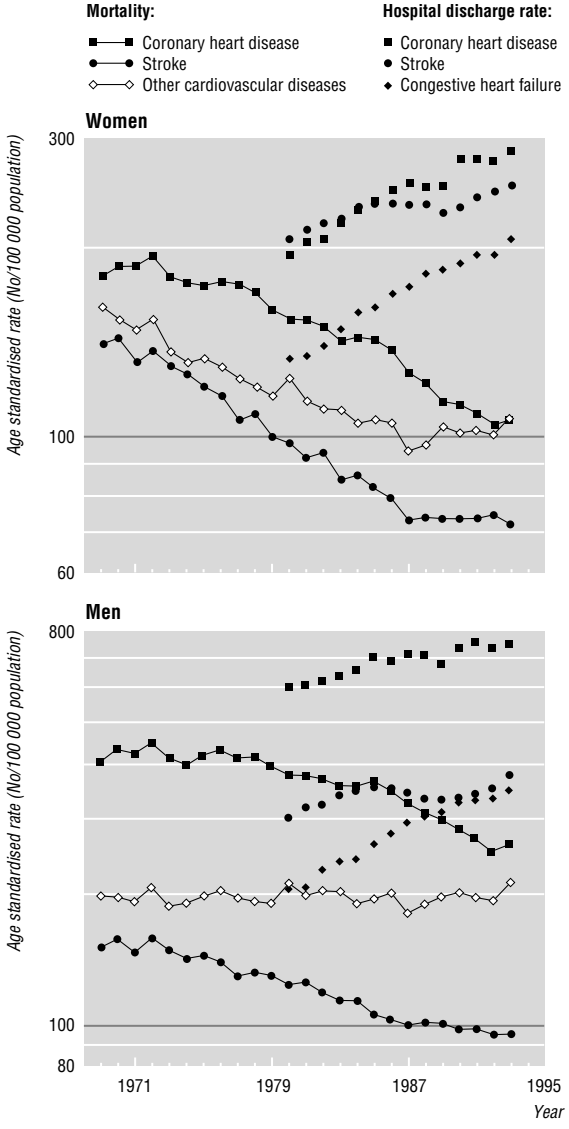

Fig 1 Age standardised (Dutch population of 1980-93 as direct standard) annual mortalities and hospital discharge rates for cardiovascular diseases in the Netherlands

Key messages

- In the Netherlands, mortality from coronary heart disease has decreased in recent years, but mortality from other cardiovascular diseases has increased
- The longstanding decline in mortality from stroke has stopped, and hospital discharge rates of patients with a diagnosis of congestive heart failure have increased
- The most parsimonious hypothesis explaining these changes is that increasing numbers of survivors of coronary heart disease are boosting the numbers of patients at high risk of other cardiovascular disorders
- Health services will have to cope with more patients disabled by chronic cardiovascular disease, with their high needs for care

Moreover, the secular trend of improving prognosis has been documented before, in the Netherlands as elsewhere, and has been linked to improved management.[4 8-10 19]

Part of the increased rates of discharge of patients with stroke and the decrease in case fatality in the early 1980s was caused by the introduction of computed tomography, which ascertained more benign lesions.[6 7 20] Since 1987, the incidence of and mortality from stroke have remained constant, suggesting a steady state in survival. The sharp decrease in mortality from coronary heart disease and the concomitant levelling off of mortality from stroke after a long period of decline has been observed in the prospective, population based Minnesota heart survey.[7 9 20] The age dependent increase in mortality from congestive heart failure has also been documented before.[21-24]

Secular changes in risk factors might explain the observed changes, but these have been modest (at best) in the period under study in the Netherlands.[25]

Conclusion

Improvements in treating coronary heart disease seem undeniable, but some of the gains made are lost again to deaths from stroke and congestive heart failure. This has important consequences for public health, as increasing numbers of surviving but disabled patients with chronic cardiovascular disease are boosting demand for health care.

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The prevalence of adult onset wheeze: longitudinal study

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In contrast to wheeze in childhood, less is known about the prevalence of and factors associated with wheeze in adulthood. We studied the onset of wheezing in adults who had had no respiratory symptoms as children.

Subjects, methods and results

A 1964 random community survey in Aberdeen of 2511 children aged 10-14 years identified 121 children with asthma and 167 with wheeze with infection. The outcome at age 34-40 years of these children with wheeze, together with that of 167 children selected from those who were asymptomatic, has been described.[1] In 1995 we tried to contact the 2056 individuals (now aged 39-45 years) who had had no childhood wheezing; 1799 subjects were traced. We posted questionnaires about symptoms, smoking, and employment to 1758 surviving subjects, of whom 1542 (87.7%) responded (75.0% of 2056).

Attacks of wheezing ever were reported by 239 (15.5%) respondents, of whom 177 (11.5% of 1542) reported adult onset wheeze—that is, onset at or after age 15 years. The prevalence of adult onset wheeze was similar for men and women (10.7% *v* 13.0%, $\chi^2 = 1.95$, $P = 0.16$). Other subjects reporting wheeze included 17 with onset at age 10-14 years, 27 with onset before age 10 years, and 18 with no age specified.

Of the 177 subjects with adult onset wheeze, 133 (75.1%) wheezed during the previous year; 90 (50.8%) wheezed during the previous week; 34 (19.2%) experienced activity limitation owing to wheeze in the previous week; 28 (15.8%) were receiving regular inhaled bronchodilators or steroids, or both; and 38 (21.5%) were receiving occasional treatment. Of the 34 subjects with activity limitation, 20 were receiving treatment for wheeze.

In logistic regression analysis current smoking and manual social class were significant independent risk factors for wheeze (table 1). Odds ratios for a variable combining smoking and social class showed a greater risk of wheeze for smokers in the manual class than those in the non-manual class; both duration and amount of smoking were significantly greater in the manual class (data not shown).

We determined the overall burden of current wheezing illness in middle age, including onset in both childhood[1] and adulthood, by examining our data for the complete cohort of 2511 subjects. Among the 1902

Table 1 Adult onset wheeze: effect of sex, smoking habit, and social class. Values are numbers (percentages) unless stated otherwise

	Adult onset wheeze (n=177)	No wheeze (n=1303)	Odds ratios* (95% CI)
Sex:			
Male	73 (41.2)	610 (46.8)	1.0
Female	104 (58.8)	693 (53.2)	1.3 (0.9 to 1.8)
Smoking habit:			
Never	64 (36.2)	621 (47.7)	1.0
Past	33 (18.6)	287 (22.0)	1.1 (0.7 to 1.7)
Current	79 (44.6)	384 (29.5)	1.8 (1.2 to 2.5)†
Social class based on own occupation:			
Non-manual	73 (41.2)	759 (58.3)	1.0
Manual	102 (57.6)	509 (39.1)	1.9 (1.4 to 2.6)†
Combination of smoking and social class:			
Never smoker, non-manual	41 (23.2)	385 (29.5)	1.0
Never smoker, manual	23 (13.0)	218 (16.7)	1.0 (0.6 to 1.7)
Past smoker, non-manual	12 (6.8)	189 (14.5)	0.6 (0.3 to 1.2)
Past smoker, manual	21 (11.9)	94 (7.2)	2.1 (1.2 to 3.7)†
Current smoker, non-manual	20 (11.3)	184 (14.1)	1.0 (0.6 to 1.8)
Current smoker, manual	57 (32.2)	191 (14.7)	2.8 (1.8 to 4.3)†

*For combined variable of smoking and social class, the odds ratios are univariate.
†P<0.05.

subjects for whom follow up information was available, 278 (14.6%) reported wheeze in the previous year; the time of onset was unclear for 32 of these subjects. Of the 246 subjects with known age of onset, 99 (40.2%) had child onset and 147 (59.8%) had adult onset symptoms.

Comment

The prevalence of adult onset wheeze at age 15-45 years was 11.5%. In the full cohort followed up in middle life, adult onset disease accounted for a greater proportion of current wheezing than child onset disease. This age-specific pattern of onset is similar to that found in other population studies of wheeze in adults.[2-4] Although wheeze in adults is likely to include both asthma and chronic airways obstruction, using a narrower definition, such as "doctor diagnosed asthma," would exclude many subjects who have not received a diagnostic label.[2-4] Underdiagnosis resulting from underreporting and misinterpretation of symptoms may result in undertreatment.[5] Over 40% of the subjects who reported limitation in their activities were not receiving treatment.

Smoking and manual social class conferred an increased risk of adult onset wheeze. A smoking effect has been shown by others[2 3] and may reflect inclusion of subjects with smoking related chronic airways obstruction. The effect of social class may be partially explained by greater cumulative cigarette exposure in the manual class. Other risk factors, such as atopy and family history, require further investigation. This study shows that adult onset wheeze represents an important source of morbidity that may be currently underrecognised and undertreated.

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Cohort study of relation between donating blood and risk of myocardial infarction in 2682 men in eastern Finland

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Mild iron deficiency has been hypothesised to reduce risk of heart disease risk,[1] while a high concentration of body iron has been suggested as a risk factor for myocardial infarction.[1 2] Menstruation in women and voluntary blood donations are the most important causes of blood loss and thus modulators of stores of body iron. We prospectively investigated the association of donating blood with the risk of acute myocardial infarction in a random population sample of middle aged men.

Patients, methods, and results

We investigated the incidence of acute myocardial infarctions in participants in the Kuopio ischaemic heart disease risk factor study.[3] During 1984-9 we carried out baseline examinations of 2682 (83%) of the 3235 men aged 42, 48, 54, or 60 whom we had invited. We obtained data on the subjects' donating blood by record linkage to files of the local Red Cross office. We registered and verified all myocardial infarctions, definite or possible, between the baseline examinations and the end of 1992.[2] The mean follow up time was 5.5 years, and, with multiple infarctions, we considered only the first. We used Cox's proportional hazard's analyses to compare the occurrence of cardiac events in blood donors and in non-donors.

In the 24 months before the baseline examinations 153 (5.7%) of the 2682 participants had donated blood. During follow up, one (0.7%) of the donors

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Table 1 Coronary risk factors in 153 male blood donors and 2529 non-donors and relative risks for acute myocardial infarction (values are means (SD) unless stated otherwise)

Risk factor	Blood donors (n=153)	Non-donors (n=2529)	P value for difference*	Relative risk (95% CI)	P value in multivariate model†
Age (years)	50.5 (5.5)	53.2 (5.1)	<0.001	1.04 (1.00 to 1.08)	0.047
No (%) with history of coronary heart disease:					
Personal history	13 (8)	665 (26)	<0.001	2.99 (2.28 to 3.93)	<0.001
Family history	72 (47)	1239 (49)	0.643	1.64 (1.25 to 2.15)	<0.001
Apolipoprotein B concentration (g/l)	0.97 (0.25)	1.04 (0.24)	0.001	3.02 (1.87 to 4.87)	<0.001
Smoking (pack years)	82 (199)	174 (345)	<0.001	1.01 (1.01 to 1.02)	<0.001
Systolic blood pressure (mm Hg)	130 (14)	134 (17)	<0.001	1.12 (1.05 to 1.20)‡	0.001
Blood donation				0.14 (0.02 to 0.97)	0.047

*From Student's *t* tests assuming unequal variances comparing blood donors and non-donors.
†Cox proportional hazards' model including all variables shown and examination years as indicator variables (not shown).
‡Per 10 mm Hg rise in blood pressure.

experienced an acute myocardial infarction compared with 226 (9.8%) of the 2529 non-donors ($P < 0.001$ for difference). Table 1 shows that, in a multivariate model adjusted for the main coronary risk factors, the blood donors' risk of acute myocardial infarction was 86% less than that of the non-donors (relative risk 0.14, 95% confidence interval 0.02 to 0.97, $P = 0.047$). Additional adjustment for a large number of measurements of medical history, health state, health practices, and psychosocial characteristics attenuated this association only marginally.

Comment

This is the first study to report a reduced risk of coronary events in male blood donors. The mechanism through which donating blood reduces the risk of coronary events could be the depletion of body iron stores. Such depletion could decrease the amount of injury promoting iron in the myocardium, alter the activity of iron dependent enzymes, increase plasma antioxidative capacity, and decrease lipid peroxidation in both the circulation and in vessel walls.[1 2 4 5] There is experimental, clinical, and epidemiological support for high iron stores increasing the risk of coronary events and atherosclerotic progression.[4 5] The lack of consistency in epidemiological studies is probably explained by large variability in estimates of iron stores and iron intake and by the diversity of study outcomes.[5]

We suggest that the loss of iron associated with giving blood might be the reason for the observed risk reduction. However, voluntary blood donors seem to be generally more health conscious and more healthy than those who do not donate blood, and this may have caused self selection bias. In our study the association between donating blood and reduced risk for myocardial infarction was weakened but remained significant after adjustment for the main coronary risk factors. Our finding needs to be confirmed in other prospective population studies, and investigation of the impact of iron depletion on atherosclerotic progression or coronary events is necessary to test the above theory.

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Conflict of interest: None.

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Social deprivation and bacterial meningitis in North East Thames region: three year study using small area statistics

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The rates of many diseases are linked to the deprivation of the area.[1] Earlier British studies have shown that lower social class and overcrowding are associated with increased risk of meningococcal meningitis.[2] Using data from a prospective study in North East Thames region (now part of North Thames region) between 1991 and 1993 we examined the relation between types of bacterial meningitis[3] and deprivation of residential area, looking at rates specific for age and ethnic group.

Subjects, methods, and results

Between 1991 and 1993, 369 cases of bacterial meningitis (177 due to *Neisseria meningitidis*; 103 to *Haemophilus influenzae*; 89 to *Streptococcus pneumoniae*) were recorded in North East Thames and had postcode data available (representing 89% of all cases collected). Deprivation was measured by Townsend score[4] and levels of overcrowding in the ward of residence and linked to cases by postcodes. The eight cases of *H influenzae* meningitis which occurred after the introduction of routine infant immunisation in 1993 were excluded.

North East Thames wards were ranked according to Townsend score and divided into three groups, with an equal number of wards in each group (labelled most deprived, intermediate, least deprived), the group formed from wards with the highest Townsend score being classified as most deprived. This process was repeated for overcrowding. Rates (per 100 000 per year) for the three causes of meningitis were calculated for each group, using the number of cases over two years (*H influenzae*) or three years (*N meningitidis* and *S pneumoniae*) as the numerators and unadjusted 1991 census population as the population base. The χ^2 test and χ^2 test for trend were calculated, using EpiInfo version 6 to determine the relation between disease rates and deprivation or overcrowding. We focused on children aged 0-4 years because the three major causes of bacterial meningitis are most common in children aged under 5 years.

Overall, rates for meningococcal meningitis were 74% higher in overcrowded areas (table 1). *H influenzae* meningitis was not associated with deprivation or overcrowding. Rates for pneumococcal meningitis were approximately twice as high in the most deprived

Table 1 Meningitis rates in North East Thames per 100 000 population (number of cases). Population data are ward based 1991 census population

Variable and group	Most	Intermediate	Least	Odds ratio (95% CI)†	P value (χ^2 for trend)
Deprivation					
Total population:					
Population base	1 529 551	1 282 795	881 118		
N meningitidis	1.77 (81)	1.69 (65)	1.17 (31)	1.51 (0.98 to 2.33)	0.071
H influenza	1.37 (42)	1.52 (39)	1.25 (22)	1.10 (0.64 to 1.90)	0.811
S pneumoniae	1.16 (53)	0.62 (24)	0.45 (12)	2.54 (1.32 to 5.02)	0.001***
White children (0-4 years):					
Population base	71 800	77 527	50050		
N meningitidis	14.86 (32)	11.18 (26)	7.99 (12)	1.86 (0.92 to 3.81)	0.056
H influenzae	17.41 (25)	19.35 (30)	21.98 (22)	0.79 (0.43 to 1.46)	0.427
S pneumoniae	5.11 (11)	3.87 (9)	2.00 (3)	2.56 (0.66 to 11.52)‡	0.139
Overcrowding					
Total population:					
Population base	1 559 788	1 294 151	839 525		
N meningitidis	1.80 (84)	1.73 (67)	1.03 (26)	1.74 (1.10 to 2.77)	0.024*
H influenzae	1.31 (41)	1.47 (38)	1.43 (24)	0.952 (0.54 to 1.57)	0.697
S pneumoniae	1.13 (53)	0.54 (21)	0.60 (15)	1.90 (1.04 to 3.52)	0.005**
White children (0-4 years):					
Population base	73 083	79 531	46 763		
N meningitidis	15.51 (34)	11.32 (27)	6.42 (9)	2.42 (1.11 to 5.41)	0.014*
H influenzae	16.42 (24)	18.23 (29)	25.66 (24)	0.64 (0.35 to 1.17)	0.129
S pneumoniae	4.10 (9)	3.35 (8)	4.28 (6)	0.96 (0.31 to 3.03)	0.992

*P<0.05, **P<0.01, ***P<0.0001.
†Comparing cases from deprived wards with those from prosperous wards.
‡Expected value <5.

wards and the most overcrowded wards. In white children under 5 years, rates for meningococcal meningitis were over twice as high in the most overcrowded wards than in the least overcrowded wards. By using the same methods we found that pneumococcal meningitis rates were significantly higher among white people of all ages in the most deprived wards (0.9/100 000 *v* 0.4/100 000 in least deprived wards).

Comment

In spite of the difficulties with ascribing socioeconomic characteristics of geographic areas to individuals living in those areas,[5] we believe that these data show that rates of meningoccocal and pneumococcal meningitis are related to measures of area deprivation. Though the small numbers involved may have had an effect in terms of the power of our study, our analysis allowed an internal comparison of effects on the rates of the three main causes of bacterial meningitis. Their similar epidemiology in preschool children led us to believe they would behave similarly with respect to overcrowding and poverty. However, relations between deprivation and rates of these three diseases differed. Studies collecting sociodemographic data at individual and area levels could clarify the basis for these differences. Our findings suggest that effective action to tackle social deprivation will have an effect on rates of bacterial meningitis.

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ONE HUNDRED YEARS AGO

A remarkable patient

At a recent meeting of the Clinical Society of the Boston City Hospital a patient presented who was convalescent from pneumonia. He was 84 years of age, and had been a sailor. At various times in his life he had been the victim of the following injuries: Fracture of the left femur, which had united with marked callus and 2½ inches of shortening; of the left patella; of the head of the right tibia; of the left clavicle; of several of the lower ribs on both sides; of the index fingers of both hands (these presented marked deformity); of the left ankle; and of the right scapula. He had also suffered from double otitis media, bronchitis, and asthma. When shown to the Society he had double incipient senile cataract. Several years ago he had had an epithelioma removed from the lower lip, and there had been no recurrence. The man's limbs are still muscular, though his age and the vicissitudes of his career have necessarily caused some wasting. His breadth of shoulders and depth of chest gave evidence of what must have been extraordinary strength and endurance. (*BMJ* 1897;ii:98.)