

SIBSHIP SIZE DOES NOT INCREASE THE RISK OF DEVELOPING RHEUMATOID ARTHRITIS

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SUMMARY

Although the cause of rheumatoid arthritis (RA) is unknown, one hypothesis is that an infectious episode may trigger the disease and this may occur in childhood. Observational studies performed at least 25 years ago have suggested that the incidence of RA is increased in individuals from large families. We therefore tested this hypothesis using data from a case-control study of 218 females with RA aged 35-70 (mean 58.9 years) and 210 similar aged osteoarthritis (OA) females. Information was obtained by postal questionnaire on sibship size, position in family and sex ratio of siblings. No significant differences were found between the cases and controls for any of these variables. This study did *not* support the hypothesis that early childhood infection as a consequence of overcrowding is an important factor in the development of RA.

KEY WORDS: Rheumatoid arthritis, Family size, Childhood infection.

THE aetiology of rheumatoid arthritis (RA) is unknown. Nevertheless it is likely to be multifactorial with genetic, hormonal and environmental factors believed to be important [1]. Of the environmental agents infection with viruses or bacteria as a possible trigger of RA have attracted the greatest attention [2]. These hypotheses have been generated mainly from laboratory and animal studies which have implicated a wide range of pathogens [3]. Although there has been little corroborating epidemiological evidence to date, recent secular trends have suggested the role of an infective agent in RA. There is evidence that RA was uncommon before the 18th century and some surveys suggest that the incidence may now be on the decrease [1,4,5]. Although the onset of RA is relatively rare before middle life, serological change can precede clinical onset by many years [6] and thus it may be exposure to infection in early life that is important. In support of this is evidence of an effect of year of birth on the risk of becoming rheumatoid factor positive in both the general population [7] and in patients with RA [8].

Infection rates in children increase with household size and specifically the number of siblings. This has been shown for respiratory disorders such as pneumonia or bronchitis (Strachan DR, personal communication) and infections such as otitis media [9], *Giardia* [10] and hepatitis [11,12]. Immune response and rates of atopy also have been shown to increase inversely with number of siblings [13]. A small case-control study of Behçet's disease, which is believed to be a form of immune complex vasculitis, suggested that large numbers of siblings and low birth order were risk factors [14]. Several early descriptive studies of RA patients suggest that increased sibship size may be an

important risk factor [15-17]. Birth order might also be correlated with length of close exposure to other siblings and consequently increased risk of infection. We therefore examined, in a case-control study, whether individuals with rheumatoid arthritis came from larger families and whether the position relative to other siblings varied systematically.

SUBJECTS AND METHODS

The data for this analysis were derived from a case-control study of women with RA investigating the possible aetiological role of reproductive and gynaecological history, details of which have been reported elsewhere [18]. The cases were women, aged between 35 and 70 years, with rheumatoid arthritis, attending the outpatient departments of five hospitals in East London during 1987. The comparison group were women with osteoarthritis (OA) in the same age group attending the same hospital outpatient departments in the same period. The survey method was by postal questionnaire. Information for this analysis was gathered on the number and sex of siblings and birth order of the individual as well as other demographic details. A reminder letter and second questionnaire were sent to all initial non-responders after six weeks. Both sets of women received identical letters and questionnaires and were unaware of the hypotheses under examination.

The results are expressed as odds ratios based on the estimated relative risk of developing rheumatoid arthritis with increasing sibship size. The disease status was based on the recorded diagnosis of the referring physician and verified by inspection of the medical records. Women in the RA group satisfied the 1958 criteria for rheumatoid arthritis. In all, 256 eligible RA and 260 OA women were recruited.

RESULTS

Questionnaires were received from 221 RA cases of which 218 included information on family size

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TABLE I
DISTRIBUTION OF SIBSHIP SIZES BETWEEN CASES AND CONTROLS

Sibship size	Rheumatoid arthritis n=218	Osteoarthritis n=210	Odds ratio (95% confidence interval)
1	14 (6.4%)	20 (9.5%)	1
2	37 (17.0%)	41 (19.5%)	1.3 (0.6-2.9)
3	46 (21.1%)	36 (17.1%)	1.8 (0.8-4.1)
4	33 (15.1%)	34 (16.2%)	1.4 (0.6-3.2)
5	32 (14.7%)	26 (12.4%)	1.8 (0.8-4.1)
>5	56 (25.7%)	53 (25.2%)	1.5 (0.7-3.3)

adequate for analysis. Of the OA controls 216 responded of whom usable replies were received from 210. Thus the final response rates were 83% and 81% for the RA and OA women respectively. The mean age at the time of the surveys of the two groups was similar—58.9 years and 59.4 years, although the RA women were slightly younger at recalled age of disease onset (mean 49.5, SD 9.8) than the OA women (51.3, SD 9.7).

The distributions by number of siblings is shown in Table I. The results show that compared to the reference exposure category (no siblings) there was no trend of increasing risk with increasing sibship size (χ^2 trend NS). All the odds ratios were close to unity and none was significant. The timing of disease onset varied widely amongst the RA women, and childhood infections may be more important in those with early disease onset. Family size was, therefore, examined in the RA women divided into tertiles based on recalled age of onset. No obvious effect or trend was seen, with no increased sibship size in those in the youngest age of onset group (Table II). As sibships of the same sex are more likely to share bedrooms, the data in Table I were reanalysed separately for the number of sisters alone (Table III). There was no suggestion that the RA women had more sisters and the ratio of females to males in the RA and OA sibships was similar. There were also no marked differences in reported birth order between RA women and controls. These are shown in Table IV.

DISCUSSION

This case-control study failed to show any differences between RA and OA control women in the

TABLE II
NUMBER OF SIBLINGS BY AGE OF ONSET IN RA INDIVIDUALS

Sibship size	Age of onset tertile*		
	Youngest n=63	Middle n=69	Oldest n=76
1	3 (4.8%)	6 (8.6%)	5 (6.6%)
2	11 (17.7%)	13 (18.6%)	11 (14.5%)
3	16 (25.8%)	14 (20.0%)	14 (18.4%)
4	5 (8.1%)	12 (17.1%)	15 (19.7%)
5 or more	28 (45.0%)	24 (34.3%)	31 (40.8%)

*There were 10 women for whom age of onset data were not available. The age span within each tertile was: youngest 19-43; middle 44-53; oldest 54-70.

TABLE III
DISTRIBUTION OF NUMBER OF SISTERS BETWEEN CASES AND CONTROLS

Number of sisters	No.	Rheumatoid arthritis n=218	Osteoarthritis n=210	Odds ratio (95% CI)
0	61 (27.7%)	57 (26.9%)	1	
1	59 (26.8%)	62 (29.2%)	0.9 (0.5-1.5)	
2	43 (19.5%)	40 (18.5%)	1.0 (0.6-1.8)	
≤3	55 (25.7%)	51 (24.3%)	1.0 (0.3-1.7)	
Ratio of females to male siblings in family mean (SD) including proband				
		1.56 (1.28)	1.68 (1.29)	

numbers of siblings, sex ratio of siblings or order of birth. These data therefore do not support the hypothesis that childhood infection resulting from overcrowding and large sibships is a risk factor for the development of RA. For the purposes of this study we have assumed that large sibships are associated with overcrowding, although there are likely to be exceptions to this generalization. The chances of acquiring childhood infections are probably related to a number of social factors which include socioeconomic status, climate, type of housing, and proximity to other children. Although we have only explored the contribution of the latter, these other factors are much more difficult to quantify and investigate accurately. The average family size, although similar in cases and controls, was larger than seen currently in the UK, reflecting national trends. Although social class differences could have occurred between our groups and were not directly measured in our study, this was unlikely. Both sets of women were attending the same hospitals and are drawn from the same areas within London. There is no obvious reason to suspect recall bias to be a problem with this kind of data and response rates were similar in the two groups studied.

Surveys have demonstrated that the prevalence of viral infections (measles, pneumonia, whooping cough, bronchitis) below the age of 5 is greater in children with larger families [19,20] (Strachan DP, personal communication). After the age of 5, however, this trend reverses. Thus children born to large families appear more likely to get infected with common viruses at an early age than those in small families. Gastrointestinal infections may also be linked to sibship size. Several studies of infection with hepatitis and *Giardia* have demonstrated that in adults the chances of being previously exposed were related to the number of sibships in the family [10-12]. It may be, therefore, that

TABLE IV
ORDER OF BIRTH

Birth rank amongst siblings	RA n=218	OA n=210
Firstborn	68 (31.1%)	68 (32.1%)
2nd	49 (22.4%)	59 (27.8%)
3rd	40 (18.3%)	27 (12.7%)
4th or greater	61 (28.0%)	56 (26.7%)

sibship size is important in the acquisition of less common infections.

The negative findings in this study suggest that early childhood infections with common viruses or bacteria are not important in the development of RA, although the possibility that infection at a later date is important is not excluded.

These findings suggest other epidemiological data which have failed to produce any confirmatory evidence of infective agents in RA [21]. There have been no reports of case clustering or marked regional differences in RA. Furthermore, RA has been found throughout the world in both hot and cold climates although its presentation and clinical features may differ [1]. There have been some reports of urban/rural differences which might be explained by exposure to infection, although this appears to be confined to developing countries where a number of different factors may be operating [7]. There have also been conflicting data on the possible aetiological role of tonsillectomy and appendectomy in RA. Two early studies reported an association which was not found in subsequent studies [22]. One unconfirmed study demonstrated prior pet ownership to be a risk factor for RA [23]. In a previous case-control study Vandenbroucke *et al.* did not find any differences in reported clinical infections prior to symptom onset between rheumatoid cases and controls [24]. Analysis of sibling pairs with RA has failed to show any consistent or close relationship of the calendar year of onset which would have suggested an environmental or infectious trigger [25,26].

Previous studies examining sibship size and RA, although suggestive of an effect, have not been conclusive. The population study in Tecumseh examined siblings and demonstrated an increase in RA siblings with family size. A study of Arizona Indians showed a positive association of both RA and rheumatoid factor with sibship size in Pima Indians, but not with Blackfoot Indians [17]. A study of siblings in Manchester reported that a similar trend was seen but no data were given [27]. Chen and Cobb quoted unpublished data from a population survey (Pittsburg Arthritis Study) that the prevalence of RA was twice that in sibship sizes 3 or 4 compared to 1 and 2, although they discuss possible biases [15]. These studies performed in the 1950s and 1960s were either based on family studies or patient surveys and did not involve a control group. No adjustments were made for year of birth or social and cultural differences. It is interesting that similar studies also produced data showing that criminals, delinquents, psychotics and neurotics and, of course, scientists, come from large families [15]. Most of these associations have been shown subsequently to be spurious.

In summary, we have not found any differences in the number of siblings between RA patients and controls nor in the birth order of the sibling who was subsequently to develop RA. These data do not support the hypothesis that childhood infection has a role in the aetiology of rheumatoid arthritis.

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REFERENCES

1. Spector TD. Rheumatoid arthritis. *Rheum Dis Clin North Am* 1990;16:513-37.
2. Venables PJW. Infection and rheumatoid arthritis. *Curr Opin Rheumatol* 1989;1:15-20.
3. Ford DK. Microbiology will give the real answers to rheumatoid arthritis. *Br J Rheumatol* 1989;28:436-9.
4. Silman AJ. Recent trends in rheumatoid arthritis. *Br J Rheumatol* 1989;28:328-30.
5. Hochberg MC. Changes in the incidence and prevalence of rheumatoid arthritis in England and Wales, 1970-1982. *Semin Arthritis Rheum* 1990;19:1-8.
6. Aho K, Palosuo T, Raunio V, Puska P, Avomaa A, Salonen JT. When does rheumatoid disease start? *Arthritis Rheum* 1985;26:485-9.
7. Lawrence JS. *Rheumatism in populations*. London: Heinemann, 1977.
8. Silman AJ, Davies P, Currey HLF, Evans SJW. Is rheumatoid arthritis becoming less severe? *J Chron Dis* 1983;36:891-57.
9. Zielhuis GA, Hevelmans-Heimen EW, Rach GH, van der Broek P. Environmental risk factors for otitis media with effusion in preschool children. *Scand J Prim Hlth Care* 1989;7:33-8.
10. Novotny TE, Hopkins RS, Shillam P, Janoff EN. Prevalence of *Giardia lamblia* and risk factors for infection among children attending day-care facilities in Denver. *Publ Hlth Rep* 1990;105:72-5.
11. Toukan AU, Sharaiha ZK, Abu-el-Rub OA, *et al.* The epidemiology of hepatitis B virus among family members in the Middle East. *Am J Epidemiol* 1990;132:220-32.
12. Green MS, Zaipe Y. Sibship size as a risk factor for hepatitis-A infection. *Am J Epidemiol* 1989;129:800-5.
13. Strachan DP. Hayfever, hygiene and household. *Br Med J* 1989;299:1259-60.
14. Cooper C, Pippard EC, Sharp H, Wickham C, Chamberlain MA, Barker DJP. Is Behçet's disease triggered by childhood infection? *Ann Rheum Dis* 1989;48:421-3.
15. Chen E, Cobb S. Family structure in relation to health and disease. *J Chron Dis* 1960;12:544-67.
16. Francis T Jr, Epstein FH. Survey methods in general populations: studies of a total community, Tecumseh, Michigan. *Milbank Mem Fund Quart* 1965;43:333-42.
17. Bennett PH, Burch TA. Rheumatoid factor in the Blackfeet and Pima Indians. In: Bennett PH, Wood PHN, eds. *Population studies of the rheumatic diseases*. Amsterdam: Excerpta Medica 1968: 192-202.
18. Spector TD, Roman E, Silman AJ. The pill, parity and rheumatoid arthritis. *Arthritis Rheum* 1990;33:782-9.
19. Colley JRT, Reid DD. The urban and social origins of childhood bronchitis in England and Wales. *Br Med J* 1970;ii:213-17.

20. Butler NR, Golding J. *From birth to five. A study of the health and behaviour of Britain's five-year-olds.* Oxford: Pergamon Press, 1986: 201-14.
21. Silman AJ. Rheumatoid arthritis and infection: a population approach. *Ann Rheum Dis* 1989; **48**:707-10.
22. Fernandez-Madsrid E, Reed AJ, Karvonen RL, *et al.* Influence of antecedent lymphoid surgery on the odds of acquiring rheumatoid arthritis. *J Rheumatol* 1985; **12**:43-8.
23. Gotlieb NL, Ditchek N, Polley J, *et al.* Pets and rheumatoid arthritis. *Arthritis Rheum* 1974; **17**:229-34.
24. Vandenbroucke JP, Kaaks R, Valkenburg HA, *et al.* Frequency of infections among rheumatoid arthritis patients before and after disease onset. *Arthritis Rheum* 1987; **30**:810-13.
25. Sanders PA, Grennan DM. Age and year of onset differences in siblings with rheumatoid arthritis. *Br J Rheumatol* 1990; **29**:128-30.
26. Silman AJ, Ollier WE. Age and calendar year of onset in sibling pairs with rheumatoid arthritis (letter). *Br J Rheumatol* 1990; **29**:399-400.
27. Lawrence JS. Discussion. In: Bennett PH, Wood PHN, eds. *Population studies of the rheumatic diseases.* Amsterdam: Excerpta Medica, 1968: 147.