Heberden Oration 1981**Epidemiology and the arthritides**

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SUMMARY The multifactorial control of serum uric acid levels is discussed from an epidemiological point of view and the principles at issue related to the epidemiology of osteoarthritis. It is shown that in osteoarthritis the clinical characteristics vary from one joint group to another. Association of x-ray changes with pain varies between joints and between sexes for the various joints. The disease tends to be commoner in females but not in all age groups. There is an association between obesity and osteoarthritis in the hands and knees but not the hips or ankles. These differences raise questions about the homogeneity of generalised osteoarthritis. Such questions might be answered by epidemiological studies which consider individual joint groups and are carefully directed towards specific hypotheses, the development of which could be facilitated by the use of iconic models.

To be invited to give the Heberden Oration is an honour I deeply appreciate. It is usual for those delivering such an address to open with an allusion to the work of the great man of the past whose name is being remembered. With your permission, Sir, I would like instead to refer first to James Lind, and then presently return to William Heberden senior, for Lind was in his own terms an epidemiologist as well as a sailor and a physician. He described¹ scurvy as 'an epidemic induced by external causes', and true epidemiologist that he was looked upon populations, not individuals, as the units at risk. Three such populations he enumerated as being at risk of scurvy were seamen on long voyages, troops under siege, and inmates of prisons. My justification for mentioning Lind here, not too far fetched I hope, is that scurvy causes acute arthritis and that he did not fail to refer to stiff and contracted knees as one of the signs of the disease. Lind's work, undertaken over 200 years ago, illustrates that the principles of epidemiology have not changed, though details have. Lind, like others after him, such as Budd, Snow, and Goldberger was able by identifying and describing 'a universal calamity' (Lind's expression¹), together with the details of the stricken population and the agony that attended them, to illuminate a dark area in medical know-

ledge. In one 10-week voyage 80 of 356 (22.5%) of the crew of a ship were prostrated.¹

The reason why Lind and many other epidemiologists besides met with their successes was because the causes of the diseases that interested them were single and simple and the diseases themselves relatively easy to diagnose and often calamitous. Here I must pause to express my gratitude to Dr C. F. B. Sanderson, who has recently used some of my own material, and data we obtained from the United States Public Health Service, as a basis for a Ph.D. degree at Cambridge,² which have been developed in arguments to come.

Fig. 1 is derived from Sanderson's work² and presents a simple model of disease which illustrates the indirect nature of cross-sectional studies. Observations and measurements are made of 'risk covariables' and correlated with the 'manifestations' of illness in the hope that light would be thrown on causes and processes of disease. Lind's work provides an admirable example of this at its very simplest. A single risk covariable, a diet devoid of vitamin C, is strongly associated with a group of unusual manifestations which include bleeding gums, swollen legs, and joint contractures. Risk covariables and manifestations are both often obvious and readily measured; they may be only indirectly linked to causes and processes of disease. The epidemiologist need not understand them. Lind identified green vegetables and citrus fruits (Fig. 2), but it is improb-

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Fig. 1 A simple causal model based on cross-sectional data.

Fig. 2 Application of model shown in Fig. 1 to scurvy.

able that he understood little more of the pathogenesis of scurvy than did Hammond when he started his great prospective investigation of carcinoma of the lung.

A simple epidemiological approach based on correlating a single risk covariable with a single set of manifestations has not been able to contribute dramatically to the understanding of disease for some decades now, any more than clinical medicine has since John Ryle's day provided advancement from the carefully written description of a series of uncontrolled clinical cases, an art at which Heberden excelled. The reason is that the diseases which are still unexplained are complex in their pathology and pathogenesis as well as their aetiology, and that causal models necessary to explain them must often reflect this complexity.

Pioneers in descriptive epidemiological studies in the field of arthritis were Kellgren and Lawrence.³⁻⁵ Many investigators have followed in their footsteps but have not had much to add, and there have been few deliberate attempts at constructing serious causal hypotheses.

Descriptive population study

My own move into the field was in 1963, 11 years after Kellgren and Moore⁶ published their clinical description of generalised osteoarthritis and 5 years after Kellgren's epidemiological report with Lawrence in the same field based on survey data from Leigh in Lancashire.³ I took my decision on the grounds that the problem of arthritis in the USA was as important as it is here, yet there was no epidemiological work in the field there apart from the later analysis of the National Health Examination Survey by Engel.^{7,8} I felt confident that a carefully conducted descriptive population study should produce important leads which might be followed in the wards or the laboratory. But, as you are all now aware, the epidemiologist working in arthritis has not in those years found anything so exciting to recount as the tale of cigarettes and lung cancer.

The arthritides are many, and time is short, and although I had originally hoped to cast my net more widely I have now decided to direct most of my attention on osteoarthritis. However, I shall start by

alluding briefly to gout because it illustrates some of the basic difficulties in interpreting epidemiological data and allows me to refer to the work of Heberden.

Heberden⁸ laid far more emphasis on gout than on 2 other rheumatic conditions he distinguished, namely, acute rheumatic fever, and the second, a condition which he claims 'that is either to be called rheumatism, or should it be distinguished by some other name from both these distempers'.⁹ (There is no agreement as to the nature of this other disease, but it may have been rheumatoid arthritis.) I am not going to repeat his terse question about those 'little hard knobs about the size of a small pea,' although it is germane to my subject, because he did not associate those little hard knobs with gout, rheumatism, or arthritis. Moreover his famous short paragraph on the subject has been cited in full by Stecher¹⁰ and Cohen¹¹ in their Heberden Orations.

To return to gout: in the New Haven Survey,¹² although a strong relationship was found between gout and social class, which was most prevalent among the rich, we confirmed Lawrence's earlier observation in Watford and Wensleydale by failing to find any relationship whatsoever between serum uric acid and social class.¹³ These observations taken with Framingham data illustrate very clearly that serum uric acid (SUA) alone is not the only factor that precipitates gout (see Fig. 3¹⁴).

Fig. 3 Prevalence percentage of gout by serum uric acid in Framingham, Massachusetts. Notice that although prevalence increases with increasing uric level, there is no level so low that gout does not occur, nor is there one so high that all cases have gout.

Thus although serum uric acid is an important risk covariable for gout there are a range of other factors, many of them now clearly understood, which may play a role in the precipitation of an attack in a patient with a relatively low SUA as well as prevent an attack in a patient whose SUA is high. For instance we found an interesting and statistically significant relationship between serum uric acid and haemoglobin in both sexes^{12 15} (Table 1).¹⁵

When we first reported this at the 3rd International Symposium on Population Studies of the Rheumatic Diseases in New York Jacox¹⁶ predicted that the elevated incidence of polycythaemia among the high Andean peoples would be accompanied by hyperuricaemia. We were subsequently able to confirm this to be the case¹⁷ (Table 2).

The complexity of the risk covariables for serum uric acid and gout are thus such that it is not surprising that this year Gardner *et al.*¹⁸ failed to find a social class gradient in the prevalence of gout in three English towns. Their work does not necessarily mean that we in New Haven, Connecticut, were incorrect, nor that Anumoye *et al.*¹⁹ in Edinburgh or Jeremy and Towson²⁰ in Sydney, Australia, were any more correct than we when they claimed to find no association between SUA and haemoglobin, for both our observations have been confirmed by Zalokar *et al.*,²¹ who did find SUA and haemoglobin to be correlated, as well as a social class pattern, in the incidence of gout in Frenchmen. The control of serum uric acid is well known to be multifactorial.^{22 23} As I have already suggested, one can therefore only conclude that in all these instances other, unidentified subtle factors are operational, so that partial correlations are being measured. I dwell on this material, although none of it is new, because it illustrates how very much more complex is the world in which today's epidemiologist struggles than that in which James Lind worked. True we have technological support and expertise which Lind lacked, but hyperuricaemia is certainly not 'a universal calamity' nor has it a single cause, so that Sanderson's simple model based on a single covariable is quite inadequate to serve as an explanation of why some people should and others should not have gout.

It illustrates the uselessness of simple causal models in modern epidemiology, for if the factors that determine gout in an individual are many, the model that predicts gout must reflect these, and the use of a cut-off point in a normal distribution is, as the Framingham data have shown, of questionable use at the bedside.

Osteoarthritis and sex

Rather than pursue this issue further I shall turn to

Table 1 Stepwise regressions by sex of serum uric acid with ponderal index and total serum protein

Step	Male				Female			
	Variables added at step	R	R ²	Increase in R ²	Variables added at step	R	R ²	Increase in R ²
1	Ponderal index*	0.1999	0.0400	0.0400	Ponderal index*	0.2576	0.0663	0.0663
2	Haemoglobin*	0.2462	0.0606	0.0206	Protein*	0.3208	0.1029	0.0366
3	Age*	0.2705	0.0732	0.0126	Age*	0.3801	0.1444	0.0415
4	Protein†	0.2846	0.0810	0.0078	Haemoglobin*	0.3920	0.1536	0.0092
5	Class	0.2876	0.0827	0.0017	Class	0.3920	0.1537	0.0001

*p<0.05 for the regression coefficient of the variable indicated.

†p<0.10 for the regression coefficient of the variable indicated.

Table 2 Mean serum uric acid by ABO blood group and altitude of residence (Columbian recruits)

Altitude (m)	Mean SUA (mg/100 ml) in Colombian recruits with blood group:				Total (weighted)*
	A	B	O	AB	
<1000	4.69 (60)	5.20 (71)	4.73 (45)	4.87 (20)	4.77
1000-1999	4.71 (61)	5.25 (49)	5.17 (58)	5.00 (20)	5.06
2000+	5.19 (29)	5.23 (30)	5.37 (31)	5.56 (7)	5.31
Total	4.80 (150)	5.23 (150)	5.07 (134)	5.02 (47)	5.02

*Weighted to take into account the varying sampling fractions of the ABO strata.

Figures in parentheses denote numbers of observations in each cell.

Fig. 4 Estimates of the numbers of joints affected by osteoarthritis grade 2 or more in the hands by age and sex applying the formula $n = N(1 - e^{-(t/10)^4/a})$ to New Haven data.

Fig. 5 Prevalence of joint pain in New Haven by joint, age, and sex (n=2100).

Fig. 6 Prevalence of joint pain in probability sample of United States population by joint, age, and sex ($n > 7000$).

aspects of osteoarthritis for which an even more complex model is necessary and devote some attention to it, and arthritic pain. Kellgren²⁴ wrote that 'one of the difficulties with osteoarthritis is that . . . we have very few clean cutting lines and as a result if you look at OA as a whole you find very few distinct, albeit very puzzling associations [of other factors with it].'

Sex is a clearly definable factor, so let us start with it and make a simple comparison of the prevalence of OA in the hands of the 2 sexes. It can be seen in Fig. 4 that the number of joints affected by osteoarthritis is greater in young men than young women, and that prevalence lines cross at about age 55. Some studies show similar cross-overs in the prevalence of pain, although the data are not consistent. In the identification of pain in New Haven our investigators asked all our respondents the same questions as had been asked in the US National Interview Survey some 5 years earlier and again by the Atomic Bomb Casualty Commission about morning stiffness, nocturnal pain, and swelling of the joints, namely, 'in the last 3

months have you felt pain in the joints at night in bed (stipulate)?'

The United States Health and Nutrition Examination Survey (HANES) modified the screening question to the following form, even though the previous question was from an earlier US National Health Survey: 'Have you had pain or aching in the (stipulate) joints on most days for the last 6 weeks?' The results are shown in Figs. 5 and 6.

In summary, the following sex differences were found: (1) Over the age of 35 more women suffer more pain in their joints than men; but men under the age of 35 suffer more pain in the ankles and knees, as well as in the knees in age groups 45–54. Patterns in the New Haven data show minor differences only. (2) The most commonly painful joints in women in both studies tend to be the hands and knees. The hips rank high in the HANES data (which relate to day rather than to night). (3) The least commonly painful joints in women are the ankles and feet (which are of course weight bearing joints). (4) The hips appear to follow a different pattern from the other joints, a point to which we shall return. The only comment worth making at this stage is that in New Haven in particular the relationship between prevalence and age in the hip differs from that of the other joints.

Pain associations

There is no way of knowing from these data alone why the joints are painful. Osteoarthritis is the commonest form of joint disease, and, like the non-specific pain we have just described, has a remarkable predilection for women, but it is just possible that some forms of pathology of the joints other than those of which we are aware may be painful. However, the New Haven data relating to the hand showed very clearly that in general a woman with pain in her joints is more likely to have radiological signs of osteoarthritis than a man (Table 3²⁵). It can be seen from this Table how the association between symptoms in the hands in the 2 sexes differs as these relate to osteoarthrotic lesions.

We show in Figs. 5 and 6 that pain was less common in the hands of men than women and in Table 3 that in men there is no evidence of any relationship between stiffness or pain and the presence of osteoarthrotic joints, but that there is a weak but significant relationship with joint swelling. In other words in men the symptoms and signs of osteoarthritis in the hands are largely independent of each other. In contrast, in women all 3 symptoms are strongly associated with signs of osteoarthritis. Thus in the hands pain and discomfort are more frequent in women; this discomfort is more frequently associated

Table 3 Persons with radiological osteoarthritis according to whether they had symptoms in their hands, classified by sex

Symptoms		Sex									
		Male					Female				
		Total no.	Mean no. of joints affected	No. with at least one joint affected	χ^2	p	Total no.	Mean no. of joints affected	No. with at least one joint affected	χ^2	p
Morning stiffness	Present	17	4.82	12	0.03	>0.8	72	7.11	57	10.21	<0.01
	Absent	461	4.57	330			577	4.56	340		
Nocturnal joint pain	Present	5	7.00	3	0.01	>0.9	32	8.37	25	3.36	>0.05
	Absent	473	4.55	339			617	4.66	372		
Joint swelling	Present	27	8.81	24	3.37	>0.05	117	9.10	100	34.24	<0.005
	Absent	451	4.32	318			532	3.91	297

Fig. 7 Schematic representation of the left hand. Numbers denote usual frequency of disease; shaded joints denote joints specially prone to damage in male.

with osteoarthritis; and osteoarthritis itself is more common in women in all but the youngest group, where it is slightly commoner in men in New Haven. The latter is not true of HANES.

The anomalous group of young men in New Haven merits further attention (see Fig. 4). Systematic data were available for each hand on a joint-by-joint basis

Fig. 8 Prevalence of pain, osteophytes, and a combination of the 2 in a probability sample of the United States by age and sex in the knees.

in New Haven but not in HANES, where information was recorded by rows of joints. Fig. 7 represents the joints in a hand. The average order in which they

become affected by osteoarthritis is designated by a number. The joints more frequently affected in young males than young females are shaded, and it will be noted that, although they are not necessarily those which are most prematurely affected joints, they are joints on the *margins* of the hands and presumably therefore those most prone to trauma. The following therefore seems to summarise the state of affairs. If these 3 joints are discounted, the excess prevalence of osteoarthritis in the hand of the young male, which had been noted by Kellgren and Lawrence³ and in the sizeable sample of the US National Health Examination by Engel,⁷ disappears, and the prevalence in the 2 sexes becomes the same. It is interesting that without providing data to support his views Kellgren attributed this excess to trauma.

This complete disappearance of the male/female decussation would seem to support the widely held hypothesis that osteoarthritis is a systemic disease which predominantly affects the female, and that unless his joints are damaged by trauma the male suffers a less severe disease and suffers it less frequently than the female. Yet this is an oversimplification, because the sex differences in neither

the knees nor the hips are wholly in accord with this pattern. In the knees of men *pain* with or without x-ray change is slightly commoner than in women to ages as late as 54 years, although the prevalence of OA with or without symptoms is higher in women. This indicates that, in contrast to the hand, the knee of the young and middle-aged male is the more susceptible of the 2 sexes to pain (see Figs. 5, 6, and 8).

Disease and symptoms

The United States Health and Nutrition Examination Survey studied over 7000 subjects, a number which greatly exceeds the 2100 which were available in the New Haven survey. The data are, of course, cross-sectional. In Figs. 8 and 9 each histogram is composed of 3 parts. The lowest *plain* part indicates the presence of pain without radiological evidence of disease; the central *stippled* portion, radiological disease without symptoms; and the upper *black* portion, a combination of disease and symptoms. The prevalence of pain (plain and black) is higher in Fig. 8 and 9 than that shown in Figs. 5 and 6, but the data base is different. Asymptomatic and symptomatic disease are judged on a radiological basis. In the knee after the age of 55 the prevalence of all signs and symptoms in the male is lower.

As was the case with our analysis of the hand and our knowledge of the activities of the knees, our data are again consistent with Kellgren's view that the excess of pain and symptomatic disease in the knees of the males in the younger age groups is probably of traumatic origin.

I should like to say a word more about the hip. Difficulties in interpreting the data in Fig. 9 are aggravated by the fact that, in order to avoid irradiating fertile gonads, no x-rays were taken of women aged under 50 years. Therefore much of the information relates to men. Nevertheless the pattern gives evidence of being more complex than that of the other joints.

The differences between the frequency of both pain and osteoarthritis in the hip and knee increases with age, but although the frequency of pain in the 2 joint groups differs little, the prevalence of radiological disease in the hips is about 1/10th of that in the knee.

A far smaller proportion of OA diagnosed by x-ray in the hip gives rise to pain than in the hand or knee (see portions shaded black) and there is an excess of this among men in the oldest age group. This male excess is not evident in the joints in the other body areas we have examined. Nevertheless—and this is important—like the hands and the knee, when the presence of x-ray changes is ignored (black-and-white bands), women suffer pain in the hip joint more

Fig. 9 Equivalent data for the hips to those shown for the knees in Fig. 8. Note that no data were collected for women aged under 50 years.

than men. Kellgren noted these same radiological differences but did not study their relationship to hip pain.

Body mass

Clinicians have taught for decades that excess body weight aggravates osteoarthritis in the weight bearing joints, especially knees and in hips. Evidence for such a relationship in the knee is abundant,^{3,4,7,8} but properly controlled evidence in support of this view is scarce in other weight bearing joints, if indeed it is extant. Kellgren and Lawrence,³ Roh *et al.*,²⁶ and Saville and Dickson²⁷ all failed to show a significant relationship between OA of the hip and weight. Although Kellgren and Lawrence⁴ did find a weak association, they did not comment on it.

These findings are anomalous because, if wear and tear of weight bearing is in fact a cause of osteoarthritis in the knee, why should the hips be spared? OA in the hallux also correlates significantly with body mass, but there was no such correlation for the ankle.^{3,8} Sanderson² in his analysis of the New Haven data found by an elaborate technique and after correcting for age a general significant correlation of osteoarthritis in the hands with overweight, as Kellgren and Lawrence³ and Engel⁸ had also done. Acheson and Collart,²⁸ however, failed to show any correlation between body mass and an aggregate index for all OA in the body when the hands were excluded. This strong association between body bulk and OA in the knees and its absence in the hips in the HANES data are shown in Table 4. Thus we are faced with a very complex picture.

It is a matter for speculation why the ankle, which bears as much human weight as the hip and knee, remains almost free of osteoarthritis, and such osteoarthritis as there is there shows little relationship to body weight. It is certainly, therefore, an oversimplification to make the unqualified statement

that OA in the lower limb is associated with obesity. In contrast the fingers show such an association in a large proportion of the population—of all ages.

The literature may be replete with statements of dubious value, but it also contains many words of wisdom which, because they do not fit our preconceptions at the time they are written, are ignored.

Robert Stecher in concluding his Heberden Oration in 1955¹⁰ said: 'It is inevitable that osteoarthritis should involve other joints in some patients with Heberden's nodes, but this association is without aetiological foundation. My accumulated experience of osteoarthritis of the finger joints, hips, and spine strongly suggests that three separate diseases have been confused by giving them the same name. . . . The fact that the histological picture of these diseases seems to be similar should not be allowed to mislead us.' Kellgren and Lawrence³ have subsequently staunchly argued that the differences, observed by Stecher, from their own perceptions are due to the fact that, whereas they sought their material in the general community, Stecher's data were derived from clinical case series. One wonders, nevertheless, whether Stecher's cases should be dismissed out of hand. Kellgren *et al.*^{3,6} established without doubt the existence of a tendency for women with Heberden's nodes to have widely generalised osteoarthritis. Table 5 suggests, however, that this is not identical in form in every joint.

It can be seen in the Table that the sex most frequently affected varies from joint to joint, as does the distribution of joint pain. It might thus still be profitable to question the justification of calling all of osteoarthritis one and the same disease, at least to any greater or less extent than cardiac failure consequent on a myocardial infarction is the same disease as cardiac failure consequent on mitral stenosis.

Investigative model

Sanderson,² drawing on the work of Meachim²⁹ and

Table 4 Relationship between index of body bulk and radiographic OA: United States Health and Nutrition Examination Survey

Knees ages 35–74	F values	Hips ages 55–74	F values
Loss of joint space	weight/height ²	Loss of joint space	weight/height ²
Men	27.0**	Men	1.21
Women	147.1**	Women	1.02
Osteophytic growth	weight/height ²	Osteophytic growth	weight/height ²
Men	31.38**	Men	0.25
Women	157.78**	Women	0.38

**p<0.001.

Table 5 Relationship between sex and associates of OA by joint

Sex, predominantly affected by radiological disease	Sex, in which disease is most likely to be painful	Significant association with body bulk (weight/height ²)
{ Hands F Feet F Knees F	F ? M, but elder women have more pain without x-ray changes	F and M F and M F and M
Hips M Ankles F	Generally men ?	None None

Wood³⁰ proposed simply as an illustrative example an investigative model which could be used for examining such issues. It allows both for multifactorial aetiology and multiple pathogenesis (see Fig. 10), and could usefully be employed with or without modification for each joint or joint group separately. Its design takes the following into account:

(a) The group of disease *manifestations* (e.g., loss of joint space visible radiologically, joint pain, etc., all associated with osteoarthritis) may be the products of several different pathological processes, in an analogous way to the many pathways to heart failure.

(b) Each disease process may be associated with various values for a set of different *risk covariables*, yet some of the covariables may be common to different pathologies.

(c) Each disease process is characterised by a particular combination of manifestations which may be in parallel or in sequence, some of which may be common to more than one pathology, and which may vary within what is apparently a given pathology.

Fig. 11 is *wholly speculative*, and has been developed by the present author for the purposes of illustrating this point. It may be appropriate to change the model joint by joint.

Epidemiology can only establish links, but to do so is important. In some instances the procedure would be relatively simple, but in circumstances such as those involving rc 1, 2, and 3 with C1, C2, and C3 this is a complex process which would involve partial correlations or other mathematical manipulations. Moreover if a *sequence of events* is to be established the study must be prospective, and to my knowledge no such study has been attempted in osteoarthritis.

Fig. 10 A complex hypothetical causal model.²

However, a retrospective case control design might, for instance, be helpful in distinguishing between the pattern of disease in patients with joint pain and others who are symptom free. Carefully standardised and validated questions about symptoms would also, of course, have to be asked.

The details shown in Fig. 11 are based on correlates of osteoarthritis in the New Haven survey which are shown in Table 6, which in many instances confirms work of other authors.^{6,32} The well established fact that women are more liable to develop Heberden's nodes more frequently than men makes it remarkable that, in the numerous laboratory studies of cartilage which have been undertaken, so little attention has been paid to the sex of the subject from which the cartilage was taken. It should not be overlooked therefore that a study by Kempson³¹ claims that female cartilage is more susceptible than male cartilage to fatigue.

Time has prevented me from discussing rheumatoid arthritis, but it is fair to say that epidemiological studies in this field, again with the exception of those of Kellgren and Lawrence and a few other authors, have in general tended to be disappointing.

You will see that few of the important clues I had so confidently anticipated in 1963 have emerged. Perhaps we have learned something about arthritic pain as it is distributed between the sexes and between the joints and also something about haemoglobin in the metabolism of uric acid. Perhaps we have given those working in the laboratories other leads for their work. Perhaps we have come to appreciate some of the differences between idiopathic

HYPOTHETICAL FACTORS IN SANDERSON'S MODEL

Fig 11 Some speculative suggestions by the author showing how the model in Fig. 10 can be used for developing hypotheses. SUA = serum uric acid. CRP = C-reactive Protein. ASO = antistreptolysin O.

Table 6 All body sites. Variables shown by multiple regression to be associated with severity of osteoarthritis by age and sex

Age (years)	Males			Females		
	Variable	R ² (cumulative)	% of variance of OA accounted for by each variable	Variable	R ² (cumulative)	% of variance OA accounted for by each variable
34 or less	ASO	0.1855	18.6*	Age	0.1972	19.7*
	Wt/ht	0.2910	10.6	Total protein	0.3195	12.2
35-54	Serum uric acid	0.1217	12.2†	Age	0.1712	17.1†
	Age	0.1590	3.7	Latex	0.2155	4.4
55+	No significant contribution from any independent variable; R ² for all variables was 0.2787			No significant contribution from any individual independent variable; R ² for all variables was 0.1818		

and traumatic osteoarthritis. But the stark fact is just how little we do not know about a very common painful disease. None of the arthritides are monolithic entities, and it is to be hoped that some young investigators will engage in careful analytical hypothesis testing, using the epidemiological approach, and meet with more success than I.

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