Seasonal variation in coronary heart disease in Scotland

A S Douglas, M G Dunnigan, T M Allan, J M Rawles

Abstract

Study objective **– Seasonality of coronary heart disease (CHD) was examined to determine whether fatal and non-fatal disease have the same annual rhythm.**

Design **– Time series analysis was carried out on retrospective data over a 10 year period and analysed by age groups (<45 to >75 years) and gender.**

Setting **– Data by month were obtained for the years 1962–71. The Registrar General provided information on deaths and the Research and Intelligence Unit of the Scottish Home and Health Department on hospital admissions.**

Subjects **– In Scotland, between 1962 and 1971, 123 000 patients were admitted to hospital for CHD, of whom 29 000 died. There were a further 97 000 CHD deaths outside hospital. These two groups were also examined as one (coronary incidence) – that is, all coronary deaths and coronary admissions discharged alive.**

Statistical analysis and main results **– Where there was a single annual peak, the sine curve was analysed by cosinor analysis. When there were two peaks the analysis was by normal approximation to Poisson distribution. In younger men (under 45 years) admitted to hospital there was a dominant spring peak and an autumn trough. A bimodal pattern of spring and winter peaks was evident for hospital admissions in older male age groups: with increasing age the spring peak diminished and the winter peak increased. In contrast, female hospital admissions showed a dominant winter/summer pattern of seasonal variation. In male and female CHD deaths seasonal variation showed a dominant pattern of winter peaks and summer troughs, with the winter peak spreading into spring in the two youngest male age groups. CHD incidence in women showed a winter/summer rhythm, but in men the spring peak was dominant up to the age of 55.**

Conclusions **– The male, age related spring peak in CHD hospital admissions suggests there is an androgenic risk factor for myocardial infarction operating through an unknown effector mechanism. As age advances and reproduction becomes less important, the well defined winter/summer pattern of seasonal variation in CHD is superimposed, and shows a close relationship with the environment, especially temperature, or the autumn and early winter fall in temperature.**

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Studies of seasonal variation in coronary heart disease (CHD) are almost entirely based on data derived from national registers of deaths. Studies based on seasonal variation of CHD hospital admissions are few. Dunnigan *et al*[1] found a bimodal pattern of seasonal variation with spring and winter peaks in a study of 47 281 admissions to all Scottish hospitals in 1962–66 in the diagnostic category ICD 420.1. The spring peak declined with age, while the winter peak became more prominent. Surprisingly, no further large studies of seasonal variation in CHD incidence have been published, but two small studies[2,3] have similarly challenged the conventional belief that all seasonality of CHD follows a winter/summer rhythm. The present investigation extends the sample size of the original Scottish study to 10 years (1962–71), and examines the effects of age and sex in more detail.

Methods

Between 1962 and 1971 inclusive, the Scottish Home and Health Department recorded 123 000 CHD discharges/admissions to all Scottish hospitals, of whom 29 000 died. The General Register Office for Scotland recorded a further 97 000 deaths from CHD outside hospital over this period. Between 1962 and 1967, the ICD 7th Revision (420.1) was used, and thereafter the 8th Revision (410). Deaths and admissions were analysed by gender, age, and month of occurrence (corrected to 31 day months). Month correction causes an annual total greater than the true total (see tables).

The General Register Office for Scotland also provided data on births between 1962 and 1971.

STATISTICAL ANALYSIS

Cosinor analysis[4,5,6]

This was used to determine the significance of seasonal variation in CHD events. This technique forces a sine curve on the data, the peak being six months ahead of the trough. The amplitude of seasonal fluctuation is expressed as a percentage above the mean for the month of highest value (acrophase, zenith, or peak). Cosinor analysis is reliable only if the data fit a single sine curve and may be invalidated by two peaks, as in part of our data. Significance

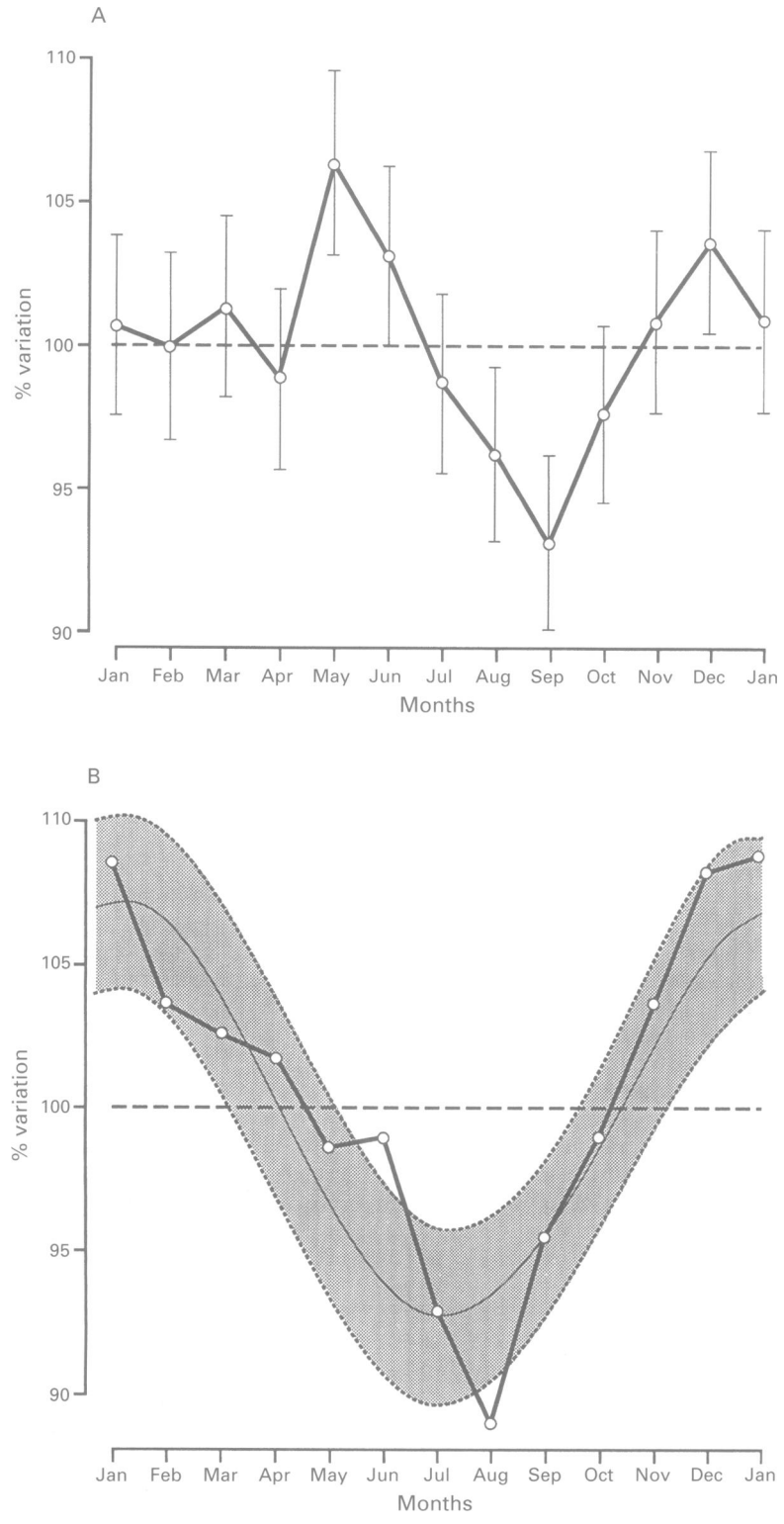

Figure 1 (A) All male admissions with coronary heart disease (CHD). All ages examined by normal approximation to Poisson distribution and 99% confidence intervals are shown. May and December are significantly raised and August and September are significantly lowered. (B) All female admissions with CHD. All ages examined by Cosinor analysis. The sine wave and 95% confidence intervals are shown. R values and the amplitude and level of significance are given in table 2.

refers to the presence or absence of seasonality. Ninety five per cent confidence limits are established.

In cosinor analysis, the year is taken as 360° and the midpoint of each month of the year is assigned an angular value t, for January (15°) through to December (345°). Multiple regression analysis is completed between monthly data and sin (t) and cos (t). This analysis gives the multiple correlation coefficient (r), its statistical significance (p), and the angular position in the year (converted to the nearest month) where the fitted sinusoidal regression line has its highest value. The technique is exemplified in figure 1(B).

Normal approximation to Poisson distribution (NAPD)

This statistical method was applied to the whole data set but was of particular value in the examination of the two peaks in the annual rhythm of non-fatal coronary onsets in patients arriving alive at hospital. In using this, two assumptions are made, firstly, that the population at risk is large compared with the number of hospital coronary admissions and, secondly, that these appear "independently" in time.

The technique is exemplified (fig 1(A)) for 79 746 male hospital admissions. The expected monthly value was calculated allowing for different month-length.

The estimated standard error of a Poisson distribution is the square root of the actual value. Ninety nine per cent confidence intervals are used (see fig 1(A)). Significance refers to the 1% level.

Results

"Hospital admissions" refer to patients who arrived alive at the hospital, whether they subsequently died or survived. "Deaths" refers to total deaths, including those at home plus those in hospital. "Coronary incidence" refers to all coronary deaths plus all coronary admissions discharged alive examined as one group.

MALE HOSPITAL ADMISSIONS (FIGS 1(A), 2, AND 4, TABLES 1 AND 2)

Total male CHD hospital admissions show a spring peak with a late summer/early autumn trough and an early winter peak. Using NAPD, the numbers for May and December are significantly higher, and those for August and September significantly lower, than the annual average (see figs 1(A) and 4). The spring peak is dominant in males under 45 years; this is significant on cosinor analysis. The bimodal pattern of spring and winter peaks is evident in older decades, with the spring peak waning and the winter peak waxing with age. This bimodal pattern of seasonal variation invalidates cosinor analysis except for the youngest age group <45 years. The amplitude of the spring peak exceeds that of the winter peak in all but the oldest age group (>75 years). In patients aged between 55–74 (60% of the total series) May, but not December, is significantly higher on NAPD (see fig 4).

FEMALE HOSPITAL ADMISSIONS (FIGS 1(B), 2, 3, AND 4, TABLES 1 AND 2)

Total female CHD hospital admissions show a winter peak and a summer trough, demonstrated by cosinor analysis (fig 1(B)) and

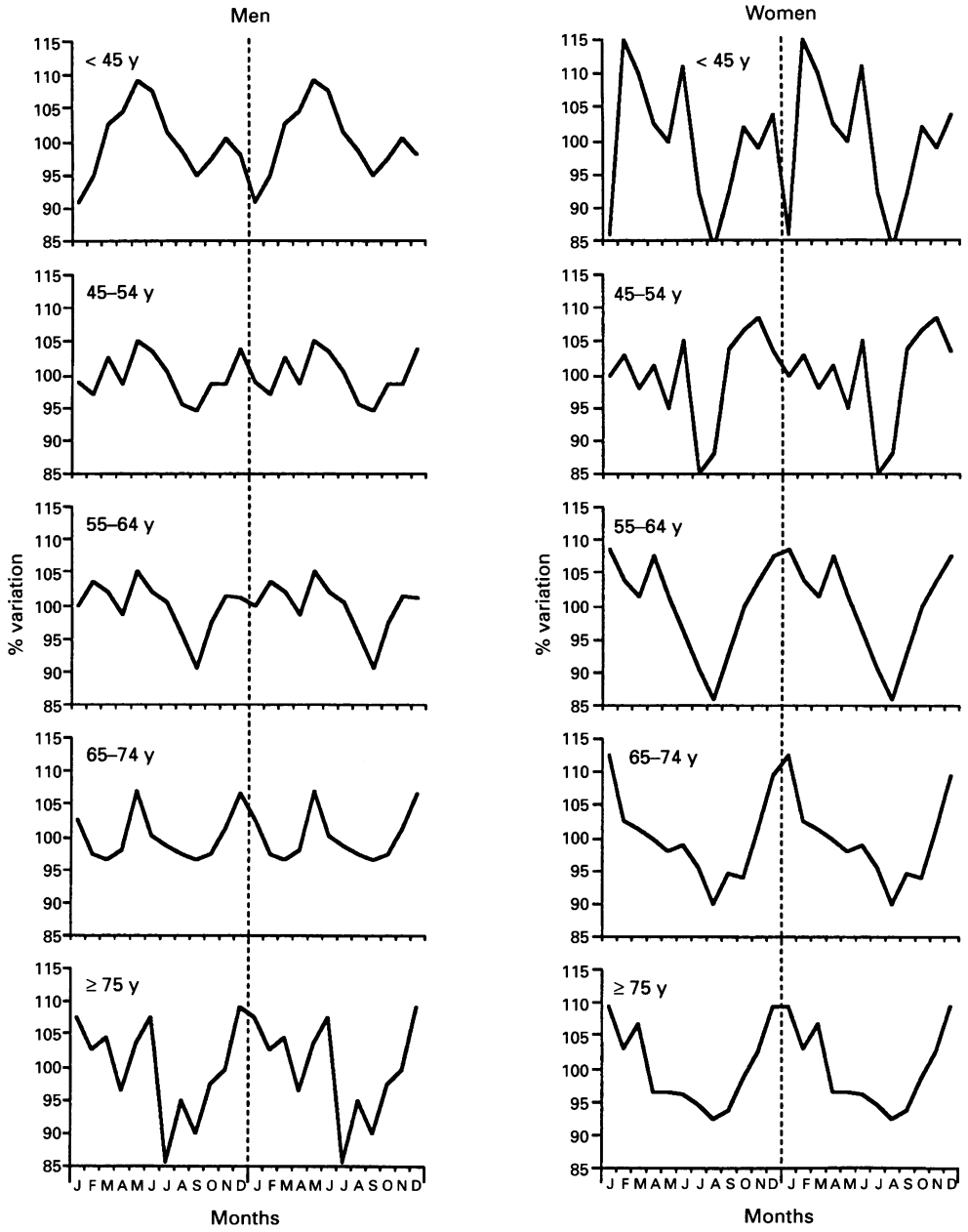

Figure 2 Patients admitted to hospital with coronary heart disease and who were discharged (alive or dead) from hospital (1962–71) in relation to sex, and age group. The vertical axis is scaled to percentages above and below the mean monthly value (100%). The horizontal axis gives the time by month. The second half of each diagram repeats the first half to illustrate the pattern of seasonal variation more clearly.

confirmed by NAPD (fig 4). Using the latter, December and January are significantly higher than the annual average at the 99% confidence interval and July, August, and September are significantly lower. The numbers in the two youngest age groups do not allow the expression of a clear pattern of seasonal variation. The three oldest age groups showed a dominant and significant pattern of winter peaks in admissions (NAPD fig 4).

MALE DEATHS (FIGS 3 AND 4, TABLES 1 AND 2)

Overall, the rhythm is winter/summer, with the three older age groups having a peak in January. The peak is in February for the 45–54 years age group, and in March for the under 45 group. In all age groups the rise in deaths in the autumn is precipitous. In the oldest age group the rises and falls to and from the winter peak are almost symmetrical. The younger the age group the slower the fall from the peak, because of a spring "shoulder". The older the age group, the greater the winter excess.

Of the 79 000 male admissions, 17 000 died in hospital. The latter deaths had a single, February peak, with an otherwise similar pattern of seasonal variation to that of male deaths as a whole. The amplitude of the seasonal variation, however, was smaller (8·7%) inside hospital than outside (12%). The proportions in each age group that died inside and outside hospital were almost identical. The amplitude difference is not related to any age difference.

FEMALE DEATHS (FIGS 3 AND 4, TABLES 1 AND 2)

A significant pattern of winter/summer variation in deaths is evident in the four oldest age

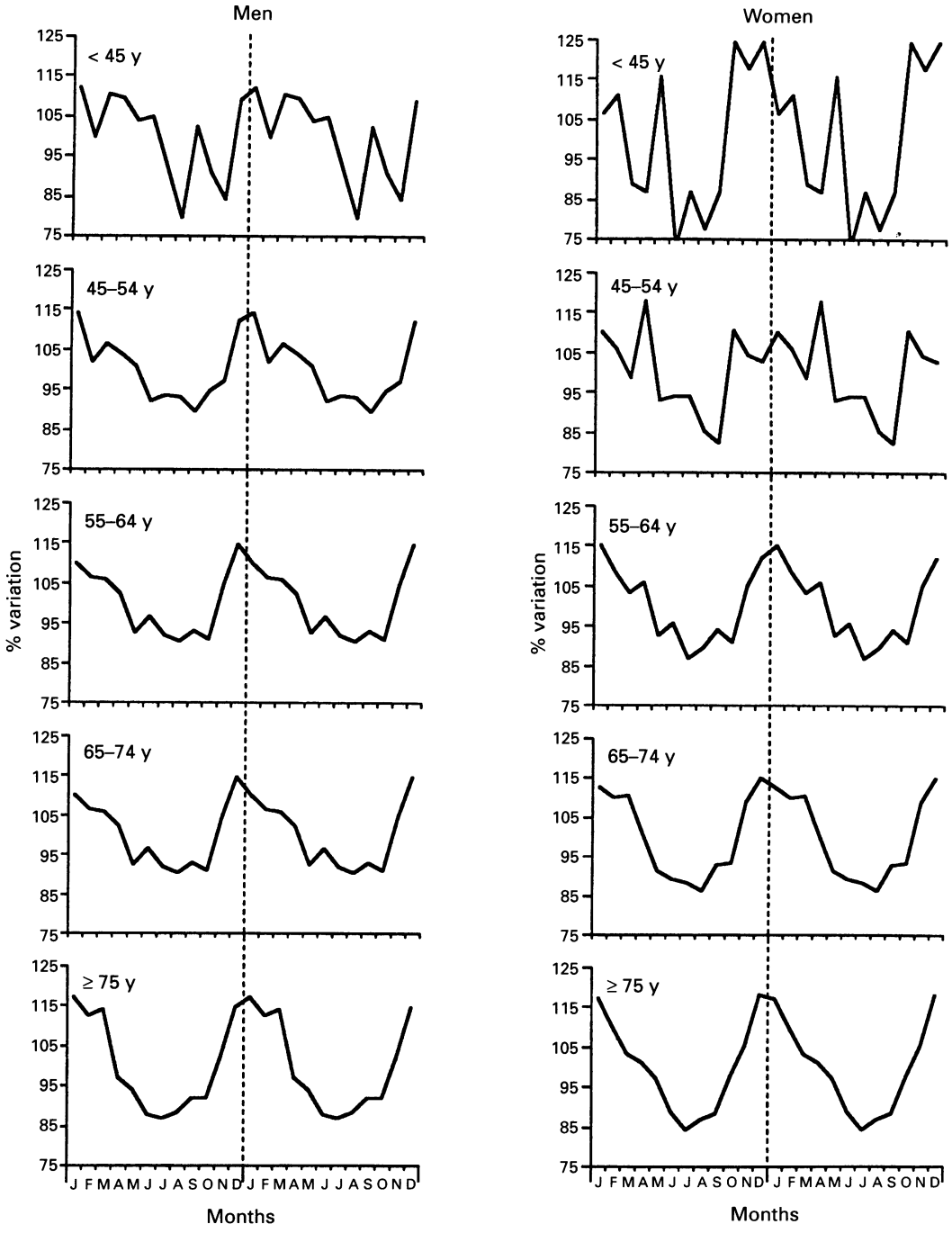

Figure 3 Deaths (1962–71) from coronary heart disease (in hospital or outwith) in relation to sex and age group. The vertical axis is scaled to percentages above and below the mean monthly value (100%). The horizontal axis gives the value by month. The second half of each diagram repeats the first half to illustrate the pattern of seasonal variation more clearly.

groups. No clear pattern of seasonal variation is evident in the youngest age group, because of the small sample size. As with males, the seasonal excess increases with age.

The amplitude of the winter/summer seasonal variation in female deaths is substantially greater than that for female hospital admissions, as is that for male deaths.

CORONARY INCIDENCE: MEN AND WOMEN (TABLE 3, FIGS 4 AND 5)

Total coronary incidence shows on cosinor analysis in men that the spring peak is present in the <45 years age group and in the group age <55 years (table 3). The addition of the deaths to admissions has given statistical significance on cosinor analysis in men under 55 years. Also, in males under 55 years on the NAPD (1% level) both May and December peaks are significant (table 3, figs 4 and 5). The May peak seen in hospital admissions of men 55–75 + was "drowned out" by the increasing deaths in these age groups when examined as coronary incidence, leaving only the winter peak (fig 5).

The number of women under the age of 55 years is relatively small and no significant peaks are found. A non-significant trend is to a winter peak style. Other female groupings show a winter peak (fig 4).

Table 1 Deaths (outside and inside hospital) and hospital admissions (survived or died) due to myocardial infarction in Scotland 1962–71 in relation to gender, age group, and month of occurrence

Month	*Deaths in age groups*					*Admissions in age groups*					*Total*	
	<45	*45–54*	*55–64*	*65–74*	*75+*	*<45*	*45–54*	*55–64*	*65–74*	*75+*	*Deaths*	*Admissions*
Men (%)	(9)	(22)	(37)	(23)	(10)	(3)	(12)	(29)	(33)	(22)		
Aug	188	746	1714	1985	1345	586	1418	2367	1525	608	5978	6504
Sep	242	718	1765	2016	1399	566	1403	2242	1506	577	6140	6294
Oct	215	758	1723	1977	1400	580	1461	2415	1519	627	6073	6602
Nov	199	781	1981	2242	1554	600	1466	2531	1589	640	6757	6826
Dec	257	900	2173	2404	1740	584	1540	2519	1668	699	7474	7010
Jan	265	916	2085	2470	1786	544	1467	2496	1610	697	7522	6814
Feb	235	816	2015	2314	1712	566	1439	2570	1524	660	7092	6759
Mar	261	855	2013	2217	1738	613	1520	2538	1514	671	7084	6856
Apr	258	833	1944	2162	1477	624	1460	2455	1531	616	6674	6685
May	245	810	1754	1973	1434	651	1560	2643	1679	665	6216	7198
Jun	247	738	1838	2024	1338	641	1535	2539	1571	690	6185	6976
Jul	218	749	1749	1836	1321	606	1497	2492	1535	546	5873	6676
Significance	*	**	**	***	***	*	NS	NS	NS	NS	***	NS
Women (%)	(1)	(5)	(17)	(35)	(42)	(3)	(11)	(29)	(35)	(22)	Total	
Aug	35	165	634	1236	1514	97	365	927	1144	761	3584	3294
Sep	39	159	668	1336	1546	107	434	1004	1218	770	3748	3533
Oct	56	214	646	1338	1713	118	442	1081	1216	810	3967	3667
Nov	53	202	745	1563	1840	115	451	1121	1310	844	4403	3841
Dec	56	199	797	1654	2073	121	430	1161	1402	900	4779	4014
Jan	48	213	820	1617	2052	100	416	1168	1451	900	4750	4035
Feb	50	205	772	1576	1925	134	429	1124	1320	847	4528	3854
Mar	40	191	734	1584	1811	128	407	1095	1308	875	4360	3813
Apr	39	228	753	1448	1768	119	422	1158	1285	792	4236	3776
May	52	180	657	1316	1700	116	395	1092	1260	795	3905	3658
Jun	33	182	680	1281	1558	129	442	1035	1274	793	3734	3673
Jul	39	182	617	1268	1478	107	353	976	1226	779	3584	3441
Significance	NS	*	***	***	***	NS	NS	***	**	**	***	***

Cosinor analysis using 12 monthly variables.
NS = not significant *p<0·05, **p<0·01, ***p<0·001.
The three highest monthly totals for each combination of gender, age group, and outcome are underlined.
The data have been month corrected.

Table 2 Cosinor analysis

	Men					*Women*				
	r	*p*	*Amplitude*	*Mean*	*Peak*	*r*	*p*	*Amplitude*	*Mean*	*Peak*
Deaths										
All	0·93	<0·001	11·1	6589	Jan	0·97	<0·001	13·7	4131	Jan
Age group:										
<45	0·7	<0·05	10·0	235	Mar	0·68	NS	17·7	45	Dec
45–54	0·86	<0·01	9·2	801	Feb	0·74	<0·05	10·4	193	Jan
55–64	0·88	<0·01	9·8	1896	Jan	0·93	<0·001	11·9	710	Jan
65–74	0·92	<0·001	11·4	2135	Jan	0·95	<0·001	13·8	1434	Jan
>75	0·92	<0·001	14·4	1520	Jan	0·95	<0·001	14·8	1748	Jan
<55	0·86	<0·01	9·1	1037	Feb	0·77	<0·05	11·2	238	Jan
>55	0·93	<0·001	11·6	5551	Jan	0·97	<0·001	13·9	3893	Jan
Admissions										
All	0·56	NS	2·7	6766	May, Dec	0·9	<0·001	7·1	3716	Jan
Age group:										
<45	0·75	<0·05*	5·7	596	May, Nov	0·54	NS	7	115	Mar
45–54	0·49	NS	2·3	1480	May, Dec	0·56	NS	5·7	415	Dec
55–64	0·66	NS	3·7	2483	May, Nov	0·91	<0·001	8·6	1078	Jan
65–74	0·23	NS	1·1	1564	May, Dec	0·82	<0·01	7·1	1284	Jan
>75	0·63	NS	6·2	641	May, Dec	0·86	<0·01	7	822	Jan
<55	0·61	NS	3·1	2077	May, Dec	0·5	NS	4·8	531	June, Nov
>55	0·58	NS	3·0	4689	May, Dec	0·91	<0·001	7·5	3185	Jan

* Two peaks but the earlier is much the larger and its cosinor analysis is significant.

Table 3 Coronary incidence in relation to month, sex, and age group

	Men					*Women*					*Total*		*Age <55 y*		*Age >55 y*	
	<45 y	*45–54 y*	*55–64 y*	*65–74 y*	*75+ y*	*<45 y*	*45–54 y*	*55–64 y*	*65–75 y*	*74 y*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
Month:																
August	734	2017	3640	3051	1672	127	487	1400	2044	1956	11 114	6014	2751	614	8363	5400
September	765	1977	3598	3113	1697	138	541	1494	2166	2002	11 150	6341	2742	679	8408	5662
October	751	2062	3731	3052	1758	162	595	1534	2185	2144	11 354	6620	2813	757	8541	5863
November	756	2052	4050	3341	1879	158	604	1653	2429	2295	12 078	7139	2808	762	9270	6377
December	791	2259	4215	3566	2099	166	587	1729	2630	2533	12 930	7643	3050	753	9880	6892
January	760	2194	4053	3540	2142	142	575	1741	2600	2520	12 689	7578	2954	717	9735	6861
February	752	2090	4095	3329	2049	167	578	1668	2481	2362	12 315	7256	2842	745	9473	6511
March	836	2176	4081	3263	2063	164	550	1610	2460	2251	12 419	7035	3012	714	9407	6321
April	837	2113	3961	3212	1802	151	598	1658	2352	2201	11 925	6960	2950	749	8975	6211
May	860	2195	3942	3178	1811	153	538	1567	2218	2104	11 986	6580	3055	691	8931	5889
June	836	2101	3938	3112	1707	159	576	1513	2181	2018	11 676	6447	2938	735	8738	5712
July	785	2068	3803	2917	1606	138	496	1416	2121	1942	11 179	6113	2853	634	8326	5479
Cosinor analysis:																
r	0·79	0·68	0·83	0·87	0·92	0·59	0·7	0·95	0·94	0·95	0·89	0·96	0·71	0·69	0·91	0·95
p	<0·05	NS	<0·01	<0·01	<0·001	NS	NS	<0·001	<0·001	<0·001	<0·001	<0·001	<0·05	NS	<0·001	<0·001
Amplitude (%)	6	3·5	5·3	7·1	12·2	6·6	6·5	9	10·6	11·9	6·1	10·2	3·6	6·4	7·3	10·6
Mean	788	2108	3925	3222	1857	152	560	1581	2322	2194	11 901	6810	2897	712	9003	6098
Acrophase	Apr/May	Feb/Mar	Jan/Feb	Jan	Jan	Jab/Feb	Jan	Jan	Jan	Jan	Jan	Jan	Mar/Apr	Jan	Jan	Jan

The three highest month totals for each combination of gender and age group are underlined.

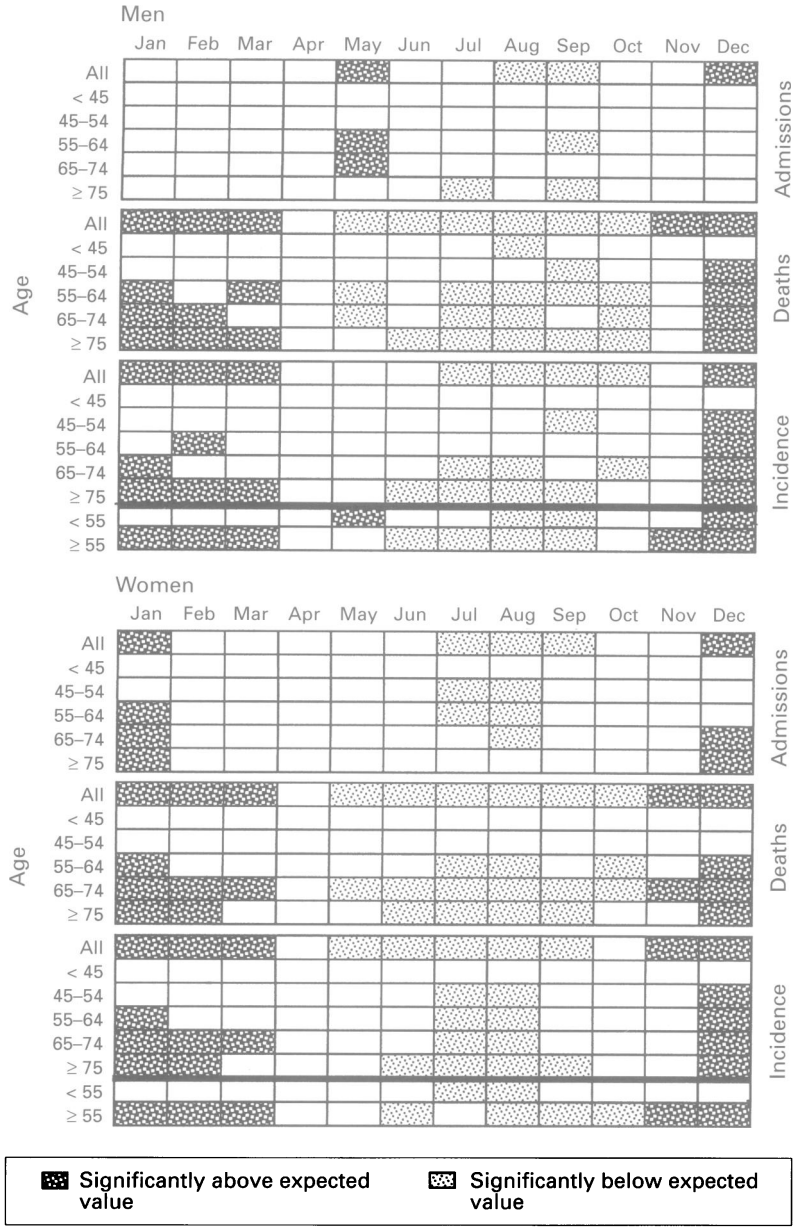

Figure 4 Incidence, deaths, and hospital admissions for coronary heart disease in relation to age and sex in Scotland (1962–71). The dark areas are months which are significantly higher than the mean and the lightly stippled areas are significantly lower than the mean. Where there is no entry these points were not significantly different from the mean. The level of significance is $p<0{\cdot}01$.

COMPARISON WITH CONCEPTIONS (FIG 6)

The General Register Office for Scotland also provided data for births between 1962 and 1971. Dates of conceptions are assumed from the dates of birth. Seasonal variation in conception has its main peak one month after the spring peak for CHD in men under 45 years (see fig 6). There is a further secondary one month peak for conceptions in January, but the small November secondary peak in CHD male admissions is non-significant.

Discussion

The original study[1] covered 1962–66; we have added to it corresponding data for 1967–71. This has made possible clarification of the earlier results, with emphasis on hospital admissions. In recent times there has been an interest in the circadian rhythm of CHD events[7 8] but no reports of seasonality of CHD focussing on non-fatal onsets. We recognise the limitations of death certification, hospital discharge documentation, and record linkage. In the earlier survey, the records of 1000 admissions under rubric ICD 420.1 showed that 87% were due to acute myocardial infarction or acute ischaemia. The term admissions has been used loosely; these are recorded as hospital discharges – that is, those who were admitted and then died or were discharged.

The familiar association between low environmental temperature and CHD mortality has been discussed in detail previously.[9 10] Our evidence suggests that this may result from the fall in temperature in autumn and early winter, rather than the absolute low temperature reached in later winter.[6] Other meteorological and environmental influences may also be involved. The effector mechanism, however, is unclear. In addition to changes in cholesterol[10] and blood pressure[11 12] there are winter increases in haematocrit,[13 14] white cell count,[15] and fibrinogen concentration,[16 17] all of which raise blood viscosity; while fibrinolysis is most active in the summer.[18] Factor VII clotting activity, C-reactive protein, and α antitrypsin values are also raised in winter.[16]

The age related spring increase in CHD non-fatal onsets is a predominantly male phenomenon. The dominant pattern of spring/autumn variation in the youngest male age group is replaced in older male age groups by a bimodal pattern in which a gradually declining spring peak exceeds the winter peak until old age (>75 years). In contrast, women aged 55 and over show a dominant pattern of winter/summer variation in CHD non-fatal onsets. The numbers in the younger female age groups are small, and a firm conclusion must await an even larger series. Seasonal variation in deaths shows a dominant winter/summer pattern in both sexes, with subsidiary spring "shoulders" on the winter peak in the two youngest male age groups. The results of examination of coronary incidence in men under 55 years of age strengthen these conclusions. The cause of the age related spring peak in non-fatal onsets is uncertain, but a risk factor which is dominant in younger men, reduces with age, and is inconspicuous in women suggests an androgenically driven effector mechanism. There is a similarity between seasonal variation of conceptions and non-fatal coronary onsets in young men. Moreover, seasonal variation in beard growth,[19] rape and attempted rape (A S Douglas, personal communication,[20–21]) spermatogenesis,[22–24] and levels of oestradiol[25] and luteinizing hormone[26] all show spring–summer peaks.

The effector mechanism through which a putative spring increase in androgenic activity might operate is also speculative. Two studies of seasonal variation in serum cholesterol in Scotland[27] and Israel[28] found the highest values in the spring, but a larger study of two-monthly seasonal variation in the United States showed a high winter, low summer pattern,[10] as have most other studies.[29] Seasonal variation in blood pressure in most reports shows a dom-

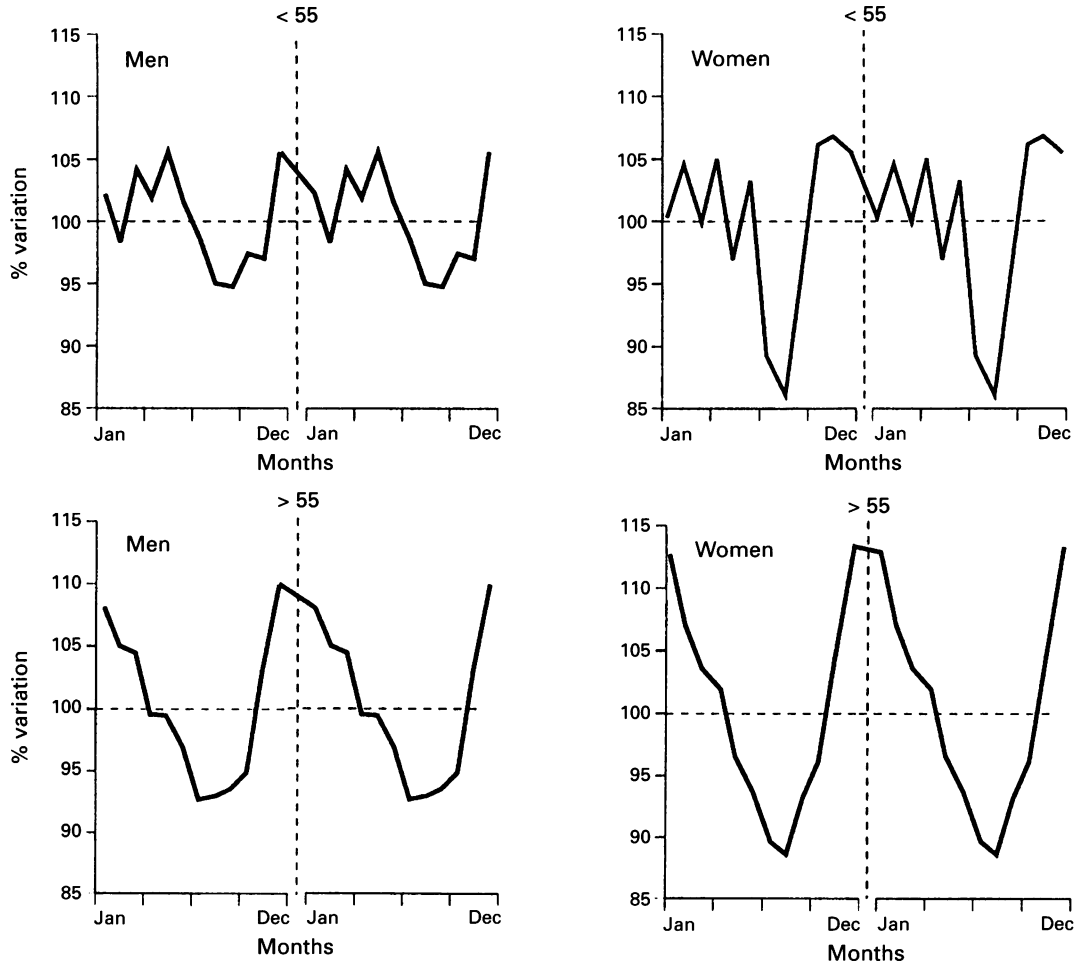

Figure 5 Incidence of coronary heart disease in Scotland (1962–71) for men and women under 55 years and 55 years or above. Incidence means coronary death and non-fatal myocardial infarction. The vertical axis is scaled to percentages above and below the mean monthly value (100%). The horizontal axis gives the value by month. The second half of each diagram repeats the first half to illustrate the pattern of seasonal variation.

inant high winter, low summer pattern[11 12] with a few showing a spring peak, for example,[30]; Eastham and Avis[31] found adhesive platelet counts to be highest and non-adhesive counts lowest in the spring. Lacoste and Wirz-Justice[11] found a spring/autumn pattern of platelet serotonin uptake strikingly similar to the spring/autumn pattern of CHD variation in the youngest group of Scottish men in the present study. Unfortunately, however, none of the foregoing studies were grouped according to age and sex. The seasonality of several parameters has been discussed, quoting only a small number of the available published papers. This paper is not a review: a recent bibliography[29] provides a fuller reference source.

It is possible that the male, age related spring rise in CHD prevalence results from the emotional and physical effects of increased sexual activity in spring in men with pre-existing cardiovascular disease. It may also be relevant that the incidence of suicide peaks in May, and that its amplitude is greater in men than in women (A S Douglas personal communication).

Confirmatory studies of the pattern of seasonal variation in CHD non-fatal onsets shown in the present study are desirable, utilising comparably large data sets. Further elucidation of the mechanism of the spring rise in CHD incidence in men would require larger studies of seasonal variation in major cardiovascular risk factors and reproductive hormones divided by age and sex.

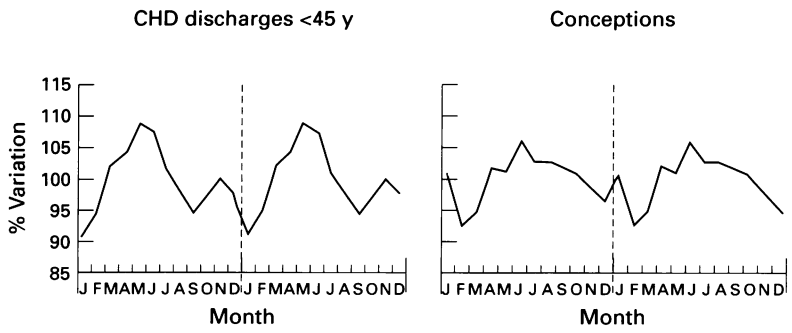

Figure 6 Discharge from hospital after an episode of coronary heart disease in men <45 years and conceptions in Scotland 1962–71. The vertical axis is scaled to percentages above and below the mean monthly value (100%). The horizontal axis gives the value by month. The second half of each diagram repeats the first half to illustrate the pattern of seasonal variation more clearly.

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