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Are Full Term Pregnancies and Induced Abortions Separate Risk Factors in Female Auto-immune Diseases?

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ABSTRACT International comparisons are made for selected European countries of hospital treatments of auto-immune disease with trends in live births and induced abortions. The hypotheses to be examined are the influence of higher fertility rates and higher abortion rates as risk factors increasing the incidence of these diseases among women using data from seven European countries in respect of which some hospital data is available. It is found that the ratios of female to male incidence for these diseases are lower in countries with low abortion and high fertility rates.

INTRODUCTION: IMMUNE DISEASE EPIDEMIOLOGY

Patterns of Incidence and Sex Differences Known for Immune Diseases

Whereas each disease can be investigated individually, data may be sparse and there are advantages in treating these diseases together in a single study. "During the 1990s it was realised that similar immune mechanisms were operative in more than one immune disease. For example, activation of the CD4 type 1 helper T(T111) cells was shown to be important in the pathogenesis of RA(Rheumatoid Arthritis, MS(Multiple Sclerosis) and IDDM(Insulin Dependent Diabetes Mellitus), although the antigenic specificities of the cells in the various diseases are quite different" (Whitacre 2001).

American estimates of the frequency of incidence of the diseases reported over 80% of the patient population for Hashimoto's and Graves' thyroiditis was female and the sex distribution was 60-75% women for RA (Rheumatoid Arthritis) and MA (Multiple Sclerosis) (Whitacre 2001).

Pregnancy and hormonal treatments are thought to be relevant to the incidence of these diseases among women. For a better understanding of these diseases among females "It will be important to focus on the interplay of hormone systems, that is, sex steroids and stress steroids (CRH and cortisol), because both profoundly change during pregnancy and parturition and can affect the immune response" (Whitacre 2001).

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Incidence and Sex Differences for Particular Immune Diseases

Thyroiditis: It is often undiagnosed. When it is diagnosed it is usually treated at primary care level by general practitioners. Incidence tends not be reported nationally and precise data is usually not available. It is known to be a common disease and much more common among women than men and it is said that 1 woman in 8 in the USA is affected.

RA (Rheumatoid Arthritis) A Local Study in Minnesota Reported in 2010: "We observed a modest increase of RA incidence in women during the study period, which followed a sharp decline in incidence during the previous 4 decades," said Dr. Gabriel. Results show that RA incidence in women increased by 2.5% per year from 1995 to 2007, while a decrease of 0.5% was noted for men (Myasoedova 2010).

MS (Multiple Sclerosis): An international study reported: The female-to-male MS ratio of Multiple Sclerosis has increased in the last five decades (Hernan AA 2008).

Possible Mechanism for Immune Disease Post Pregnancy

Most immune diseases are more common among women than among men. In addition to

genetic and hormonal influences, foetal progenitor T-cells passing from the foetus to the mother during pregnancy might be responsible for the increased incidence of auto-immune diseases among women.

In pregnancies carried to full term, more transfer of cells between a larger foetus and the mother is likely. "Foetal microchimerism is the transfer of intact living foetal cells into the maternal circulation and occurs in all pregnancies and increases with gestational age. Microchimerism can be portrayed as a legacy of pregnancy that persists for decades via foetal cell engraftment in maternal bone marrow or other tissues" (Miech 2010). "Foetal microchimerism has been demonstrated in Hashimoto's thyroiditis and Graves's Disease but found to be absent in normal thyroids" (Miech 2010). The hypothesis, that microchimerism might be the underlying basis for the higher prevalence of autoimmune disease in women "is supported by the similarities of chronic graft versus host disease (GVHD) to some autoimmune conditions, the prevalence of these diseases among women, their increased incidence after reproductive years, and the fact that GVHD increases with HLA (Human Leukocyte Antigens) incompatibility of the donor" (Khashan et al. 2011).

Particular risks of auto-immune diseases may be incurred through induced abortions. "There is an increased foetal-to-maternal transfer of foetal undifferentiated progenitor cells during an abortion procedure as the placenta is being destroyed" (Miech 2010). "Fetomaternal haemorrhage as a result of first trimester termination of pregnancy has been shown to cause an 80-fold increase in the number of fetal cells in maternal blood. Fetomaternal haemorrhage is also likely to be greater …and more microchimerism should be established after caesarean section delivery" (Khashan 2011). This study (Khashan 2011), which used Danish register data, found "Our results confirm an increase in AID in the first year after CS. The unexpected finding of a reduction in AID risk after abortion may be explained by...a higher number of fetal stem or progenitor cells to enter maternal blood,...more likely to engraft maternal cells long-term, and be beneficial…" The Danish data was derived from hospital records. Whereas CS is associated with more testing in hospitals before and after delivery while women having induced abortions are conversely less likely to be tested in hospitals for AID and AID among these women may go unreported on the Danish Registers.

METHODOLOGY

In recent years comparisons were made of female/male ratios for patients treated for autoimmune diseases in selected European countries with (1) diet (2) birth rates and (3) abortion rates.

Response Variable: Hospital Treatments of Diseases of Immune System

Five diseases of the immune system were considered: Hashimoto's thyroiditis, Graves's Disease, Rheumatoid Arthritis, Multiple Sclerosis and Systemic Sclerosis. As a measurement of incidence, hospital data was used from seven European countries: Sweden, England, Finland, Scotland, the Irish Republic, Northern Ireland and the Czech Republic (thyroiditis only).

National Data of Hospital treatments may be counts of patients treated in a year, either a calendar year or a financial year, or of counts of hospital discharges of patients in a year.

In any particular country, such hospital data reflects incidence, diagnosis and referral practice in cases of these diseases. The data numbers of patient episodes can include several counts for the same patient who is discharged and re-admitted or even transferred to another consultant within the year.

Since men are unaffected by risk factors due to pregnancy and abortion, the ratio of female to male incidence of an auto-immune disease is an indication of how such risk factors contribute to the increased incidence of auto-immune diseases among females.

DIET: INTERNATIONAL TRENDS

Trends in Live Births and Induced Abortions in Recent Decades

For all European countries there is a published on national and international web sites a TFR (Total Fertility Rate, the sum of all age specific fertility rates each year) for each calendar year and these are graphed in Figure 1 to show the trend in the past 40 years.

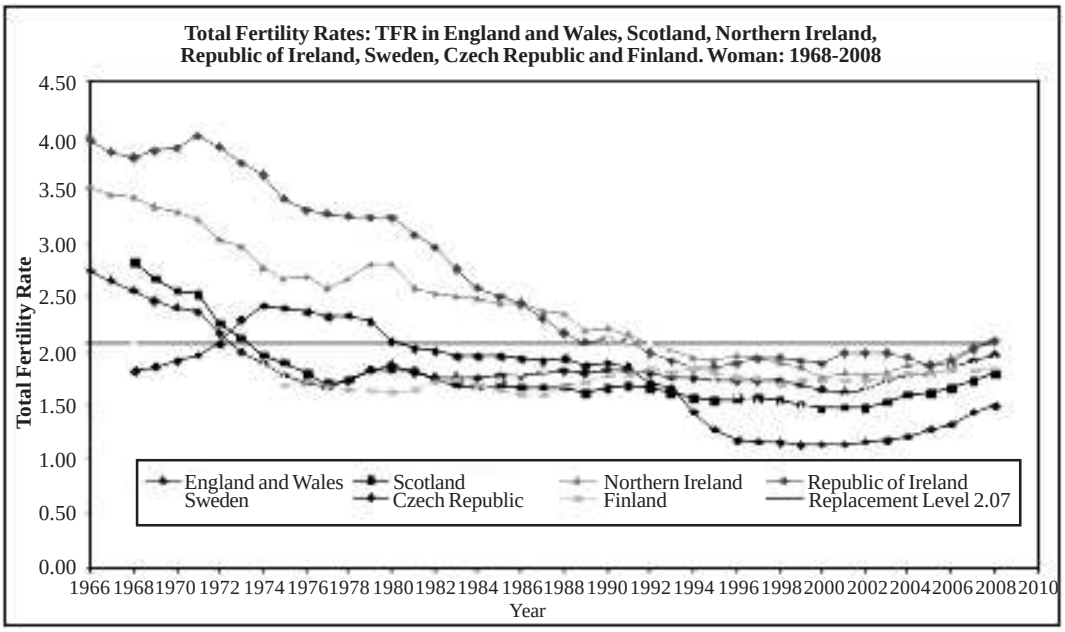

Fig. 1. Total Fertility Rates for seven countries

In these selected European countries, with the exception of Ireland, there is believed to be a full count of legally induced abortions by age of women in officially reported abortion statistics on the national health statistics web sites, from which can be derived a TAR (Total Abortion Rate, the sum of all age specific abortion rates each year) by using official population estimates of the female population at each age as denominator. These TARs derived by the author

Fig. 2. Total Abortion Rates for seven countries

Table 1: Fertility and abortion rates for selected European countries

European countries	*Total Fertility Rate TFR*			*Total Abortion Rate TAR*		
	2000	*2008*	*2007*	*2000*	*2008*	*2007*
Sweden	1.54	1.91	1.88	0.58	0.67	0.66
England and Wales	1.65	1.97	1.91	0.51	0.54	0.55
Czech Republic	1.14	1.50	1.44	0.44	0.34	0.34
Finland	1.73	1.85	1.83	0.33	0.32	0.33
Scotland	1.48	1.80	1.73	0.35	0.40	0.40
Irish Republic	1.89	2.10	2.03	0.21	0.14	0.15
Northern Ireland	1.75	2.11	2.02	0.13	0.09	0.10

have the same dimensionality as the officially produced TFRs with which they are compared. The TARs are graphed in Figure 2 to show the trend since liberalisation of the laws in Europe in the 1960s and 1970s.

For both Irish jurisdictions, older more restrictive abortion laws are in force. Estimates of Irish TARs are derived from numbers of Irish resident women reported in Abortion Statistics (Abortion Statistics) for England and Wales and in the case of the Republic some allowance is also made for abortions reported in the Netherlands of abortions on Irish resident women (Crisis Pregnancy Agency Annual Report). Irish abortion rates are lower than other countries considered as shown in Figure 2.

Live Births and Abortions in Recent Years

Table 1 shows these TFRs and TARs for 2000, 2007 and 2008. The countries can be grouped into

Sweden, England - higher birth rate, highest abortion rate

Scotland, Finland, Czech Republic – intermediate or lower birth rate, intermediate abortion rate

Republic of Ireland, Northern Ireland - highest birth rate, lowest abortion rate

International Comparisons

Thyroiditis

Most cases of thyroiditis are treated at primary care level by General Practitioners with hospital treatment sought for more serious cases. Tables 2 and 3 show respectively the incidence numbers and the incidence rates derived from hospital data for Graves Disease. Tables 4 shows the numbers for Hashimoto's disease, which indicates the data is rather too sparse to derive rates to make useful international comparisons for seven countries.

The ratio of female to male incidence is lower in both Irish jurisdictions which supports the hypothesis that induced abortions are especially conducive to this disease as Irish abortion rates are low. Irish birth rates are comparatively high so that full term pregnancies cannot be considered as a contributing factor in the low female/male ratio of incidence of Irish thyroiditis.

The low rates for both sexes in Scotland suggests that Scottish doctors rarely refer such cases to hospitals. More puzzling is the high female to male ratio in Scottish and Finnish incidence of thyroiditis. Both the birth rate and the abortion rates have in these countries been lower than in England. Is it possible that the poor diet

Table 2: Numbers of patients and discharges
Graves' disease ICD-10 E05
Toxic diffused Goitre

European countries	*2008*			*2007*		
	Male	*Female*	*Female to male ratio*	*Male*	*Female*	*Female to male ratio*
Sweden	172	723	4.2	136	635	4.7
England	482	1640	3.4	385	1413	3.7
Czech Republic	216	766	3.5	227	876	3.9
Finland	65	290	4.5	83	377	4.5
Scotland	28	135	4.8	27	124	4.6
Irish Republic	114	294	2.6	73	242	3.3
Northern Ireland	14	36	2.6	1	24	24.0

**2008 figures are provisional for the Irish Republic*

Table 3: Rates per 100,000 males or females of hospital treatments
Graves' disease ICD-10 E05
Toxic diffused Goitre

European countries	*2008*			*2007*		
	Male	*Female*	*Female to male ratio*	*Male*	*Female*	*Female to male ratio*
Sweden (Hospital discharges)	5.0	20.2	4.1	4.0	17.9	4.5
Sweden (Patients)	3.8	16.1	4.3	3.4	15.1	4.4
England	1.9	6.3	3.3	1.5	5.4	3.5
Czech Republic	5.3	17.8	3.3	5.7	20.5	3.6
Finland (Hospital discharges)	3.3	13.7	4.2	4.2	17.9	4.3
Finland (Patients)	2.4	11.3	4.8	3.2	14.3	4.4
Scotland	1.1	5.1	4.5	1.1	4.7	4.3
Irish Republic	7.1	18.0	2.5	4.6	15.2	3.3
Northern Ireland	2.2	5.4	2.4	0.2	3.6	22.3

**2008 figures are provisional for the Irish Republic*

Table 4: Numbers of patients and discharges
Hashimoto's disease ICD-10 E06.3
Chronic Lymphocytic Thyroidits

European countries	*2008*			*2007*		
	Male	*Female*	*Female to male ratio*	*Male*	*Female*	*Female to male ratio*
Sweden	25	226	9.0	31	226	7.3
England	28	266	9.5	45	293	6.5
Czech Republic	23	188	8.2	16	187	11.7
Finland	9	80	8.9	8	46	5.8
Scotland	0	28	-	0	17	-
Irish Republic	8	50	6.3	8	87	10.9
Northern Ireland	1	12	12.0	0	18	-

**2008 figures are provisional for the Irish Republic*

in Scotland interacts with female hormones to increase the risk for women of this condition?

When four years of data are combined and the numbers compared for Ireland and outside Ireland in Table 5 we find for Graves that the odds ratio (the ratio of the two F/M ratios) 0.91 and the 95% confidence interval for this is (0.8, 1.04). This lower ratio of female to male incidence in Ireland is consistent with the lower abortion rate in Ireland. While Irish women benefit from any reduced risk of Graves' thyroiditis brought by a lower abortion rate, Irish men do not. For Hashimoto's thyroiditis numbers are small and inference is unclear.

Table 5: Numbers of patients discharged 2005-2008 in non-Irish and in Irish jurisdictions. Odds ratios and 95% CIs (Confidence Intervals)
Graves' disease ICD-10 E05
Toxic diffused Goitre

Graves' disease ICD-10 E05	*2005-2008*		*M/F ratio*
	Male	*Female*	
Countries except Ireland	4707	17967	3.8
Ireland (NR+Rep)	325	1132	3.5
Odds ratio	0.91249753		
95% CI	0.80330445	1.03653	

Rheumatoid Arthritis

Hospital patient counts for Rheumatoid Arthritis are shown in Tables 6 and rates in Table 7 for all countries for 2007 and 2008 and for Irish and nonIrish combined for 2005-8 in Table 8. The much higher incidence rate in Northern Ireland compared to the Irish Republic and England and the somewhat high rate in Finland are puzzling and so is the low incidence rate especially for men in Scotland. Perhaps Northern Ireland is especially well provided with hospital specialists in Rheumatology and there are few of such specialists in Scotland? Or does the high fat and sugar diet in Scotland really help men to escape Rheumatoid Arthritis?

When data for the four years is combined in Table 8 we find that the difference in Female to Male ratios is significantly less in Ireland (Ireland's Gain 2011). The odds ratio is 0.82

Table 6: Numbers of patients and discharges
Rheumatoid Arthritis ICD-10 AMM05-M06

European countries	*2008*			*2007*		
	Male	*Female*	*Female to Male Ratio*	*Male*	*Female*	*Female to Male Ratio*
Sweden	6407	18599	2.9	6057	17374	2.9
England	13767	38593	2.8	12583	35358	2.8
Finland	4535	14970	3.3	4504	15066	3.3
Scotland	367	1418	3.9	551	2110	3.8
Irish Republic	1653	3235	2.0	1597	2954	1.8
Northern Ireland	1486	4557	3.1	1403	4007	2.9

**2008 figures are provisional for the Irish Republic*

Table 7: Rates per 100,000 males or females of hospital treatments
Rheumatoid Arthritis ICD-10 AMM05-M06

European countries	*Rates per 100,000*					
	2008			*2007*		
	Male	*Female*	*Female to male ratio*	*Male*	*Female*	*Female to male ratio*
Sweden (Hospital discharges)	115.9	322.6	2.8	110.2	301.1	2.7
Sweden (Patients)	69.1	197.7	2.9	66.4	188.8	2.8
England	54.4	147.6	2.7	50.1	136.1	2.7
Finland (Hospital discharges)	136.2	422.2	3.1	136.6	425.0	3.1
Finland (Patients)	92.1	285.5	3.1	92.0	291.3	3.2
Scotland	14.7	53.1	3.6	22.2	79.4	3.6
Irish Republic	101.6	185.0	1.8	103.7	198.3	1.9
Northern Ireland	238.3	681.1	2.9	228.3	605.0	2.6

**2008 figures are provisional for the Irish Republic*

with 95%C (0.8, 0.84), that does not straddle 1. We can conclude that the difference in the Female to Male ratios between Irish and non Irish populations is significant. Their low abortion rate is a likely cause for Irish women escaping this disease. The disease over this epoch is less common relatively among Irish women who have a higher birth rate and a much lower abortion rate than the non Irish.

Table 8: Numbers of patients discharged 2005-2008 in non-Irish and in Irish jurisdictions. Odds ratios and 95% CIs(Confidence Intervals)
Rheumatoid Arthritis ICD-10 AMM05-M06

	2005-2008		*M/F Ratio*
	Male	*Female*	
Countries except Ireland	81928	239769	2.9
Ireland (NR+Rep)	12334	29514	2.4
Odds ratio	0.8176		
95% CI	0.7995	0.836216	

Multiple Sclerosis and Systemic Sclerosis

Tables 9 and 10 reflect hospital data on Multiple Sclerosis and Table 11 shows the counts of cases of Systemic Sclerosis. Here again the low incidence with high female to male ratio in Scotland is puzzling. Does Scotland lack hospital specialists for this condition?

When the data for 2005-08 is combined we see from Table 12 for Multiple Sclerosis that there is a significantly lower female to male ratio in Ireland. The odds ratio is 0.95 with 95% C.I. (0.92, 0.97), which doe not straddle 1. We can conclude that the difference in the Female to Male ratios between Irish and non Irish populations is significant. Their low abortion rate is a likely cause for Irish women escaping this disease. For Systemic Sclerosis the numbers are smaller and the difference is not so significant.

TIME TREND: ENGLAND

Hospital Data

By reference to older Hospital Enquiry data in England, which was usually a sample drown from some hospitals rather than a survey of all hospitals, it is possible to track the trend since

Table 9: Numbers of patients and discharges
Multiple Sclerosis ICD10 AMG35

European countries	*2008*			*2007*		
	Male	*Female*	*Female to male ratio*	*Male*	*Female*	*Female to male ratio*
Sweden	3108	5949	1.9	2709	5107	1.9
England	6831	13242	1.9	6040	10801	1.8
Finland	1791	3472	1.9	1756	3171	1.8
Scotland	296	778	2.6	314	711	2.3
Irish Republic	1644	3227	2.0	1114	2415	2.2
Northern Ireland	769	1202	1.6	731	1093	1.5

**2008 figures are provisional for the Irish Republic*

Table 10: Rates per 100,000 males or females of hospital treatments
Multiple Sclerosis ICD10 AMG35

European countries	*Rates per 100,000*					
	2008			*2007*		
	Male	*Female*	*Female to male ratio*	*Male*	*Female*	*Female to male ratio*
Sweden (Hospital discharges)	60.2	110.1	1.8	52.7	92.4	1.8
Sweden (Patients)	29.6	56.3	1.9	26.4	51.7	2.0
England	27.0	50.7	1.9	24.0	41.6	1.7
Finland (Hospital discharges)	59.7	105.7	1.8	59.4	94.8	1.6
Finland (Patients)	30.5	58.4	1.9	29.7	56.0	1.9
Scotland	11.8	29.2	2.5	12.6	26.7	2.1
Irish Republic	103.1	197.8	1.9	70.8	151.3	2.1
Northern Ireland	123.3	179.6	1.5	119.0	165.0	1.4

**2008 figures are provisional for the Irish Republic*

Table 11: Numbers of patients and discharges

European countries	*2008*			*2007*		
	Male	*Female*	*Female to male ratio*	*Male*	*Female*	*Female to male ratio*
Sweden	270	950	4.6	232	947	4.1
England	38	106	2.8	65	182	2.8
Finland	60	236	3.9	31	256	8.3
Scotland	10	128	12.8	7	145	20.7
Irish Republic	183	203	1.1	127	172	1.4
Northern Ireland	14	306	21.9	26	270	10.4

**2008 figures are provisional for the Irish Republic*

Table 12: Numbers of patients discharged 2005-2008 in non-Irish and in Irish jurisdictions. Odds ratios and 95% CIs(Confidence Intervals)
Multiple Sclerosis ICD10 AMG35

Multiple Sclerosis ICD10 AMG35	*2005-2008*		
	Male	*Female*	*M/F ratio*
Countries except Ireland	37327	71788	1.9
Ireland (NR+Rep)	7360	13377	1.8
Odds ratio	0.945		
95% CI	0.9161	0.974871	

the 1950s of patients treated in hospitals for these conditions.

Thyroiditis

Figure 3 shows that the female to male incidence ratios for thyroiditis declined from 6:1 to 4:1 from 1955 to 1999. Over this epoch the abortion rate in England has increased perhaps ten fold [see Figure 1] (estimates vary as to the n umber of illegal abortions taking place in the 1950s) and the birth rate has declined (see Fig. 2) considerably.

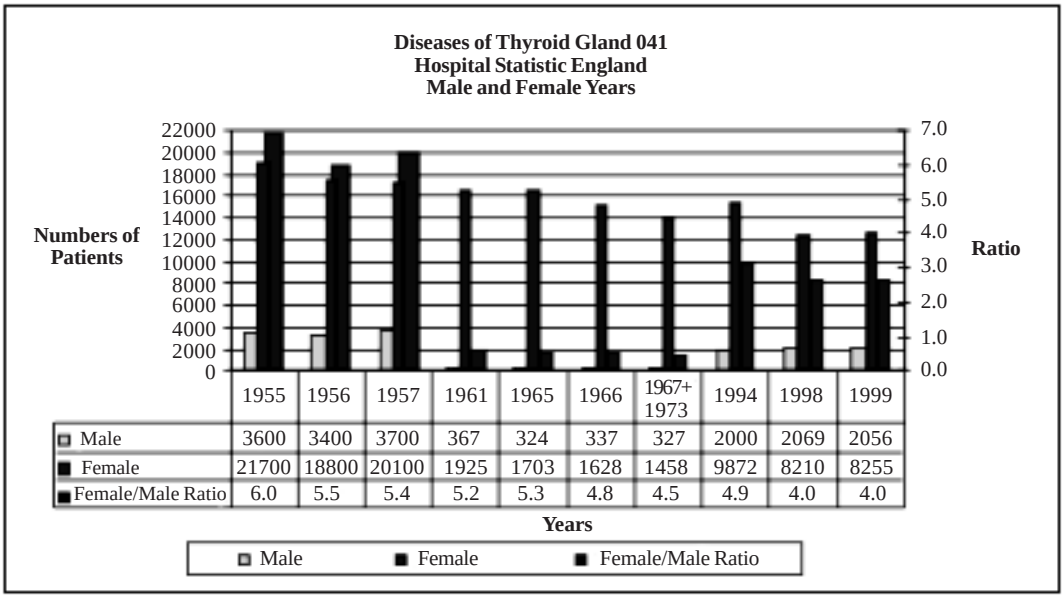

Fig. 3. Thyroiditis in England since 1955

This trend that is shown in Figure 3 of a decline in the female to male ratio from 6:1 to 4:1 continues as Table 2 shows a further decline in the ratio for Graves' disease to 3.7:1 in 2007 and 3.4:1 in 2008. If referral practice for thyroiditis has been unchanged for men and women this observed trend is consistent with full term pregnancies increase the risk of this disease among women, as in the post World War II epoch of a high birth rate in the 1950s and early 1960s. In modern conditions most cases of thyroiditis are treated by GPs in Primary Care so that the apparent decline in incidence shown in the graph of Figure 3 since the 1950s reflects only cases treated in hospitals and is not indicative of national incidence.

Rheumatoid Arthritis

Figure 4 shows that the female to male ratios for Rheumatoid Arthritis has increased from 1.9:1 to 2.6:1, since the 1950s. Table 8 shows a further increase in this ratio for England to 2.8:1 for 2007 and 2008. This 40% increase suggests that induced abortion could be a significant risk factor for this disease.

Multiple Sclerosis

Figure 5 shows that for Multiple Sclerosis the increase in the female to male ratio is from 1.2:1 to 2:1. Table 11 shows a ratio of 1.8:1 for 2007 and 1.9:1 for 2008, little changed in the most recent years. The English time trend for these diseases is also consistent with more women being affected by abortion so as to exhibit a higher incidence of Multiple Sclerosis.

CONCLUSION

These international comparisons between Irish and non-Irish countries show a lower female to male ratio in Ireland for these diseases over the 4 year epoch. When Irish birth rates are higher and Irish abortion rates much lower, this suggests that abortions rather than full term pregnancies are indicated as a factor conducive to these diseases among women. The time trend in English hospital data since the 1950s is also supportive for this hypothesis.

ACKNOWLEDGEMENTS

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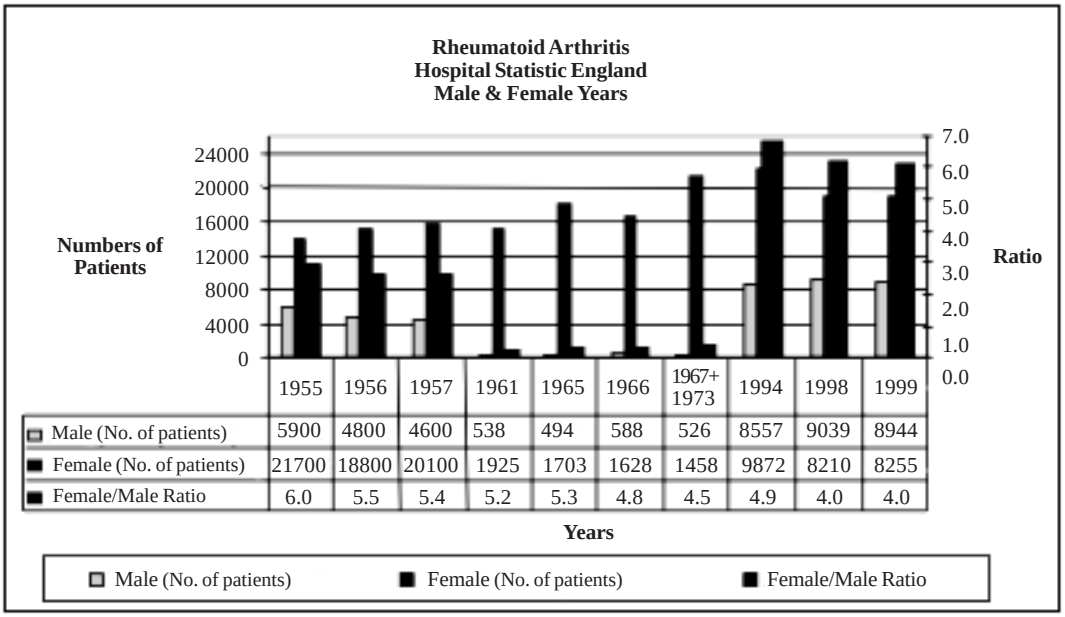
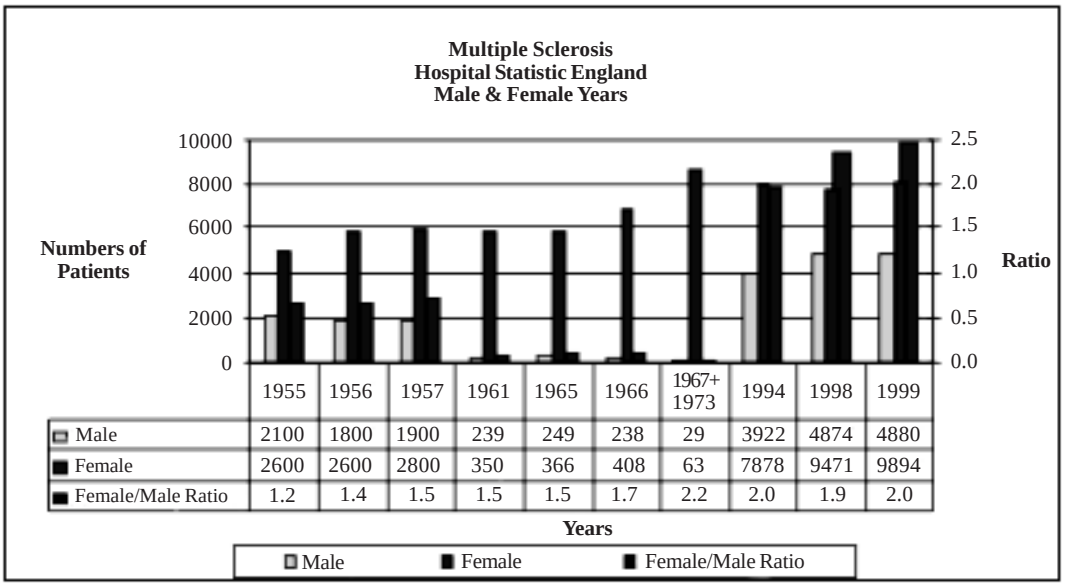


	1955	1956	1957	1961	1965	1966	1967+ 1973	1994	1998	1999
Male (No. of patients)	5900	4800	4600	538	494	588	526	8557	9039	8944
Female (No. of patients)	21700	18800	20100	1925	1703	1628	1458	9872	8210	8255
Female/Male Ratio	6.0	5.5	5.4	5.2	5.3	4.8	4.5	4.9	4.0	4.0

Fig. 4. Rheumatoid Arthritis in England since 1955



	1955	1956	1957	1961	1965	1966	1967+ 1973	1994	1998	1999
Male	2100	1800	1900	239	249	238	29	3922	4874	4880
Female	2600	2600	2800	350	366	408	63	7878	9471	9894
Female/Male Ratio	1.2	1.4	1.5	1.5	1.5	1.7	2.2	2.0	1.9	2.0

Fig. 5. Multiple Sclerosis in England since 1955

Ireland, for all the five immune diseases considered and by the Ministry of Health in the Czech Republic age specific data for Graves' and Hashimoto's thyroiditis. English data came from the Hospital Episode Statistics on the NHS web site and from printed volumes of Hospital Enquiries in the British Library and the library of the Welcome Foundation in respect of years before 1989.

Computing was done by Nisha Maisuria and Jeel Shah. Dr Ralph Miech advised on the medical aspects.

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