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The burden of co-morbidity in Systemic Lupus Erythematosus in the United Kingdom 1999-2012

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Abstract

Objectives: To estimate the co-morbidity associated with Systemic Lupus Erythematosus (SLE) in the UK during 1999-2012.

Methods: A retrospective cohort study using the UK Clinical Practice Research Datalink (CPRD) was conducted. Prevalent cases of SLE were matched by age, sex, and practice to 4 controls. The incidence of cardiovascular disease (CVD), stroke, end-stage renal failure (ESRF), cancer, osteoporosis and infection were calculated per 1,000 person-years during the study period and compared to controls using Poisson regression to obtain incidence rate ratios (IRR). IRR were adjusted for baseline age, gender, body mass index, smoking status, alcohol intake, hypertension, hyperlipidaemia, Charlson index and prednisolone use. Age and gender-specific incidence rates were calculated.

Results: Comparing the 7,732 prevalent cases of SLE with 28,079 matched controls the unadjusted IRR for CVD was 1.98 (95% CI: 1.69, 2.31), stroke 1.81 (95% CI: 1.49, 2.19), ESRF 7.81 (95% CI: 4.68, 13.05), cancer 1.28 (95% CI: 1.17, 1.40), osteoporosis 2.53 (95% CI: 2.27, 2.82) and infection 1.49 (95% CI: 1.40, 1.58). After adjustment, the rates remained significantly higher in cases. Men with SLE had higher rates of CVD, stroke and cancer whereas women had higher rates of infection and osteoporosis. Those at younger ages were at the greatest relative risk compared with controls. Cases had significantly higher Charlson Index scores at baseline.

Conclusions: People with SLE in the UK have a greater burden of co-morbidity and are more likely to develop CVD, stroke, ESRF, cancer, osteoporosis and infection than people of the same age and gender.

Significance

- People with SLE in the UK have a greater burden of co-morbidity and are more likely to develop CVD, stroke, ESRF, cancer, osteoporosis and infection than people of the same age and gender.
- Those at younger ages are at greatest relative risk compared with people of the same age.
- People with SLE are at increased risk of lung cancer, lymphoma (Hodgkin's and non-Hodgkin) and other haematological malignancies.
- Clinicians should be aware of these increased risks and target primary prevention accordingly by encouraging smoking cessation, minimising steroid use, controlling disease activity and regular monitoring of risk factors such as blood pressure, lipids and urinalysis.

INTRODUCTION

SLE is a chronic multi-system autoimmune disease characterised by episodes of disease flare and remission. Recent studies have found a disease prevalence of 0.073% in the United States [1 ,2] and 0.097% in the United Kingdom [3] with a suggestion that the prevalence of SLE is increasing.[3] SLE is associated with significant morbidity which impacts on quality of life [4] and life-expectancy [5 ,6]. People with SLE are recognised to be at increased risk of developing certain co-morbidities such as cardiovascular disease (CVD), [7 ,8] stroke[9], osteoporosis [10-12] and infection [13-15], with recent guidelines recommending monitoring of risk factors for these conditions and institution of preventative treatment.[16] However, some studies into CVD and stroke only found an increased risk in young people.[8 ,9 ,17] The majority of osteoporosis studies have focused on women.[10-12] Most studies into infection are based in secondary care.[13-15] The risk of malignancy in SLE is controversial with conflicting evidence as to whether overall malignancy occurs more frequently in people with SLE compared with that of the general population or whether people with SLE are at increased risk of certain malignancies such as Hodgkin's lymphoma.[18-22] End-stage renal failure (ESRF) as a consequence of lupus nephritis is well documented [23 ,24] but the incidence of ESRF in people with SLE is less well studied. The incidence rate of CVD, Stroke, ESRF, cancer and infection have not previously been studied from a community perspective in a large SLE population in the UK. We therefore aimed to estimate the current incidence of CVD, stroke, ESRF, cancer, osteoporosis and infection in people with SLE in the UK for the period 1999-2012 by age and gender from a community perspective.

METHOD

Study design and source population

A retrospective cohort study was conducted using the Clinical Practice Research Datalink (CPRD). The CPRD is a longitudinal database of general practice records deemed to be representative of the UK population which has been described in detail previously.[3 ,25] Data are entered at the practice level using Read codes, and anonymised records are accessed by researchers from a central database or annual release of flat files. As of January 2013 there were primary care records from 660 practices for approximately 12 million people in all four countries of the UK.

For this study participants were males and females contributing data during the study period 1st January 1999 to 31st December 2012. Participants were eligible from the date their practice was deemed to be contributing “up-to-standard” (UTS) data as verified by the CPRD.

Study sample

The study sample included a cohort of cases and controls. Cases were prevalent cases of SLE who had one of 14 Read codes for SLE (list available on request) and were on the CPRD meeting the eligibility criteria on the 1st July of each calendar year of the study period. Controls were age (within 5 years), sex and practice-matched individuals contributing data during the study period to the CPRD without SLE matched in a 1:4 ratio. Controls were given an index date the same as the diagnosis date of the matched case.

For this study the entry date was the latest of 1st January 1999, SLE diagnosis or matched index date, registration plus 365 days and UTS date. The exit date was the

earliest date of transfer-out of the participating practice, death, date of development of the co-morbidity or 31st December 2012.

Outcome measures

The six specific co-morbidities chosen for estimation were CVD, stroke, ESRF, cancer, osteoporosis and infection. In addition, the incidence rates for selected cancer sites were estimated. Read code lists for each co-morbidity are available on request. Co-morbidities were scored as 1 for present and 0 for absent.

A Charlson Index score was calculated at baseline (study entry date) for cases and controls using all diagnoses in the records following practice registration and UTS date and prior to baseline start date. The Charlson Index [26] is a validated weighted co-morbidity score which contains 17 diagnostic categories: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes mellitus (DM), DM with chronic complications, renal diseases, any malignancy (including leukaemia and lymphoma), metastatic solid tumour and human immunodeficiency virus (HIV) infection. Each category is assigned a score of 1 to 6, depending on mortality risk, and a cumulative score is calculated for each individual. With increasing score there is a stepwise increased risk of death. Charlson comorbidity index was categorised as 0, 1-2, 3-5 and >5. SLE was excluded from the score to ensure comparability between cases and controls.

The following confounding variables were searched for in the records of eligible participants: Body Mass Index (BMI) (categorised as underweight (BMI<19) , normal (BMI 19-25), overweight (BMI 26-29), obese (BMI30-39), severely obese (BMI≥40),

or missing), smoking status (non-smoker, smoker, ex-smoker or missing), alcohol intake (none, alcohol in moderation, alcohol excess, ex-drinker, missing), hypertension (yes or no, yes defined as either a record of hypertension in the clinical notes or 2 or more blood pressure (BP) readings with systolic BP>140mmHg and/or diastolic BP>90mmHg prior to study entry), hyperlipidaemia (yes or no, yes defined as either a record of hyperlipidaemia in the clinical notes or a laboratory reading of total cholesterol>5mmol/l, HDL cholesterol<1mmol/l, non-HDL cholesterol>4mmol/l, triglycerides>1.7mmol/l, LDL cholesterol>3mmol/l, cholesterol:HDL ratio>4 or HDL:LDL ratio>4.5 prior to study entry) and prednisolone prescription within the year prior to study entry (yes or no). Where there was more than one record for BMI, smoking status or alcohol intake the closest record to the study entry date was chosen.

Statistical analysis

Differences in baseline Charlson Index and confounding variables between cases and controls were compared using Chi-squared test.

The incidence rate in cases for each co-morbidity or cancer site was calculated by dividing the number of SLE cases who developed the co-morbidity by the number of person-years for people with SLE during follow-up. Cases with the selected co-morbidity at baseline were excluded. Due to the frequency and acute nature of infections the analysis was repeated for infection without excluding individuals with an infection prior to diagnosis date as a comparison. Crude incidence rates of co-morbidities were calculated with 95% confidence intervals (CI) using the stptime command in Stata which assumes a Poisson distribution. Sex- and age-specific SLE co-morbidity incidence rates were calculated for the study period and expressed as per 1,000 person-years. Age was grouped into <40 years, 40-69 years and

70+years. The incidence rates in cases were compared with the incidence rate in controls using Poisson regression to obtain an incidence rate ratio (IRR). Overall IRR were adjusted for age at baseline, gender, baseline Charlson Index and the confounding variables listed above.[27] Significance of IRR was tested using likelihood ratios.

Data management and analysis was performed using StataMP4 software, version 13 (Statacorp, Texas, USA). Independent Scientific Advisory Committee (ISAC) for MHRA Database Research approval was gained for this study on 4th June 2013 (Protocol 13_092).

RESULTS

There were 7,732 prevalent cases of SLE and 28,079 matched controls. Baseline demographics are shown in table 1. There was a significant trend for BMI, alcohol, smoking and Charlson Index suggesting that controls had a higher BMI and drank more alcohol whereas cases were more likely to smoke and have a higher baseline Charlson Index. Cases were significantly more likely to have hypertension or hyperlipidaemia and have used prednisolone in the year before study entry. The median follow-up time for cases (8.4 years, (IQR 3.7, 12.8 years)) was shorter than that for controls (10.8 years (IQR: 5.8, 13.9 years)) ($p<0.001$).

Table 2 shows the incidence rates in cases and controls and IRRs for each of the six co-morbidities during the study period. The incidence rates of all six co-morbidities were significantly higher in people with SLE compared with controls (all p values <0.001) and remained significant after adjustment for age, gender and other confounding variables. The rate of infection remained significantly higher in people

with SLE regardless of whether cases or controls with an infection prior to baseline were excluded ($p<0.001$).

***Gender differences*:** The incidence rates of the co-morbidities by gender are shown in Table 3. For both men and women SLE cases had higher rates of all co-morbidities compared to controls ($p<0.001$). Men with SLE had higher incidence rates of CVD, stroke and cancer compared to women with SLE, whereas women had higher rates of infection and osteoporosis. This was also true of matched controls. Despite having a lower absolute risk, men with SLE had a higher relative risk for osteoporosis than women.

Age differences: Table 4 shows the difference in age-specific incidence for each co-morbidity. Within every age group cases had a higher incidence of every co-morbidity than controls, although this was not significant for those aged over 70 years for ESRF and cancer. In cases, the incidence of CVD, stroke, cancer and osteoporosis increased with age, the incidence of infection remained stable and the incidence of ESRF reduced with age. Compared with controls, the greatest risk for all co-morbidities except infection was at younger ages. Age group overall had a significant effect on all co-morbidities apart from infection and cancer.

Cancer sites: Table 5 shows the incidence rates of cancer sites in cases compared with controls and table 6 shows the incidence rates of those cancers that were only or predominantly found in women. After adjustment for confounders people with SLE were at significantly increased risk of lung cancer, lymphoma (Hodgkin's and non-Hodgkin) and other haematological malignancies.

DISCUSSION

This study found an increased incidence rate of co-morbidity in people with SLE. People with SLE were more likely to develop CVD, stroke, ESRF, cancer, osteoporosis and infection than people without SLE. Men with SLE had higher incidence rates of CVD, stroke and cancer compared to women with SLE, whereas women had higher incidence rates of infection and osteoporosis. Those at younger ages were at the greatest relative risk of co-morbidity compared with people of the same age.

Previous studies have found an association between SLE and the development of certain comorbidities. The increased incidence rate of CVD and stroke found in our study is consistent with findings from previous studies.[5 ,7-9 ,17] However, in contrast to Ward [8], Mok et al. [9] and Bengtsson et al [17] we found an increased incidence rate of CVD and stroke across all age groups not just younger ages. Although we found those at the youngest age groups had the greatest relative risk (for CVD: IRR 40.31 95% CI: 5.11-318.14 for age <40 years vs 1.41 95% CI: 1.09-1.82 aged >70 years) those at older ages had the greatest absolute risk. This may be because our study was from a community rather than a secondary care perspective. Men with SLE had higher incidence rates of CVD and stroke than women with SLE, but this is likely to reflect the background population risk as this was also true of male compared with female controls. Reasons for the increased vascular risk in SLE appear to be due to a combination of increased conventional risk factors for atherosclerosis such as hypertension, diabetes mellitus and hypercholesterolemia, in conjunction with added risks caused by chronic inflammation, secondary anti-phospholipid syndrome, renal failure, early menopause and long-term steroid-therapy.[28 ,29] In our study the rate in cases remained

significantly higher than controls even after adjusting for age, gender, smoking, hypertension, hyperlipidaemia, BMI, prednisolone use and baseline Charlson Index which included diabetes and renal disease. Clearly primary prevention applies to all age groups but physicians need to remember to target both young and older people. Increased awareness of these risks in conjunction with good disease control and recommended monitoring and primary prevention strategies [16] should reduce the rates of CVD and stroke in future.

ESRF had the biggest difference in incidence rates between cases and controls, even after adjustment. Although the confidence intervals were wide, the incidence of ESRF decreased with age in cases but increased with age in controls. This may be because people with SLE who develop lupus nephritis and subsequently ESRF develop it early in the disease process. This would fit with previous research which found that although people with SLE could develop ESRF at any time the greatest risk was in the first 5-10 years following diagnosis.[30]

The incidence of infection was increased in SLE cases compared to controls regardless of whether people with previous infections were excluded. Consistent with previous studies the increase in infection rate in SLE is considered to be partly due to the disease process itself, but also due to the immunosuppressant drugs used to treat SLE. [13-15] Adjusting for steroid use reduced the rate ratio, but it remained significant, suggesting this increase was in part due to the SLE itself or residual confounding, for example due to use of other immunosuppressants.

Our study found an increase in the incidence rate of cancer overall. This supports the findings from a recent large international study [21] which found people with SLE had a small increased risk of cancer overall (standardised incidence rate 1.14, 95%

CI: 1.05-1.23). Our study also confirmed the increased risk of lung cancer, lymphoma (Hodgkin's and non-Hodgkin) and other haematological malignancies which have been found previously.[21 ,22] However, we did not find a significantly increased risk of vulval, thyroid or pancreatic cancer or significantly reduced risks of breast and endometrial cancers which have been previously reported. [20 ,21]. Disordered immune surveillance, immunosuppressive drugs, and an increase in "usual" risk factors for malignancy such as smoking have been suggested as hypotheses for the increased malignancy risk in SLE.[19] Patients should therefore be encouraged to modify behavioural risks such as smoking which was increased at baseline in people with SLE in this study and report new symptoms of persistent cough, haemoptysis, enlarged lymph glands or the occurrence of night sweats, fevers and unexplained weight loss (B symptoms).

The rate of osteoporosis was increased for both males and females with SLE. Most previous research has focused on women with SLE [10 ,11 ,31] and although women had higher incidence rates of osteoporosis, men with SLE were at a much greater relative risk compared to their controls. The increased risk of osteoporosis is considered to be due to steroid usage, disease process and, in women, premature menopause.[18] Clinicians need to continue to be vigilant of this risk, minimising steroid usage and screening when appropriate, including men.

Despite excluding SLE from the score, the Charlson Index in people with SLE was raised at baseline, suggesting that people with SLE have an increased global burden of comorbidity compared with controls. This score was developed to predict future mortality [26] suggesting further work should be carried out to reduce this risk to reduce premature mortality in SLE.

The main advantage of this study was the large sample size available through the CPRD and hence the generalizability of results to the UK population. This study is the first to examine the incidence of CVD, stroke, cancer, ESRF and infection in a large cohort of SLE patients from a community perspective compared with age and sex- matched controls in the UK. The main limitation of this study is that we were reliant on the accuracy of data entry at the GP practices and therefore there may have been miscoded data, which may have introduced misclassification bias, and missing data, for example as found for our confounding variables particularly BMI where approximately 37% of participants had no BMI recorded. There is potential ascertainment bias for comorbidities in cases if they were receiving more regular follow-up. It was not possible to classify all participants with a code for cancer due to the use of non-specific Read codes such as “Neoplasm”. Not all cancer sites were explored. There may be residual confounding due to variables not considered for adjustment, such as immunosuppressant use. Finally, we used prevalent cases to increase our cohort size, but in doing so we may have missed severely ill incident cases who were diagnosed and died before the start of the study period. This may have biased the sample towards the less severe prevalent cases who survived.

In summary, we found in a large UK community-based cohort people with SLE had greater co-morbidity than people without SLE. This was found in a global baseline co-morbidity score and specifically in the incidence of CVD, stroke, ESRF, cancer, osteoporosis and infection. Men with SLE had higher incidence rates of CVD, stroke and cancer whereas women had higher incidence rates of infection and osteoporosis. Young people with SLE were at the greatest relative risk of CVD, stroke, ESRF and osteoporosis compared with people of the same age, although people of older age were at greater absolute risk of CVD, stroke and osteoporosis.

Clinicians should be aware of these increased risks and target primary prevention accordingly by encouraging smoking cessation, controlling disease activity, minimising steroid use and regular monitoring of risk factors such as blood pressure, lipids and urinalysis. Ongoing research is required to explain why people with SLE are at increased risk beyond the “usual” risk factors to enable refinement of primary prevention strategies to reduce the excess morbidity associated with SLE.

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Table 1: Demographics and confounding variables at baseline

	Cases (%) N=7,732	**Controls (%)** N=28,079	**P value**
Gender			
Male	1,098 (14.2)	3,980 (14.2)	
Female	6,634 (85.8)	24,099 (85.8)	0.953[a]
Age			
Mean age at baseline, years (SD)	48.1 (17.1)	48.1 (17.2)	0.903 [c]
Disease duration at baseline			
Median time from index date to baseline, years (IQR)	2.4 (0-9.3)	2.9 (0-9.1)	0.003[d]
BMI			
Underweight	145 (1.9)	376 (1.3)	
Normal	2,227 (28.8)	7,744 (27.6)	
Overweight	1,255 (16.2)	4,950 (17.6)	
Obese	1,028 (13.3)	3,899 (13.9)	
Severely obese	177 (2.3)	624 (2.2)	
Missing	2,900 (37.5)	13,486 (37.3)	<0.001 [b]
Smoking			
Non-smoker	4,056 (52.5)	16,673 (59.4)	
Smoker	2,154 (27.9)	6,328 (22.5)	
Ex-smoker	1,330 (17.2)	4,412 (15.7)	
Missing	192 (2.5)	666 (2.4)	<0.001 [b]
Alcohol			
Non-drinker	1,861 (23.9)	5,800 (20.7)	
Drinks alcohol	4,775 (61.8)	18,366 (65.4)	
Drinks alcohol over limits	78 (1.0)	348 (1.2)	
Ex-drinker	181 (2.3)	446 (1.6)	
Missing	847 (11.0)	3,119 (11.1)	<0.001 [b]
Charlson Index			
0	4,382 (56.7)	21,094 (75.1)	
1-2	2,668 (34.5)	6,060 (21.6)	
3-5	615 (8.0)	850 (3.0)	
>5	67 (0.9)	75 (0.3)	<0.001 [b]
Hypertension			
No	7,006 (90.6)	25,651 (91.4)	
Yes	726 (9.4)	2,428 (8.7)	0.041 [a]
Hyperlipidaemia			
No	6,096 (79)	22,945 (82)	
Yes	1,636 (21)	5,134 (18)	<0.001 [a]
Prednisolone use in year before baseline			
No	6,024 (78)	27,419 (98)	
Yes	1,708 (22)	660 (2)	<0.001 [a]

a= Chi-squared, b= Chi-squared p for trend, c= t-test, d=Wilcoxon rank-sum

Table 2 Incidence rates of co-morbidity

Co-morbidity	Case-control status	Number of eligible people	Person-years	Number of people who developed co-morbidity	IR of co-morbidity, per 1,000 person-years (95% CI)			IRR	(95% CI) [e]		Adjusted IRR (95% CI) [b e]			Adjusted IRR (95% CI) [c e]		
CVD	controls	26,683	203,135	533	2.62	(2.41	2.86)									
	cases	7,033	44,177	229	5.18	(4.55	5.90)	1.98	(1.69	2.31)	2.14	(1.83	2.50)	1.65	(1.40	1.95)
Stroke	controls	27,295	210,019	369	1.76	(1.59	1.95)									
	cases	7,291	46,265	147	3.18	(2.70	3.73)	1.81	(1.49	2.19)	1.95	(1.61	2.36)	1.47	(1.20	1.80)
ESRF	controls	27,560	213,055	23	0.11	(0.07	0.16)									
	cases	7,440	47,432	40	0.84	(0.62	1.15)	7.81	(4.68	13.05)	7.83	(4.69	13.08)	3.41	(1.93	6.05)
Cancer	controls	25,111	184,470	2,142	11.61	(11.13	12.11)									
	cases	6,636	40,366	599	14.84	(13.70	16.08)	1.28	(1.17	1.40)	1.31	(1.20	1.44)	1.15	(1.05	1.27)
Osteoporosis	controls	27,030	205,413	925	4.50	(4.22	4.80)									
	cases	7,048	42,838	488	11.39	(10.42	12.45)	2.53	(2.27	2.82)	2.71	(2.43	3.03)	1.92	(1.70	2.16)
Infection	controls	10,067	46,219	5,665	122.57	(119.42	125.80)									
	cases	1,984	6,497	1,183	182.09	(172.01	192.77)	1.49	(1.40	1.58)	1.48	(1.39	1.57)	1.10	(1.03	1.18)
Infection[a]	controls	27,527	98,388	18,119	184.16	(181.50	186.86)									
	cases	7,420	17,586	5,240	297.97	(290.01	306.15)	1.62	(1.57	1.67)	1.62	(1.57	1.67)	1.35	(1.26	1.44)

[a]=not excluding co-morbidity at baseline. [b] = adjusted for age and gender. [c] = b plus alcohol, smoking, hypertension, hyperlipidaemia, BMI, prednisolone use, and baseline Charlson index. [e]all p<0.001 CVD=cardiovascular disease. ESRF=end-stage renal failure.

Table 3 Gender-specific incidence rates of co-morbidity

Co-morbidity	Gender	IR of co-morbidity, per 1,000 person-years (95% CI) in controls			IR of co-morbidity, per 1,000 person-years (95% CI) in cases			IRR (cases compared with controls) [e] (95% CI)		
CVD	Males	5.46	(4.67	6.39)	8.34	(6.30	11.03)	1.53	(1.11	2.10)
	Females	2.16	(1.96	2.39)	4.70	(4.06	5.44)	2.17	(1.82	2.59)
Stroke	Males	2.60	(2.08	3.24)	5.06	(3.60	7.12)	1.95	(1.30	2.93)
	Females	1.61	(1.44	1.81)	2.87	(2.39	3.45)	1.78	(1.43	2.21)
ESRF	Males	0.06	(0.02	0.26)	1.19	(0.59	2.38)	18.55	(3.94	87.36)
	Females	0.12	(0.08	0.18)	0.79	(0.56	1.11)	6.81	(3.93	11.80)
Cancer	Males	13.47	(12.16	14.92)	19.15	(15.88	23.08)	1.42	(1.15	1.76)
	Females	11.29	(10.78	11.83)	14.12	(12.93	15.43)	1.25	(1.13	1.38)
Osteoporosis	Males	1.16	(0.84	1.61)	6.22	(4.56	8.47)	5.35	(3.41	8.40)
	Females	5.10	(4.77	5.44)	12.31	(11.22	13.50)	2.41	(2.16	2.70)
Infection	Males	94.11	(87.85	100.82)	150.67	(129.98	174.66)	1.60	(1.36	1.88)
	Females	129.09	(125.51	132.77)	188.98	(177.66	201.02)	1.46	(1.37	1.57)

[e]all $p<0.01$, CVD=cardiovascular disease. ESRF=end-stage renal failure, IR=incidence rate, IRR=incidence rate ratio

Table 4 Age-specific incidence rates of co-morbidity

Co-morbidity	Age group (years)	IR of co-morbidity, per 1,000 person-years (95% CI) in controls			IR of co-morbidity, per 1,000 person-years (95% CI) in cases			IRR (cases compared with controls) (95% CI)			P value
CVD	<40	0.03	(0.00	0.18)	1.03	(0.54	1.98)	40.31	(5.11	318.14)	
	40-69	1.96	(1.73	2.22)	5.17	(4.40	6.08)	2.64	(2.15	3.24)	
	70+	7.27	(6.48	8.16)	10.24	(8.15	12.86)	1.41	(1.09	1.82)	<0.001
Stroke	<40	0.08	(0.02	0.24)	1.15	(0.62	2.14)	15.00	(4.13	54.49)	
	40-69	0.86	(0.71	1.04)	2.19	(1.71	2.79)	2.54	(1.87	3.47)	
	70+	5.83	(5.16	6.59)	8.79	(6.99	11.06)	1.51	(1.16	1.95)	<0.001
ESRF	<40	0.03	(0.00	0.18)	1.61	(0.95	2.72)	63.06	(8.29	479.56)	
	40-69	0.08	(0.04	0.15)	0.77	(0.51	1.16)	9.83	(4.68	20.66)	
	70+	0.26	(0.15	0.46)	0.34	(0.11	1.05)	1.30	(0.37	4.61)	<0.001
Cancer	<40	4.63	(3.99	5.37)	5.58	(4.18	7.45)	1.21	(0.87	1.67)	
	40-69	10.15	(9.57	10.75)	14.53	(13.12	16.08)	1.43	(1.27	1.61)	
	70+	23.68	(22.12	25.34)	27.62	(23.88	31.94)	1.17	(0.99	1.37)	0.1066
Osteoporosis	<40	0.31	(0.17	0.54)	3.62	(2.55	5.15)	11.80	(6.06	22.97)	
	40-69	3.19	(2.90	3.52)	10.75	(9.59	12.06)	3.37	(2.90	3.92)	
	70+	12.42	(11.39	13.54)	23.32	(20.01	27.18)	1.88	(1.58	2.24)	<0.001
Infection	<40	156.88	(148.52	165.71)	210.76	(187.84	236.46)	1.34	(1.18	1.53)	
	40-69	114.59	(110.70	118.62)	171.49	(159.05	184.89)	1.50	(1.38	1.63)	
	70+	107.20	(101.21	113.54)	184.22	(161.17	210.56)	1.58	(1.36	1.82)	0.2248

CVD=cardiovascular disease. ESRF=end-stage renal failure, IR=incidence rate, IRR=incidence rate ratio

Table 5: Incidence rates of cancer by site

Cancer site	Case status	Person-time	Number of people with cancer site	Incidence rate, per 1,000 person-years (95% CI)			IRR	(95%	CI)	Adjusted IRR[a] (95% CI)		
Breast	Control	184,771	361	1.95	(1.76	2.17)						
	Case	40,445	65	1.61	(1.26	2.05)	0.82	(0.63	1.07)	0.85	(0.65	1.13)
Lung	Control	184,480	44	0.24	(0.18	0.32)						
	Case	40,365	37	0.92	(0.66	1.27)	3.84	(2.48	5.95)*	3.27	(2.06	5.18)*
Colorectal	Control	184,508	96	0.52	(0.43	0.64)						
	Case	40,374	19	0.47	(0.30	0.74)	0.90	(0.55	1.48)	0.91	(0.54	1.53)
Hodgkin's lymphoma	Control	184,487	6	0.03	(0.01	0.07)						
	Case	40,371	5	0.12	(0.05	0.30)	3.81	(1.16	2.48)*	3.55	(1.01	12.51)*
Non-Hodgkin's	Control	184,507	49	0.27	(0.20	0.35)						
Lymphoma	Case	40,377	31	0.77	(0.54	1.09)	2.89	(1.84	4.53)*	2.44	(1.48	4.02)*
Other	Control	184,509	65	0.35	(0.28	0.45)						
haematological	Case	40,387	35	0.87	(0.62	1.21)	2.46	(1.63	3.71)*	2.43	(1.56	3.78)*
Pancreas	Control	184,469	14	0.08	(0.04	0.13)						
	Case	40,378	10	0.25	(0.13	0.46)	3.26	(1.45	7.35)*	1.92	(0.74	5.00)
Liver or biliary tree	Control	184,470	8	0.04	(0.02	0.09)						
	Case	40,366	3	0.07	(0.02	0.23)	1.71	(0.45	6.46)	1.56	(0.38	6.45)
Melanoma	Control	184,515	65	0.35	(0.28	0.45)						
	Case	40,375	11	0.27	(0.15	0.49)	0.77	(0.41	1.47)	0.82	(0.42	1.60)
Non-melanoma	Control	185,016	610	3.30	(3.05	3.57)						
skin cancer	Case	40,512	148	3.65	(3.11	4.29)	1.11	(0.93	1.33)	1.08	(0.89	1.31)
Bladder	Control	184,501	51	0.28	(0.21	0.36)						
	Case	40,383	9	0.22	(0.12	0.43)	0.81	(0.40	1.64)	0.69	(0.33	1.46)
Renal	Control	184,471	19	0.10	(0.07	0.16)						
	Case	40,372	3	0.07	(0.02	0.23)	0.72	(0.21	2.44)	0.64	(0.17	2.38)

*P<0.05, [a]adjusted for age and gender, alcohol, smoking, hypertension, BMI, baseline Charlson index, hyperlipidaemia, and prednisolone use in the past year, IRR=incidence rate ratio

Table 6: Incidence rates by cancer site for women only

Cancer site	Case status	Person-time	Number of people with cancer site	Incidence rate, per 1,000 person-years (95% CI)			IRR	(95%	CI)	Adjusted IRR[a] (95% CI)		
Breast	Control	157,603	360	2.28	(2.06	2.53)						
	Case	34,700	64	1.84	(1.44	2.36)	0.81	(0.62	1.05)	0.85	(0.64	1.13)
Thyroid	Control	157,302	8	0.05	(0.03	0.10)						
	Case	34,630	4	0.12	(0.04	0.31)	2.27	(0.68	7.54)	1.37	(0.33	5.74)
Cervix	Control	157,339	25	0.16	(0.11	0.24)						
	Case	34,646	9	0.26	(0.14	0.50)	1.63	(0.76	3.50)	1.86	(0.82	4.22)
Ovary	Control	157,325	29	0.18	(0.13	0.27)						
	Case	34,634	11	0.32	(0.18	0.57)	1.72	(0.86	3.45)	1.28	(0.58	2.80)
Vulval	Control	157,303	10	0.06	(0.03	0.12)						
	Case	34,620	5	0.14	(0.06	0.35)	2.27	(0.78	6.65)	1.04	(0.30	3.64)
Uterus	Control	157,359	39	0.25	(0.18	0.34)						
	Case	34,624	7	0.20	(0.10	0.42)	0.82	(0.36	1.82)	1.04	(0.45	2.38)

[a]adjusted for age and gender, alcohol, smoking, hypertension, BMI, baseline Charlson index, hyperlipidaemia, and prednisolone use in the past year, IRR=incidence rate ratio