Title: Rheumatoid arthritis is getting less frequent - results of a nationwide population based cohort study.

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Abstract

Objectives: The objectives of this study were to examine changes in incidence and prevalence of RA between 1990 and 2014, and to explore if there is any geographic variation in incidence and prevalence of RA in the UK

Methods:

Design Prospective cohort study

Setting Primary care

Participants People contributing acceptable data to Clinical Practice Research Datalink (CPRD) between 01/01/1990 and 31/12/2014 were included. Read codes were used to identify RA cases ≥18 years in age.

Outcomes Prevalence and incidence rates for each year standardised to the 2014 population. Region specific incidence and prevalence of RA for the year 2014 standardized to the overall population.

Results: The incidence and prevalence of RA was 3.81 per 10,000 person-years and 0.67% respectively in 2014. The annual incidence of RA reduced by -1.6%(-0.8% to -2.5%) between 1990 and 2014, with significant joinpoints at 1994 and 2002. The prevalence of RA increased by 3.7%(3.2% to 4.1%)/year from 1990 to 2005; and reduced by -1.1%(-2.0% to -0.2%)/year between 2005 and 2014. There were significant differences in the occurrence of RA throughout different regions of the UK, with highest incidence in East Midlands, Yorkshire and Humber; and highest prevalence in North East, and Yorkshire and Humber.

Conclusion: The incidence of RA is decreasing, with a reduction in prevalence in recent years. There is significant geographic variation in occurrence of RA in UK. Further research is required to identify the reasons underlying this phenomenon so that public-health interventions can be designed to further reduce the incidence of RA.

Keywords: Rheumatoid arthirtis, incidence, prevalence, geographic variation

Introduction

Rheumatoid arthritis (RA) is the commonest auto-immune inflammatory arthritis with a prevalence of 0.5%-1.0% and an incidence of 24–45/100,000 person-years(1, 2). It occurs due to a combination of genetic, environmental and constitutional risk factors, but unlike gout and osteoarthritis (OA) paleo-epidemiologic studies do not provide convincing evidence that it has been around for longer than a few hundred years(3). Moreover, unlike most common complex disorders like type 2 diabetes(4), obesity(5) and hypertension(6) whose incidence and prevalence have increased over time, there is considerable controversy as to whether the incidence of RA has reduced rather than increased. While most studies report a progressive reduction in the incidence of RA in the USA, Finland, and Japan (7-12), others have reported either an increasing (13-15) or stable incidence (16) in the USA, and Denmark; and Greece respectively . Several explanations for reduced incidence of RA including birth-cohort effect (17-19) and increased uptake of hormonal contraception(10-12, 20) have been suggested. However, the oral contraceptive hypothesis is not supported by all studies(12, 21), and the increase in the mean age of incident RA cases observed in cross-sectional studies conducted in the same geographic area several decades apart, and used to suggest the presence of a birth cohort effect could be explained by an ageing general population(17, 18). Moreover, it is difficult to draw definite conclusions on temporal trends in the incidence and prevalence of RA as many published studies are relatively small (8, 9, 12, 13, 15-17, 19, 21). Thus, it is necessary to revisit the temporal trends in epidemiology of RA.

The overall aim of this study was to explore variations in the incidence and prevalence of RA in the UK between 1990 and 2014. The specific objectives were to: [1] provide contemporary data on epidemiology of RA; [2] examine changes in prevalence and

incidence of RA between 1990 and 2014; and [3] explore whether there is geographic variation in occurrence of RA in the UK since this may help explore possible environmental risk factors for the disease.

Methods

Source of data: Data from the Clinical Practice Research Datalink (CPRD) were used. CPRD is one of the largest databases of longitudinal medical records from primary care. Established in 1987, it contains anonymised healthcare records from over 13 million individuals and represents 8% of the UK population at any one time. The data in CPRD undergoes thorough quality checks and is of reliable research standard with a high validity of recorded diagnoses, including a median proportion of cases with a confirmed diagnosis of 89% for 183 different conditions including chronic auto-immune conditions(22). The study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Regulatory Authority, London, UK (Ref: 15_101R)

Study population: The study comprised all participants who contributed acceptable quality data to the CPRD between 1st January 1990 and 31st December 2014. The denominator for prevalence estimation for each calendar year included all individuals registered on 1st July of each calendar year with a GP. For the incidence of RA, at-risk cohorts for each calendar year were constructed, which comprised all individuals registered with up-to-standard practices (practices meeting the specified data entry criteria) during the year specified who had never been coded as having RA before the latest of current registration date plus 365 days or 1st January of the calendar year specified. Person-years of follow-up were calculated from the latest of 1st January or the date of current registration plus 365 days to the earliest date of transfer-out, incident RA diagnosis, death or 31st December of the specified year.

Definition of RA: RA was defined using a previously published Read code list(23). This list was modified after discussions among the investigators (rheumatologists (AA, MD, C-FK), academic GP with expertise of CPRD research (CDM), statistician (MJG)

and epidemiologist (WZ)) to exclude codes for Adult Still's Disease, Adult-onset Still's disease and Juvenile ankylosing spondylitis since they are distinct diseases.

Case definition: Prevalent cases of RA were participants of at least 18 years in age on the 1st July of each calendar year who had a medical Read code that has been used previously to identify cases with RA(23). Incident cases of RA were those who had no medical code for RA prior to the latest of current registration date plus 365 days or 1st January of each calendar year but developed RA during that year, and were at least 18 years of age at the index date. To be eligible as an incident case, participants had to have at least 1-year registration prior to the first date of RA diagnosis as this has been shown to reduce the risk of prevalent cases being counted as incident cases in chronic conditions such as RA(24). To examine whether this period was sufficiently long to exclude these potentially prevalent cases, we also classified cases to have at least 3-year registration prior to the first date of RA diagnosis in a sensitivity analysis.

Statistical analysis: Point prevalence of RA on the 1st July of each year was calculated and 95% confidence interval (CI) calculated. Incidence rates by year were calculated using the number of incident RA cases during that year as the numerator and the total person-years occurring during the same year as the denominator. Incidence and prevalence rates were stratified by sex. Poisson regression was used to examine the association between sex and prevalent and incident RA.

To determine the trends in prevalence and incidence of RA, age-, sex- and length of data contribution-standardised prevalence and incidence of RA were calculated for each calendar year from 1990 to 2013 with the population structure in year 2014 as reference. Ten year age-bands were selected for age stratification. The incidence and prevalence were standardized for the length of data contribution, as the longer the

period a person contributes data to the CPRD the greater the chance that a chronic health event will be recorded at some point. The length of data contribution of each patient was defined as the period from the current date of registration to the 1st July of each calendar year for prevalence or to 1st January of the calendar year specified for incidence. The length of data contribution was categorized as 0-3 years, 4-6 years, 7-9 years, and 10 years or more. Temporal trends in the incidence and prevalence of RA were examined using Joinpoints analysis. For this the Joinpoint Regression Program was used(25) (See supplementary material).

The incidence rate of RA for each ten year age-band was calculated in 1994, 2004 and 2014 to look for the presence of a birth cohort effect. This was stratified by sex. Finally, prevalence and incidence of RA were calculated separately for 13 regions in the UK for the year 2014 (See supplementary material). To remove the effect of different age and gender structures, the prevalence and incidence were standardized to the overall CPRD population structure in 2014. Incidence rates were calculated, and a likelihood ratio test was performed to find out if there was a statistically significant overall geographic variation in the incidence and prevalence. Choropleth maps were used to illustrate geographic variations. Data management and analysis were performed using Stata software V.13 (Statacorp, Texas, USA). The significance level was $p < 0.05$.

Results

Prevalence and incidence Of the 3,966,443 eligible individuals in 2014, 26,385 prevalent cases of RA were identified, giving a prevalence (95%CI) of 0.67%(0.66-0.67). Women had a higher prevalence (0.93%(0.91-0.94)) than men (0.40%(0.39-0.41)) with age-adjusted rate ratio (95%CI) of 2.08(2.02-2.13). The prevalence of RA increased with age (Figure 1A).

There were a total of 3,413,043 person-years of follow-up in 2014 during which 1299 incident cases of RA were identified, giving an incidence (95% CI) of 3.81(3.61-4.02) per 10,000 person-years. The incidence of RA increased with age (Figure 1B). Women had a higher incidence (95% CI) per 10,000 person-years than men (5.09(4.75-5.42) vs. 2.51(2.28-2.75)), with an age adjusted IRR (95%CI) of 1.85(1.65-2.07).

Prevalence and incidence of RA between 1990 and 2014

In general, crude, age-sex standardised, and age, sex, length of data contributed standardized estimates of prevalence of RA increased over time (Table 1, Figure 2). The overall annual increase in prevalence was 2.10%(1.5% to 2.70%). However, there was one significant joinpoint at 2005 (Figure S1). The prevalence of RA increased by 3.7%(3.2 % to 4.1%) per-year from 1990 to 2005, and reduced by -1.1%(-2.0% to -0.2%) per-year from 2005 to 2014.

The standardised incidence of RA reduced during the study period (Table 2, Figure 3). On average, the incidence of RA reduced by -1.6%(-0.8% to -2.5%) per year from 1990-2014. However, there were two significant join points at 1994 and 2002 respectively (Figure S1). The incidence of RA reduced by -15.7%(-8.4% to -22.4%) per year between 1990 and 1994; plateaued between 1994 and 2002 with an annual change in incidence of 3.0%(-0.5% to 6.7%); and again reduced by -3.8%(-1.3% to -

4.3%) per year between 2002 and 2014. As the incidence of RA was significantly higher in 1990 and 1991, we re-analysed the data on temporal trends in the incidence of RA after excluding data from these two years. Even after this, there was a statistically significant reduction in annual incidence of RA of -0.9%(-0.1% to -1.6%) per year between 1992 and 2014, and the incidence of RA reduced significantly between 2003 and 2014 with an average reduction of -2.6%(-0.6% to -4.6%) per year. These findings did not change when the analysis was restricted to participants with a 3 year period of registration prior to the 1st January of each year (Figure S2).

Age specific incidence of RA in 1994, 2004 and 2014 The peak age of onset of RA remained between 70-80 years in age, and did not change between 1994 and 2014 (Table 3). Similar findings were observed when data from men and women were analysed separately (Table 3).

Geographic variation in 2014

There were statistically significant differences in the prevalence and incidence of RA throughout the UK ($p<0.001$), Figure 4. The age-sex standardised prevalence of RA was highest in the North East, Yorkshire and Humber, and Northern Ireland. Regions with the lowest prevalence of RA were South Central and London. The East Midlands, Yorkshire and Humber, and South West were the regions with the highest standardised incidence of RA, while North East, West Midlands and Wales had the lowest incidence.

Discussion

This is the largest study to examine temporal trends in the incidence and prevalence of RA. It reports an increase in the point prevalence of RA from 1990 to 2005, but a subsequent reduction between 2005 and 2014, and a gradual reduction in its incidence over time. It also reports that the peak age of incidence of RA is in the eighth decade of life, which has not changed over the past 20 years. In addition, this study found evidence of significant geographic variation in the incidence and prevalence of RA in the UK.

There was an increase in the prevalence of RA from 1990 to 2005, but not in subsequent years. This finding is contrary to that of a Global Burden of Diseases study which reported that the prevalence of RA remained unchanged between 1990 and 2010(26). However, that was a systematic review of published studies, which would have different observation periods for each study; hence it would be difficult to determine the temporal change. This contrasts with studies from Ontario, Canada (27), and Rochester, USA(13), where the prevalence of RA increased over time, with no reduction in recent years. Further research is required to explore factors underlying this, but this could include migration and mortality. Findings from several recent studies demonstrate that the standardized mortality rate in RA has not improved over time despite improvements in the treatment of RA(28-30).

In our study, the incidence of RA reduced over time. However, it was significantly higher in 1990 and 1991 compared to later years despite our taking precautions to prevent prevalent cases being classified as incident cases by requiring participants to have 12 months of registration prior to being coded as having incident RA. We also undertook a sensitivity analysis by specifying a three year prior registration period before a participant could be coded to have incident RA. The latter approach did not

reduce the significantly higher incidence rate in 1990 and 1991. Thus, we are reasonably certain that the high incidence rate in 1990 and 1991 is not related to prevalent RA cases being more likely to be coded as incident RA in the early years of the CPRD.

We observed an increase in incidence of RA in the early 2000s. This could be explained by the increasing availability of anti-CCP antibody testing in the UK, which would allow cases previously coded as having sero-negative inflammatory arthritis or inflammatory arthritis to be coded as RA(31). Similarly, the initial NICE approval for use of anti-TNF treatments in patients with RA in the year 2000 could have prompted rheumatologists to better classify their patients.

It is noteworthy that the recent 2010 ACR/EULAR criteria for the classification of RA did increase the incidence of RA(32). The 2010 ACR/EULAR classification criteria allows patients to be classified as RA at an earlier, less severe stage than the 1987 ACR criteria(33), and allows a greater number of patients with unclassified inflammatory arthritis to meet the classification criteria for RA(34). This finding suggests that either the incidence of RA has reduced more significantly, and is being masked by a change in disease classification criteria, or that physicians are slow to adapt to changes in nomenclature and classification systems. We do not believe that the reduction in incidence of RA over time is due to exclusion of previous incident cases as this phenomenon would have resulted in a reduction in the incidence of other diseases such as gout(35) and type 2 diabetes for which the incidence in the CPRD has remained stable and risen respectively(36).

RA is a common complex disease where genetic predisposition (shared epitope(37)); constitutional risk factors (obesity(38)); and environmental exposures (smoking) interact to cause chronic joint inflammation(39). As the genetic make-up of a

population does not change over relatively short periods of time, and the prevalence of obesity is increasing(5), the reduction in incidence of RA could be related to reducing prevalence of cigarette smoking in the UK. The prevalence of cigarette smoking has reduced from 45% in 1974 to 19% in 2013 in the UK, with similar reductions in both men and women (http://ash.org.uk/files/documents/ASH_106.pdf). The fact that reducing incidence of RA may be related to smoking is further supported by the fact that areas with high prevalence of cigarette smoking have high prevalence of RA, and vice versa. For example, North East of England, Yorkshire and the Humber, Scotland, and Wales have high prevalence both of RA and cigarette smoking, while South Central, London and East of England have lower prevalence of RA and lower prevalence of cigarette smoking (http://www.ons.gov.uk/ons/dcp171778_386291.pdf). However, geographic variation in the prevalence of RA could be related to other aetiological changes such as socio-economic deprivation which also co-associate with smoking(40).

This study provides contemporary data on the epidemiology of RA. The prevalence and incidence of RA in the UK, and the female predominance reported in this study are in accord with the findings of previous epidemiological studies, and provide external validity to these findings. We standardized the crude incidence and prevalence of RA to the 2014 population structure, and also to the number of years for which data were contributed prior to 1st January or 1st July of that year. This reduces the possibility of confounding due to changes in population structure over time, and events occurring prior to the start of study period. Thus, we are reasonably confident that the reduction in incidence of RA over time is a valid finding.

The main limitations of this study are those inherent in the use of a large consultation based database such as the CPRD. However, the accuracy of diagnosis of RA has

been validated previously, which minimizes the possibility of incorrect diagnosis. The index date reflects the date of allocation of Read codes for RA, and does not reflect disease onset, or the date of diagnosis. However, the date of allocation of a Read code for RA (which may happen after a hospital letter confirming a diagnosis of RA) would be expected to be within a few months of the date of diagnosis, and does not invalidate the findings on the temporal trends in the epidemiology of RA over a 25 year period. We modified the published Read code list for identifying RA cases to increase its face validity. However, we did not perform a sensitivity analysis to examine the effects of these changes on the results. We do not think a change in the Read code list will alter the findings on temporal trends in epidemiology of RA.

In summary, the incidence of RA in the UK is decreasing. These data confirm the known predilection of RA in women, but contrary to general opinion the peak age of diagnosis of RA is in later years. There was UK-wide variation in the incidence and prevalence of RA, and further research is required to identify the reasons underlying this phenomenon. Further research is also required to examine temporal trends in mortality of RA, and to find out if the reduction in incidence of RA is due to reduced prevalence of cigarette smoking.

Key messages:

- The incidence of RA is reducing gradually.
- The prevalence of RA has reduced recently.
- There is significant geographic variation in the occurrence of RA in the UK.

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Contribution: AA, MD, WZ, C F-K, CM conceptualised the study. Data analysis was performed by AA and supervised by WZ and MG. C F-K drew the choropleth maps. All authors read and approved the final version of the manuscript for submission. MG is the overall guarantor of the research. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Prevalence of RA from 1990 - 2014

Year	Population	Prevalence (%)		
		Crude	Age – sex standardised	Age – sex and duration of data contribution standardised
1990	3118382	0.34 (0.34 - 0.35)	0.36 (0.36-0.37)	0.41 (0.38-0.43)
1991	3360131	0.38 (0.37 - 0.38)	0.40 (0.39-0.41)	0.43 (0.42-0.44)
1992	3566906	0.40 (0.40 - 0.41)	0.43 (0.42-0.43)	0.43 (0.42-0.44)
1993	3788948	0.43 (0.42 - 0.43)	0.45 (0.44-0.46)	0.48 (0.47-0.49)
1994	4021774	0.45 (0.44 - 0.45)	0.47 (0.46-0.48)	0.50 (0.49-0.51)
1995	4230629	0.46 (0.46 - 0.47)	0.49 (0.48-0.49)	0.52 (0.51-0.54)
1996	4431788	0.48 (0.47 - 0.49)	0.50 (0.50-0.51)	0.51 (0.51-0.52)
1997	4591476	0.50 (0.49 - 0.50)	0.52 (0.51-0.52)	0.55 (0.54-0.56)
1998	4693233	0.51 (0.51 - 0.52)	0.53 (0.53-0.54)	0.54 (0.53-0.55)
1999	4781898	0.53 (0.52 -0.53)	0.55 (0.54-0.55)	0.55 (0.55-0.56)
2000	4860654	0.54 (0.54 -0.55)	0.56 (0.56-0.57)	0.59 (0.58-0.61)
2001	4918467	0.56 (0.56 -0.57)	0.58 (0.58-0.59)	0.62 (0.60-0.63)
2002	4952188	0.59 (0.58 -0.59)	0.61 (0.60-0.62)	0.61 (0.61-0.62)
2003	4996092	0.61 (0.60 -0.61)	0.63 (0.62-0.63)	0.67 (0.65-0.68)
2004	5039357	0.62 (0.62 -0.63)	0.64 (0.64-0.65)	0.69 (0.68-0.71)
2005	5097746	0.64 (0.63 -0.65)	0.66 (0.65-0.67)	0.76 (0.73-0.78)
2006	5096933	0.65 (0.64 - 0.66)	0.67 (0.66-0.67)	0.75 (0.72-0.77)
2007	5092482	0.65 (0.65 - 0.66)	0.67 (0.66-0.68)	0.67 (0.66-0.68)
2008	5068313	0.66 (0.65 -0.66)	0.67 (0.66-0.68)	0.67 (0.67- 0.68)
2009	5035895	0.66 (0.65 - 0.67)	0.67 (0.67-0.68)	0.67 (0.67-0.68)
2010	4946060	0.67 (0.66 -0.67)	0.67 (0.67-0.68)	0.68 (0.67-0.68)
2011	4821377	0.67 (0.66 - 0.67)	0.67 (0.67-0.68)	0.67 (0.67-0.68)
2012	4724886	0.66 (0.66 - 0.67)	0.67 (0.66-0.68)	0.67 (0.67-0.68)
2013	4456895	0.66 (0.65 - 0.67)	0.67 (0.66-0.67)	0.67 (0.66-0.67)
2014	3966443	0.67 (0.66 - 0.67)	-/-	-/-

Table 2: Incidence of RA from 1990-2014

Year	Person-years	Incidence rate (95% CI) per 10,000 person-years		
		Crude	Age – sex standardised[1]	Age – sex duration of data contributed standardised[1]
1990	402627	7.67 (6.86-8.58)	7.81 (6.93-8.68)	7.46 (6.22 – 8.70)
1991	772376	5.44 (4.94-5.98)	5.73 (5.17-6.29)	6.46 (4.55 – 8.37)
1992	950289	4.76 (4.34-5.22)	5.01 (4.54-5.48)	4.93 (4.12 – 5.75)
1993	1090675	4.69 (4.30-5.11)	4.83 (4.41-5.25)	4.36 (3.75 – 4.97)
1994	1189540	3.94 (3.60-4.32)	4.02 (3.66-4.39)	3.85 (3.21 – 4.49)
1995	1303325	4.12 (3.79-4.48)	4.38 (4.00-4.75)	3.93 (2.89 – 4.97)
1996	1398690	3.85 (3.53-4.19)	4.02 (3.68-4.36)	3.58 (3.08 – 4.08)
1997	1624108	4.54 (4.23-4.88)	4.62 (4.28-4.95)	4.67 (4.11 – 5.24)
1998	1877971	3.98 (3.71-4.28)	4.01 (3.72-4.30)	4.22 (3.47 – 4.96)
1999	2210469	4.11 (3.85-4.38)	4.23 (3.95-4.51)	3.94 (3.52 – 4.35)
2000	2737196	4.42 (4.18-4.68)	4.61 (4.35-4.87)	4.76 (4.20 – 5.32)
2001	3146122	4.48 (4.26-4.73)	4.61 (4.36-4.85)	4.71 (4.22 – 5.21)
2002	3493910	4.64 (4.42-4.87)	4.76 (4.53-5.00)	4.64 (4.24 – 5.04)
2003	3751801	4.41 (4.20-4.62)	4.60 (4.37-4.82)	4.94 (4.40 – 5.48)
2004	3953837	4.62 (4.41-4.84)	4.80 (4.57-5.02)	5.20 (4.68 - 5.72)
2005	4112549	4.04 (3.85-4.24)	4.13 (3.94-4.33)	4.25 (3.86 – 4.65)
2006	4172806	3.92 (3.74-4.12)	3.99 (3.79-4.18)	4.18 (3.77 – 4.58)
2007	4185156	3.86 (3.68-4.05)	3.97 (3.78-4.17)	3.66 (3.32 – 4.01)
2008	4226454	3.67 (3.49-3.86)	3.78 (3.59-3.97)	3.52 (3.16 – 3.87)
2009	4237654	3.92 (3.73-4.11)	3.95 (3.76-4.14)	3.72 (3.39 – 4.06)
2010	4165240	3.72 (3.54-3.91)	3.75 (3.56-3.93)	3.52 (3.17 – 3.87)
2011	4076348	3.66 (3.48-3.85)	3.73 (3.54-3.92)	3.62 (3.28 – 3.96)
2012	4016632	3.67 (3.49-3.87)	3.76 (3.57-3.96)	3.55 (3.20 – 3.90)
2013	3773084	4.04 (3.84-4.24)	4.06 (3.85-4.26)	3.73 (3.38 – 4.09)
2014	3413043	3.81(3.61 –4.02)	-/-	-/-

[1]to the 2014 population

Table 3: Incidence of RA by age 1994, 2004 and 2014

	Incidence rate (95% CI) per 10,000 person-years		
Age (years)	1994	2004	2014
Overall			
<20	-/-	0.21 (0.11-0.41)	0.08 (0.03 - 0.25)
≥20 & <30	0.79 (0.45 - 1.39)	1.09 (0.83 - 1.44)	0.81 (0.57 - 1.16)
≥30 & <40	2.47 (1.85 - 3.30)	2.18 (1.82 - 2.61)	2.09 (1.70 - 2.57)
≥40 & <50	3.82 (3.02 - 4.83)	3.73 (3.29 - 4.22)	3.48 (3.00 - 4.03)
≥50 & <60	6.60 (5.41 - 8.04)	6.98 (6.30 - 7.75)	5.95 (5.30 - 6.67)
≥60 & <70	7.35 (5.99 - 9.00)	10.44 (9.55 - 11.42)	7.41 (6.62 - 8.29)
≥70 & <80	10.27 (8.47 - 12.45)	12.08 (10.86 - 13.44)	10.27 (9.15 - 11.53)
≥80 & <90	7.39 (5.36 - 10.20)	11.79 (10.30 - 13.52)	6.97 (5.76 - 8.44)
≥90	10.81 (5.62 - 20.77)	7.13 (4.55 - 11.17)	3.41 (1.94 - 6.01)
Female			
<20	-/-	0.41 (0.20 – 0.81)	0.11 (0.03 – 0.45)
≥20 & <30	1.09 (0.54 - 2.17)	1.80 (1.31 - 2.46)	1.26 (0.83 - 1.89)
≥30 & <40	3.77 (2.71 - 5.26)	3.16 (2.55 -3.91)	3.34 (2.65 - 4.22)
≥40 & <50	5.52 (4.18 - 7.28)	5.81 (5.05 - 6.70)	4.99 (4.20 - 5.94)
≥50 & <60	10.33 (8.25 - 12.93)	9.33 (8.21 - 10.61)	8.32 (7.24 - 9.55)
≥60 & <70	8.60 (6.62 - 11.18)	13.04 (11.65 - 14.60)	8.96 (7.75 - 10.35)
≥70 & <80	12.08 (9.56 - 15.27)	14.43 (12.65 - 16.47)	12.20 (10.55 - 14.12)
≥80 & <90	9.01 (6.30 - 12.88)	14.35 (12.29 - 16.75)	8.50 (6.78 - 10.66)
≥90	13.85 (7.21 - 26.62)	7.42 (4.47 - 12.31)	3.24 (1.62 - 6.47)
Male			
<20	-/-	0.04 (0.01 - 0.32)	0.05 (0.01 – 0.38)
≥20 & <30	0.51 (0.19 - 1.35)	0.46 (0.25 - 0.83)	0.40 (0.20 - 0.81)
≥30 & <40	1.18 (0.65 - 2.12)	1.24 (0.88 - 1.73)	0.84 (0.53 - 1.34)
≥40 & <50	2.16 (1.39 - 3.34)	1.72 (1.33 - 2.22)	1.99 (1.52 - 2.61)
≥50 & <60	2.93 (1.93 - 4.46)	4.70 (3.94 - 5.62)	3.63 (2.96 - 4.47)
≥60 & <70	6.02 (4.36 - 8.30)	7.81 (6.75 - 9.04)	5.82 (4.86 - 6.98)
≥70 & <80	7.85 (5.61 - 10.98)	9.25 (7.72 - 11.09)	8.11 (6.71 - 9.80)
≥80 & <90	4.18 (1.99 - 8.77)	7.35 (5.52 - 9.78)	4.81 (3.36 - 6.88)
≥90	-/-	6.21 (2.33 - 16.53)	3.82 (1.43 - 10.18)