RESEARCH PAPER

HIV and lower risk of multiple sclerosis: beginning to unravel a mystery using a record-linked database study

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ABSTRACT

Objectives Even though multiple sclerosis (MS) and HIV infection are well-documented conditions in clinical medicine, there is only a single case report of a patient with MS and HIV treated with HIV antiretroviral therapies. In this report, the patient's MS symptoms resolved completely after starting combination antiretroviral therapy and remain subsided for more than 12 years. Authors hypothesised that because the pathogenesis of MS has been linked to human endogenous retroviruses, antiretroviral therapy for HIV may be coincidentally treating or preventing progression of MS. This led researchers from Denmark to conduct an epidemiological study on the incidence of MS in a newly diagnosed HIV population (5018 HIV cases compared with 50 149 controls followed for 31 875 and 393 871 person-years, respectively). The incidence rate ratio for an HIV patient acquiring MS was low at 0.3 (95% CI 0.04 to 2.20) but did not reach statistical significance possibly due to the relatively small numbers in both groups. Our study was designed to further investigate the possible association between HIV and MS.

Methods We conducted a comparative cohort study accessing one of the world's largest linked medical data sets with a cohort of 21 207 HIV-positive patients and 5 298 496 controls stratified by age, sex, year of first hospital admission, region of residence and socioeconomic status and 'followed up' by record linkage.

Results Overall, the rate ratio of developing MS in people with HIV, relative to those without HIV, was 0.38 (95% CI 0.15 to 0.79).

Conclusions HIV infection is associated with a significantly decreased risk of developing MS. Mechanisms of this observed possibly protective association may include immunosuppression induced by chronic HIV infection and antiretroviral medications.

INTRODUCTION

Even though multiple sclerosis (MS) and HIV infection are two of the most documented conditions in clinical medicine, with more than one million peer-reviewed papers combined, there is only a single case report of a patient with MS and HIV treated with HIV antiretroviral therapies.[1] In this case report, the patient's MS symptoms resolved completely after starting combination antiretroviral therapy (cART) and remain subsided for more than 12 years of follow-up. In the report, the authors hypothesised that because the pathogenesis of MS has been linked to several human endogenous retroviruses (HERVs),[2 3] antiretroviral therapy for HIV may be coincidentally treating or preventing progression of MS. Publication of this report led investigators from Denmark to conduct an analysis of the incidence of MS in a newly diagnosed HIV population by utilising the Danish National Registry of Patients (1994–2011), which is linked to Civil Registration System and the Danish MS Registry. Their analysis determined that among 5018 first presenting HIV patients and 50 149 controls, matched for age and sex and followed for 31 875 and 393 871 person-years, respectively, the incidence rate ratio (IRR) for an HIV patient acquiring MS was 0.3 (95% CI 0.04 to 2.20). This IRR did not reach statistical significance, possibly due to the relatively small numbers of people who developed MS in each group.[4] These authors also suggested that HIV therapies may be coincidentally ameliorating the MS and that, if so, this could provide an explanation for the relatively large observed protective effect of HIV on the development of MS. This was the first record linkage study exploring an association between HIV and MS. In order to further test this hypothesis, we explored one of the world's largest linked medical data sets to investigate the possible relationship between HIV and developing MS.

METHODS

We analysed a national linked data set of English Hospital Episode Statistics (HES) to identify all people with HIV who were discharged from National Health Service hospitals, between 1999 and 2011, as a hospital day-patient or inpatient, irrespective of the reason for this contact. HIV was recorded on the chart, even though the contact may have been for a condition unrelated to HIV. Successive discharge records relating to the same person were linked together as a cumulative statistical record for that person, and these were linked to any death record. HES was provided by the English National Health and Social Care Information Centre; death records were provided by the Office for National Statistics. All data were anonymised by encryption of personal identifiers before being supplied to the Oxford study team for record linkage. The statistical analysis was carried out using analytical software designed within the Oxford research unit using the statistical analysis software package SAS (release V.9.2, SAS Institute

Inc, Cary, North Carolina, USA). Additional statistical methodology is explained more fully and referenced in the online supplementary appendix.

The earliest record of HIV in HES was the record used for analysis. Having identified all people in the data set with HIV, we stratified them into 5-year age bands, sex, year of first hospital admission, region of residence and quintiles of Index of Multiple Deprivation (a standard national measure of socioeconomic status). We then 'followed up' these people, through record linkage until 31 December 2011, for any subsequent record of MS. Anyone who had a record of MS prior to or concurrent with the HIV record was excluded from the cohort. This excluded five people with prior MS and three people with a simultaneous record of HIV and MS.

For comparison, we also identified a cohort of people without HIV. These were hospital controls selected from our data set; they comprised all people in HES from 1999 to 2011 whose principal reason for an episode of care was for a minor medical or surgical condition or injury (the earliest, for any individual person, of any of those listed in the footnote to table 1). We stratified this cohort in the same way as the HIV cohort, and 'followed up' this cohort, too, for any subsequent record of MS. As with the HIV cohort, anyone with a record of MS prior to or at the same time as the first admission for a reference condition was excluded from the reference cohort. This excluded 877 people with prior MS and 1767 people with a simultaneous record of a reference condition and MS.

Expected numbers of people with MS were determined in each stratum of each cohort, by calculating the rate of MS in the combined population of the HIV and reference cohorts, based on person-days at risk; we then applied that rate to the person-days at risk in the corresponding stratum in, first, the HIV cohort and, second, the reference cohort. This gave stratum-specific expected numbers of people with MS in the HIV and the reference cohort. The expected numbers were added to give all-strata totals in each cohort, which were compared with the observed numbers. Stratum-standardised summary estimates of relative risk were then calculated according to standard statistical practice described elsewhere.[5] The rate ratio (RR) was calculated using the formula (O^{HIV}/E^{HIV}):(O^{ref}/E^{ref}), where the Os and Es are the observed and expected numbers of people with MS in, respectively, the HIV cohort and the reference cohort.

Subanalyses were performed, restricting the outcome of MS to include only the people whose first record of MS, known to us, was more than a year, and then more than 5 years, after the first record of HIV. The reason for this was to identify the sequence of HIV occurring before MS as best we could. In addition, we performed separate analyses for each ethnic group.

Table 1 Age distribution of people entering the HIV cohort, the percentage who were female, and the number of people who entered the reference cohort*

Age (years)	HIV cohort Number	(% of total)	Female (%)	Reference cohort Number
0–4	139	(0.7)	44.6	112 355
5–9	168	(0.8)	45.2	145 618
10–14	138	(0.7)	57.2	113 372
15–19	173	(0.8)	59.0	166 198
20–24	653	(3.1)	44.4	200 079
25–29	2136	(10.1)	43.9	264 771
30–34	4066	(19.2)	36.9	377 462
35–39	4792	(22.6)	29.6	444 962
40–44	3701	(17.5)	24.9	390 356
45–49	2228	(10.5)	20.6	329 573
50–54	1293	(6.1)	18.6	345 117
55–59	776	(3.7)	17.4	375 702
60–64	480	(2.3)	16.3	377 503
65–69	274	(1.3)	21.2	387 109
70–74	98	(0.5)	21.4	397 229
75–79	37	(0.2)	27.0	385 998
80–84	22	(0.1)	22.7	282 933
85+	33	(0.2)	45.5	202 159
All ages	21 207	(100)	30.2	5 298 496

Note that all eligible controls were used (there is no merit in discarding controls to equalise numbers in each age group); and that all analyses were done within strata (eg, the 112 355 controls aged 0–4 were compared with the 139 in the HIV cohort). The expected numbers in each stratum were then summed to give age-standardised comparisons of expected and observed numbers with MS in each cohort.
*The reference cohort consisted of people admitted with the following conditions coded under the Office of Population, Censuses and Surveys code (OPCS) edition 4 for operations and the ICD revision 10 for diagnoses: adenoidectomy (OPCS4 E20), tonsillectomy (F34+F36), appendectomy (H01–H03), total hip replacement (W37–W39), total knee replacement (W40–W42), cataract (ICD 10 H25), otitis externa/media (H60–H67), varicose veins (I83), haemorrhoids (I84), deflected septum, nasal polyp (J33+J34.2), inguinal hernia (K40), gallbladder disease (K80–K81), in–growing toenail and other diseases of nail (L60), sebaceous cyst (L72.1), bunion (M20.1), internal derangement of knee (M23).
MS, multiple sclerosis.

RESULTS

The total number of people who entered the HIV cohort was 21 207 (152 618 person-years at risk); the total number of people who entered the reference cohort was 5 298 496 (39 998 613 person-years at risk). The median follow-up period for the HIV cohort was 2454 days (IQR 1790 days); the median follow-up period for the reference cohort was 2756 days (IQR 1951 days). Table 1 shows the age distribution of the HIV cohort, the percentage who were women, and the number of people who entered the reference cohort. The distribution of all other variables by which we stratified the cohorts in the analyses are shown in the online supplementary appendix table. Overall, the RR of MS in people with HIV, relative to those without HIV, was 0.38 (95% CI 0.15 to 0.79), based on 7 observed and 18.3 expected cases (table 2). Restricting the outcome to include only the people whose first record of MS, known to us, was more than a year after the first record of HIV, the RR was 0.25 (95% CI 0.07 to 0.65), based on 4 observed and 15.8 expected cases. Restricting the outcome to include only the people whose first record of MS was more than 5 years after the first record of HIV, the RR was 0.15 (95% CI<0.01 to 0.83), based on 1 observed and 6.7 expected cases (table 2).

Table 2 Observed (MS obs) and expected (MS exp) numbers of people in the HIV cohort who had a subsequent record of multiple sclerosis (MS), shown by age at entry to the HIV cohort and by time interval from the first HIV record to the first MS record; rate ratios and 95% CIs

Age at entry to HIV cohort (years)	Time interval (years)	MS obs	MS exp	RR (95% CI)
All	All	7	18.3	0.38 (0.15 to 0.79)
All	1+	4	15.8	0.25 (0.07 to 0.65)
All	5+	1	6.7	0.15 (<0.01 to 0.83)
<45	All	3	13.9	0.22 (0.04 to 0.63)

When confining the analysis to people whose ethnicity was recorded as White British, the RR was 0.37 (95% CI 0.08 to 1.08), based on 3 observed and 8.1 expected cases in the HIV cohort. When we confined the analysis to other ethnic groups, numbers were small. Furthermore, data on ethnicity were often recorded as 'not known' or not recorded at all. Combining all other specified ethnic groups, there were 1 observed and 6.8 expected MS cases in a cohort of 5353 people; where ethnicity was either recorded as 'not stated' or where ethnicity was not recorded at all, there were three observed and four expected cases in an HIV cohort of 10 849 people.

Sensitivity analyses

We repeated the analyses including the cases with MS on the first record of HIV or reference condition. The observed number of cases of MS in the HIV cohort rose to 10, the expected to 22.4, and the RR was 0.45 (0.21–0.82). We re-ran the analyses excluding people aged 70 and over from both cohorts in case the upper age groups, with fewer people, had any distorting effect. The RR was 0.34 (0.12–0.74), based on 6 observed and 17.7 expected cases.

DISCUSSION

Our findings are consistent with the national study in Denmark, but, crucially, given the size of the cohorts in the exposure as well as control groups in our study, the negative association between HIV and MS was statistically significant. If subsequent studies demonstrate there is a causal protective effect of HIV (and/or its treatment), and if the magnitude of it proves to be similar to our rate ratio of 0.38, this would be the largest protective effect of any factor, yet observed in relation to the development of MS. Previous studies have shown that factors such as smoking,[6–8] specific gene markers,[9 10] vitamin D deficiency[11 12] and many different viruses[13–16] increase the risk of either acquiring MS or of MS progressing, compared with controls. However, not having these risks may not be protective if the relative risk, compared with the general population, simply returned to 1.

There are several possible explanations for the observed association in our study.

First, immunodeficiency induced by HIV itself (even in the absence of antiretroviral treatment) may prevent development of MS. HIV impairs immune cell homoeostasis and targets a wide range of immune cells and signalling pathways overlapping with MS pathogenesis. Second, antiretroviral medications used to suppress HIV replication potentially may suppress other viral pathogens implicated in MS, for instance HERVs and herpes viruses.[17]

If having HIV is associated with a significantly lower risk of subsequent MS and the association is in the causal chain, it is either because of some biological effect of HIV itself on the pathogenesis of MS, or because the treatment for HIV are coincidentally also treating or preventing development of MS. Unfortunately, neither this study nor any study design that is feasible at present can prove which mechanism may be correct. However, we have made some reasonable assumptions, below, to assist in furthering this issue.

The pendulum of when to start HIV therapy has swung over the past two decades from early treatment, in order to preserve the remaining CD4 cells to later treatment, when it was observed that the CD4 counts recovered when HIV load was suppressed and now back to early treatment in the most recent WHO recommendations. As the exposure (HIV) cohort was determined during or after 1999, it is probable that the majority of patients would be taking highly active antiretroviral therapy (HAART), which started to become widely used in the UK after 1995. At that time, the trend in clinical management of patients with HIV was to recommend start of cART as early as possible[18] and therefore it is likely that most of the exposed cohort were taking antiretroviral therapies. This assumption is supported by the global meta-analysis of temporal trends in CD4 cell counts from 1992 to 2011 that determined the mean CD4 cell count among HIV-positive patients in the UK was around 300 cells/μL, which was during our period of observation, and this was a level at which it is most likely cART would have been started.[19] It is also probable that a number of patients were first identified as having HIV infection during the hospital admission when they entered the HES cohort. In order to further test the hypothesis that cART restricts the development of MS, we investigated the RR of MS cases in the exposed cohort relative to the reference cohort 1 and 5 years, after the initial admission for HIV or reference condition. These data revealed a further reduction in the RR from 0.38 (95% CI 0.15 to 0.79) overall, to 0.25 (95% CI 0.07 to 0.65; $p<0.005$) after 1 year, and 0.15 (95% CI<0.01 to 0.83; $p=0.04$) after 5 years. The overlapping CIs of these point estimates mean that these differences are not statistically significant. However, if the progressive decline in risk over time is real, a possible explanation is that during the first admission for HIV some patients were started on cART and the effect of cART on the risk of MS did not begin until an undetermined time period after discharge. Our data, indicating the possible protective effect of cART increases at least 1 year after the HIV indicator admission, may support this observation.

Strengths and weaknesses

Strengths of our study are that it is national, in a population of about 55 million and that we compared the exposed (HIV) cohort with a large number of controls. The very large number of controls per exposed person in each stratum (approximately 300:1), and the wide range of different control conditions, would dilute any single factor that may bias the comparison of the HIV and reference cohorts. The very large number of controls also allowed for precise calculation of the number of cases of MS expected in the HIV cohort. Given that the hypothesis is that there would be few cases of MS in the HIV cohort, precision in estimating the number of expected cases is particularly important. Weaknesses of this type of study are numerous. Data on ethnicity were sometimes missing. However, even though we did not have ethnicity data for every participant we demonstrated that the deficit appears not to be restricted to one ethnic group. Our results are consistent with the pattern of ethnicity of the HIV population in the UK, which is predominantly Caucasian men. We have assumed that the time intervals between the first record of HIV and the first record of MS, as known to us, are generally reliable, but we have no way of knowing this is absolutely certain.

We lack data on the proportion of the exposed population who were actually taking cART and the exact combination of drugs they may have been taking during the period of observation. We assume, from what is known about clinical practice during the 12 years of data collection, that the majority of HIV patients were probably either already on cART at the time of entering the exposed cohort or were started on cART if HIV was confirmed at the time of the first admission.

The ideal design for a study of the type reported would be a randomised controlled intervention study where HIV-positive patients are randomised to cART or no cART and followed to determine their risk of developing MS. Clearly, this study is not feasible. Another option would be to try and investigate what happened in the pre-cART time from 1981 when HIV was first described, until 1995, when cART was introduced. Unfortunately, this is also not possible as there are no cohorts large enough, in that era, to give a reasonable incidence of MS. Moreover, there is always a possibility of misdiagnosis. HIV infection may clinically present as MS-like symptoms with production of oligoclonal bands in cerebrospinal fluid indistinguishable from MS. In the pre-cART era, with no gadolinium-enhancing MRI available, patients with HIV who presented with MS-like symptoms would generally have been thought to have an HIV-related neurological condition rather than diagnosed as having MS. HIV itself may cause various diseases of the white matter, in addition to an opportunistic infection, such as progressive multifocal leukoencephalopathy. If, in reality, patients had MS, they would most likely have died before the MS would become apparent. When cART became available around 1995, any patients with HIV, presenting with MS-like symptoms, would be assumed to have an HIV neurological condition and immediately started on cART. If MS were the true underlying cause of their condition and their MS symptoms persisted even following cART, one would expect they would be diagnosed with MS, while their HIV was controlled.

The unresolved question is that after almost 20 years of available cART, why do there seem to be almost no documented cases of patients, in the literature so far, with coexisting MS and HIV? Given that both MS and HIV result affect the immune system, it is interesting to note that no pharmaceutical companies who produce therapies for either HIV or MS (no companies produce therapies for both HIV and MS) have guidelines on how to treat patients who have HIV and MS. In fact, medical and marketing personnel at companies that produce MS disease modifying treatments (DMTs) do not recall ever receiving an inquiry about how to use these DMTs in patients with HIV who are taking cART (personal communication).

Conclusion

This report is the largest record linkage study undertaken to investigate a possible association between HIV and MS. Our investigation revealed that having HIV, and presumptively being on HAART, provided a significant and potentially protective effect in relation to the risk of development of MS. The magnitude of this effect (>60%) is at the highest level of any prognostic risk factor investigated to date. Nonetheless, there are inevitable methodological uncertainties in our study design and our findings should be regarded as speculative rather than definitive. We have had to make reasonable assumptions about the likelihood of our exposed HIV cohort being treated with cART during the period of observation. Further consideration may also be warranted on conducting other proof-of-concept studies on using antiretroviral drugs in patients with different types of MS. The first clinical study with Raltegravir in patients with relapsing remitting MS is already recruiting in the UK.[20] Further investigation of our finding has the potential, after more than 170 years since MS was first described by Jean-Martin Charcot, to help reveal the aetiology of MS.

Contributors All authors fulfil the authorship requirements and have approved the final version of the manuscript. JG, HM and GG developed the research question. JG, RG, MG and DY developed the study design in consultation with the other authors. RG, MG and DY conducted the data preparation and data analysis. JG, RG, MG and HM wrote the first draft of the manuscript to which all authors made significant subsequent contributions. GG provided practical guiding in-put to the study as well as to the writing and review process.

Competing interests None.

Ethics approval Ethical approval for the construction and analysis of the linked data set was granted by the Central and South Bristol Research Ethics Committee (ref 04/Q2006/176).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional data can be generated from the HES database if requested.

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JOURNAL OF NEUROLOGY NEUROSURGERY & PSYCHIATRY

HIV infection linked to lower multiple sclerosis risk

Antiretroviral drugs and chronic immune system suppression might explain link

[HIV and lower risk of multiple sclerosis: beginning to unravel a mystery using a record-linked database study Online First doi 10.1136/jnnp-2014-307932]
And
[Does antiretroviral therapy for HIV reduce the risk of developing multiple sclerosis? Online First doi10.1136/jnnp-2014-308297] (Editorial)

HIV infection is linked to a significantly lower risk of developing multiple sclerosis (MS), indicates observational research published online in the ***Journal of Neurology Neurosurgery & Psychiatry***.

Chronic dampening down of the immune system as a result of the infection and/or the antiretroviral drugs used to treat it might explain this association, say the researchers.

If subsequently found to be causal, this could have considerable implications for the treatment of MS, they suggest.

Following the case of an HIV positive man with MS, whose MS symptoms disappeared for more than 12 years after antiretroviral treatment for his HIV infection, a Danish research team attempted to find out if antiretroviral drugs might treat or slow the progression of MS.

Their results suggested this might be a possibility, but the numbers were too small to reach statistical significance, prompting the current researchers to carry out a much larger comparative study.

They did this by looking at episodes of hospital care between 1999 and 2011 in England.

In all, more than 21,000 people infected with HIV were treated during this period, as were almost 5.3 million people treated for minor conditions or injuries, who acted as the comparison group.

The development of MS was tracked in all participants for seven years, with the actual number of cases arising compared with the number expected to have arisen in the population.

Compared with those who did not have HIV, those who did were 62% less likely to develop MS, based on seven actual diagnoses of MS during that period versus the 18 that would have been expected.

The degree of protection seemingly conferred by HIV increased the more time that elapsed between a diagnosis of HIV and one of MS, the analysis indicated.

After more than a year between the two diagnoses, HIV positive patients were 75% less likely to develop MS, based on four actual diagnoses versus the 16 that would have been expected.

And after more than five years this increased to 85%, based on one actual case versus the 6.5 that would have been expected.

The findings back those of the Danish authors, but with the crucial difference that the new findings are statistically significant, say the researchers.

They emphasise that their findings are speculative rather than definitive, because the study is observational, added to which they have no information on whether the HIV positive participants had taken antiretroviral drugs, or for how long.

But they write: “If subsequent studies demonstrate there is a causal protective effect of HIV and/or its treatment, and if the magnitude of it proves to be similar…this would be the largest protective effect of any factor yet observed in relation to the development of MS.”

HIV infection may itself stave off the development of MS, or it could be that antiretroviral drugs to dampen down the proliferation of the virus may also have the same effect on other viral agents implicated in the development of MS, they suggest.

In an accompanying editorial, Mia van der Kop, an epidemiologist at the University of British Columbia in Vancouver, Canada, says the findings add to the body of evidence pointing to a link between HIV, or its treatment, and MS.

“However, additional work is required to move beyond hypothesis generation,” she cautions.

Statistical appendix [for inclusion in paper] jnnp-2014-307932.R2

The method used, and software, was adapted from that designed by Richard Peto, Richard Doll and Martin Vessey in their Oxford-based cohort studies of women using different contraceptive methods.[1-3] In the contraceptive study (which ran from the 1970s to 2013, with the methods extensively tested and used)), the investigators compared women in different contraceptive user groups in strata of 4 age groups, 2 parity groups, 3 social class groups, and 3 smoking groups. With 17,032 subjects, and 72 strata (4x2x3x3), this gave an average of 236 people per stratum. In the present HIV/MS study we had 16,200 strata (18 ages, 2 sexes, 10 calendar years, 9 regions, 5 quintiles of deprivation) which, with 5,319,703 subjects, which gives an average of 328 people in each stratum (a greater number than in the original Doll/Peto study). Analyses were run using SAS (release 9.2, SAS Institute Inc., Cary, NC, USA).

The key numbers are those in the combined HIV and reference cohort (dominated numerically by the reference cohort). This is the 'standard population'. The stratum-specific rates in the standard population were applied to each equivalent stratum in, first, the HIV cohort and, second, the reference cohort. Taking the largest HIV age stratum (aged 35-39), subdivided into an additional 900 strata (2 sexes x 10 years x 9 regions x 5 deprivation quintiles), the analysis was based on 449,754 people (average 500 people per stratum); taking the smallest (aged 80-84), the analysis was based on 282,955 people (average 314 people per stratum). Some strata in the standard population will have no people in the stratum: the stratum contributes nothing to either the expected number or (by definition) to the observed number. Rates in strata in the standard cohort that include numbers will give a tiny stratum-specific rate. We calculate this to a very large number of significant digits – up to 16, when 16 is arithmetically possible - to ensure that the sum of the rates is very exact. Summing across all strata gives an expected number (e.g. 18.3 cases of MS in the HIV cohort in the main calculation in the manuscript). The observed number – 7 – is simply the overall count in the HIV cohort and is unmodified by any of the stratification and standardising procedures or calculations.

We always run each individual condition in the reference cohort against all others combined. In the HIV/MS analysis, for example, the appendicitis sub-cohort, run for MS as an outcome, compared with all other conditions in the reference cohort combined, has a rate ratio (RR) for MS of 1.01; the cohort of people with internal derangement of the knee has a RR for MS of 1.02; bunion is 0.97; contraceptive management is 0.92; gall bladder disease is 1.08; inguinal hernia is 0.91. In other words, the stratified analyses show that there is neither any important increase nor decrease in the risk of MS in these sub-cohorts. This indicates that the method works in cohorts where there is no reason to expect an increased or decreased risk of MS. It gives rates that approximate to 1, where 1 is expected.

We considered the possibility that there could be a distorting effect in using strata with relatively small numbers of cases in the HIV cohort. We therefore ran the analyses again excluding people aged over 70 (table 1 in the manuscript). In this "sensitivity" analysis the number of observed cases of MS in people less than 70 years old was 6, the number expected was 17.7, and the rate ratio was 0.34 (95% CI 0.12 to 0.74).

[1]Vessey M. Doll R, Peto R, Johnson B, Wiggins P. A long-term follow-up study of women using different methods of contraception – an interim report. Journal of Biosocial Science 1976, 8(4): 373-427 (see Appendix 2)

[2] Vessey MP, Villard-Mackintosh L, McPherson K, Yeates D. Mortality among oral contraceptive users: 20 year follow up of women in a cohort study. BMJ 1989, 299: 1487-1491.

[3]Vessey M, Yeates D. Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study. Contraception 2013, 88 (6): 678-683.

Appendix table: distribution of the HIV cohort and reference cohort, by age, sex, year of cohort entry, Government office region of residence, and IMD score in quintiles

	HIV cohort		Reference cohort	
Age (years)	**N**	**% of total**	**N**	**% of total**
0-4	139	0.7	112355	2.1
5-9	168	0.8	145618	2.7
10-14	138	0.7	113372	2.1
15-19	173	0.8	166198	3.1
20-24	653	3.1	200079	3.8
25-29	2136	10.1	264771	5
30-34	4066	19.2	377462	7.1
35-39	4792	22.6	444962	8.4
40-44	3701	17.5	390356	7.4
45-49	2228	10.5	329573	6.2
50-54	1293	6.1	345117	6.5
55-59	776	3.7	375702	7.1
60-64	480	2.3	377503	7.1
65-69	274	1.3	387109	7.3
70-74	98	0.5	397229	7.5
75-79	37	0.2	385998	7.3
80-84	22	0.1	282933	5.3
85+	33	0.2	202159	3.8
Sex				
Male	14799	69.8	2667741	50.3
Female	6408	30.2	2630755	49.7
Year of cohort entry				
1999	2355	11.1	629145	11.9
2000	1650	7.8	580046	10.9
2001	1509	7.1	541347	10.2
2002	1946	9.2	530489	10
2003	2097	9.9	539918	10.2
2004	2454	11.6	527297	10
2005	2471	11.7	496994	9.4
2006	2798	13.2	472465	8.9
2007	2889	13.6	484195	9.1
2008	1038	4.9	496600	9.4
Government office region of residence				
North East	604	2.8	336934	6.4
North West	2177	10.3	813517	15.4
Yorshire and The Humber	1043	4.9	550812	10.4
East Midlands	530	2.5	423886	8

West Midlands	1050	5	566552	10.7
East of England	1062	5	576729	10.9
London	11771	55.5	610704	11.5
South East	2138	10.1	799742	15.1
South West	832	3.9	619620	11.7
IMD score				
I	1215	5.7	762286	14.4
II	1674	7.9	871938	16.5
III	1908	9	862085	16.3
IV	4901	23.1	1108249	20.9
V	11509	54.3	1693938	32
Total	21207	100	5298496	100