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# Outbreaks of a Presumed Infectious Agent Associated with Changes in Fertility, Stillbirth, Congenital Abnormalities and the Gender Ratio at Birth

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***Author's contribution***

*Author RPJ is the sole author and conducted all analysis and wrote the paper.*

***Article Information***

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## ABSTRACT

**Aims:** To investigate changes in the gender ratio (M/F) at birth, fertility and stillbirth rates in England and Wales.
**Study Design:** Analysis of average GR (1974-2010) for 570 UK local government areas. Re-analysis of average GR for births in the UK (2007-2014), by place of birth of the mother. Trend analysis of monthly births and stillbirths. Analysis of annual births (2001-2014) with small area data aggregated to 74 social groups.
**Place and Duration of Study:** England and Wales, 1974 to 2015.
**Methodology:** Average GR ±95% CI over a 35-year period in local government areas, role of population density and deprivation. Analysis of year-to-year volatility in the GR. GR by place of birth of the mother re-analyzed by proportion of countries outside an assumed Poisson distribution. A running 12-month total of monthly births or year-to-year differences in annual male and female births in 181,408 small areas.
**Results:** No evidence for an overall change in the GR between 1974 and 2010. Average GR ranges from 1.004 ± 0.021 in Bridgnorth (Shropshire) to 1.108±0.032 in Maldon (Essex). High population density and levels of deprivation, act to reduce the GR. Country of birth of the mother

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leads to instances of higher or lower than average GR. Low levels of nuclear radiation are associated with higher GR. Year-to-year volatility in the GR is independent of the average GR and is not influenced by population density or deprivation. After adjusting for size the average volatility ranges from ± 2.28% in Brighton to ± 10.06% in Nottingham, i.e. both average GR and the volatility are independently influenced by the local environment. The running 12-month total (moving total) of births reveals a series of events where the fertility rate suddenly jumps stays high for around 12 months, and then suddenly reverts to the baseline. The GR also jumps to a higher level, as does the stillbirth rate. Mini-outbreaks of a presumed infectious agent can occur at any time, but appear to cluster at certain times to create larger national events. Different social groups show higher levels of penetration and magnitude of the increase in births or change in the gender ratio. Preliminary analysis of increased hospital admissions associated with these outbreaks reveal increases in a range of conditions affecting reproduction, pregnancy, neonates and specific types of congenital malformation.

**Conclusion:** The GR is sensitive to place of birth of the mother, population density, deprivation, location and social group. Year-to-year volatility in the GR is location and social group specific. Fertility rate, gender ratio and stillbirth rate respond to outbreaks of a presumed infectious agent. Fertility, GR and stillbirths all stay high for around 12-months before reverting to baseline. Social behaviors play a role in the magnitude of the effect. The increased fertility rate associated with these outbreaks has capacity implications for maternity units. It is likely that the proposed agent exerts its effect in the period 2 to 15 weeks after conception when female fetal mortality is highest. The primary effect of the proposed agent is likely to be via immune manipulation. A potential role for the immune modifying virus, cytomegalovirus, is discussed.

*Keywords: Fertility rate; gender ratio; infection; cytomegalovirus; immune function; congenital malformations; trend analysis; environmental volatility; syndemics.*

## ABBREVIATIONS

*CMV : Cytomegalovirus*
*GR : Gender Ratio (M/F)*
*LOAC : London Output Area Classification, an OAC specific to London*
*OA : Output Area, a small spatial unit containing around 300 people of similar social characteristics*
*OAC : Output Area Classification, a social group classification derived from census data*
*ONS : Office for National Statistics*
*SD : Standard Deviation*
*STDEV : Standard Deviation Equivalents, difference between two years converted to STDEV*

## 1. INTRODUCTION

Trends in the gender ratio at birth are one of those enigmatic areas in which a multitude of factors appear to play a role [reviewed in 1]. Fig. 1 gives an example of this complexity for the ratio of male to female births in Scotland between 1855 and 2016. There is a minimum around 1905 to 1915, and a set of long-term cycles which appear to interact with a set of short-term cycles, with 2016 appearing to set an all-time high. As with most studies on the gender ratio the data uses calendar year totals, and it is conceivable that such calendar year totals may be acting to conceal the true nature and extent of the shorter-term cycles.

Evidence has now emerged for the existence of outbreaks of a novel (presumed) pathogen which is not only able to alter the gender ratio, but also increase deaths, emergency department attendances, medical admissions (mainly in the elderly), NHS staff sickness absence rates, GP referral for outpatient attendance, and the ratio of follow-up to first attendances [see reviews 2-9].

The novel aspect of these outbreaks is that all the above measures of human health simultaneously jump together, stay high for 12-months, and then suddenly revert to baseline, i.e. on/off or high/low switching. This behavior has been documented outside of the UK [8,10-11], is associated with very small-area transmission of the agent [12-20], and shows single-year-of-age patterns in severity [21]. The sudden shifts to higher deaths and medical admissions are alarmingly high [11-22], and can be traced back to the 1950s [23]. While not confined to in-hospital mortality [24], they are sufficient to distort the calculation of both raw and standardized hospital mortality rates [25,26].

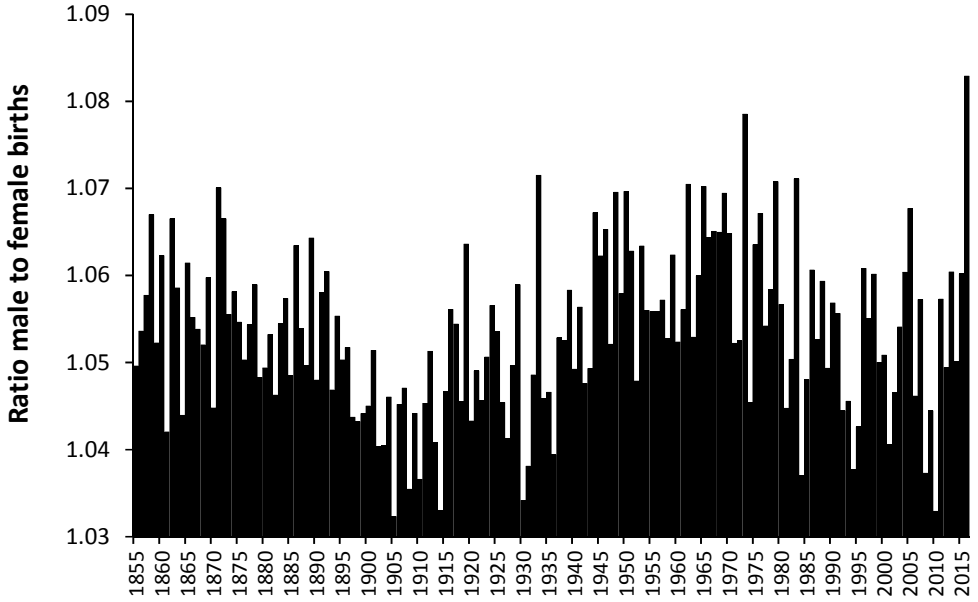


**Fig. 1. Gender ratio (Male/Female) in Scotland, 1855 to 2016**
*Data from National Records of Scotland. 2016 is for first three quarters*

Based on the range of medical conditions associated with higher medical admissions and deaths it has been suggested that the ubiquitous and immune modifying virus, cytomegalovirus (CMV), may be in some way involved [5,6,9,27-30].

CMV can infect almost all cell types in both male and female genital tracts [31], is present in semen [31], vaginal lavage [32], can infect sperm and spermatogenic cells [31,33]. Shedding of CMV in female cervicovaginal lavage and male semen increases with markers of a poor immune function [32,34], although prolonged shedding can occur in seemingly 'healthy' adults and children [35]. CMV is a known cause of adverse outcomes during pregnancy such as spontaneous abortion and stillbirth [36-40], and neurological and other complications in infants infected during pregnancy [36]. In addition, there is a prodigious set of immune manipulations and associated enhancements to disease expression [3,5,6,9,27-30,41,42,43].

This study will firstly examine the evidence that the GR in the UK can show statistically significant differences by location, population density, deprivation, and place of birth of the mother. These supporting studies are presented in the Appendix. Having established the broad principles specifically applicable to births in the UK, the main document will examine the evidence for outbreaks of a novel (presumed infectious) agent using very small area data, and the potential effects against the fertility rate and GR. Implications to the level of congenital malformations will also be discussed.

## 2. DATA AND METHODS

### 2.1 Gender Ratio in UK Local Government Areas

Annual (calendar year) counts of live births by gender were obtained across all parts of the UK. Those for England and Wales from the Office of National Statistics, for Scotland from the National Records of Scotlan0, and for Northern Ireland from the Northern Ireland Statistics and Research Agency. A total of 560 local authority, county, regional and country-based geographies were available of which 399 (72%), mainly from England and Wales, covered the entire 40-year time span, 106 (20%) locations mainly in Northern Ireland and Scotland had 20-22 years of data while the remaining 8% (locations with major boundary changes) had either 12-18 or 23-32 years of data.

The volatility, i.e. year-to-year difference in the gender ratio (male/female), was calculated as a percentage difference. Both the standard deviation and average of the volatility were

calculated. Births were taken as the minimum number of births in each location over the available years. All calculated values for the standard deviation or volatility were adjusted to that for a full 37 years, i.e. observed value multiplied by the square root of (n-1)/(37-1), where n = number of years where data is available. This calculation will apply to the 28% of locations where fewer years data was available.

Population density (UV02) was obtained from the Neighborhood Statistics website, and was available for 405 geographical areas in England and Wales, while the Index of Multiple Deprivation (IMD 2011) was obtained from the gov.uk website, and was available for 418 local authority areas in England. For the small area analysis (2001 to 2014) IMD 2015 was obtained for all OA in England and Wales form the Office for National Statistics.

The average volatility for 37 data points was calculated assuming male or female births were essentially a Poisson distribution, i.e. integer values distributed about an average. Hence for (say) 1,000 births that basic unit would be approximately 500 male or female births. The standard deviation of a Poisson distribution is defined as equal to the square root of the average. The relationship between the standard deviation and year-to-year volatility was obtained by linear regression. For the 560 locations using averages derived from 37 data points the volatility was 1.1292 times the standard deviation. This analysis can be found in Section A1 of the Appendix.

### 2.2 Country of Birth of the Mother and Gender Ratio of Births in the UK

Data was extracted from a Department of Health Report on the Gender Ratio [44]. This data was re-analyzed assuming the GR by country of birth of the mother, in the absence of environmental effects, should follow a Poisson distribution. Proportion of countries lying ±1 or ±2 standard deviation from the average were compared to the proportion expected from a Poisson distribution. This analysis can be found in Section A2 of the Appendix.

### 2.3 Running (Moving) 12-month Total of Male and Female Births in England and Wales (1980-2015)

Monthly counts of male and female live births in England and Wales were obtained from the Office for National Statistics (January 1980 to August 2015). A running 12-month total (or moving total) of births and the gender ratio was calculated from this monthly data. This data is used in Figs. 2 and 3, and in Table 1.

### 2.4 Very Small Area Birth Data and Presumed Infectious Outbreaks (2001-2014)

Annual counts of male and female live births for occurring in 181,408 output areas within England and Wales were obtained by request from the Office for National Statistics. In 2011 each output area (OA) contained an average of 129 households and 309 persons [45].

A social group classification, called the output area classification (OAC), is available for each OA and is based on data collected during the 2011 census [46]. The OAC for each OA was also obtained from the Office for National Statistics. Other measures such as population density and the Index of Multiple Deprivation (IMD) were also obtained from the Office for National Statistics.

As with previous small-area studies on deaths and medical admissions, the volatility in both male and female births between successive years within each OA was converted into standard deviation equivalents (STDEV) or percentage differences using the formula (n2 – n1)/square root (average births), or (n2-n1)/average births (n), see [11-13,15-16,18-20].

### 2.5 Monthly and Annual Data on Stillbirths

Monthly data relating to stillbirths between 1993 and 2015 was obtained from the ONS. This data was analyzed using the methods applicable to running (moving) 12-moth totals. The ONS also supplied annual data on stillbirths between 2012 and 2014 for the population covered by English Clinical Commissioning Groups and Welsh Health Boards. This data was analyzed using the methods for year-on-year differences.

## 3. RESULTS AND DISCUSSION

### 3.1 Trend in Monthly Male/Female Births (1980 to 2015)

Most studies on the GR use calendar year totals to avoid undue scatter arising from smaller monthly data [47]. However, a running (or

moving) 12-month total provides additional insight which will be missed in calendar year totals.

For example, a series of on/off or up/down movements in the data will show up as saw-tooth features in the running (moving) total. The base of the saw-tooth marks the onset of a sudden increase in births, while the point 12-months on reveals the magnitude of the sudden step-like change, as does the slope of the saw-tooth face. A sudden shift back to lower births generates a downward face to the saw-tooth.

This behavior is illustrated in Fig. 2 where the two large peaks, commencing in 1983 and 2002, arise out of the World War II baby boom as each successive cohort reaches child bearing age, i.e. approximately 21 years apart. The height of the most recent peak was exaggerated by inward immigration from the European Union Accession 8 countries (commencing in May 2004), plus an influx of refugees and economic migrants.

However, note the smaller saw-tooth features which occur during the proposed outbreaks of the agent, but are displaced by around 9 months due to the gestation period. For example, the 1993 outbreak commenced early in 1993 [8,23], but the corresponding step-up in births starts around August 1993. In the absence of a knowledge of the existence of the proposed outbreaks the significance of these small saw-tooth features would be missed.

The two larger peaks arising from the WW II baby boom have the potential to hide some of the saw-tooth features, and the overall trend was linearized by subtracting the slope of a simple linear regression line applied to each of the WWII cohorts in both the upward and downward parts of the trend. This process of linearization allows the magnitude of the increased fertility rate during each outbreak to be estimated. For example, the 2003/04 outbreak is largely obscured as a shoulder on the unadjusted trend. These estimates are presented in Table 1.

As can be seen the fertility rate for male babies increases from somewhere between 2.1% to 3.7% depending on the year of the event, while that for female babies increases by around 1.4% to 3.5%. Up to the present, such small increases in the fertility rate would have gone either unnoticed or else been explained away as a statistical blip.

**Table 1. Estimates of the increase in fertility rates after adjusting for the background WWII baby boom effects, England and Wales**

| Event | Male | Female |
|---|---|---|
| 1980/81 | >2.5% | 2.50% |
| 1982/83 | 2.10% | 1.90% |
| 1984/85 | 2.57% | 2.24% |
| 1986/87 | 2.90% | 2.55% |
| 1991/92 | 2.68% | 2.42% |
| 1993/94 | 2.20% | 1.88% |
| 1996/97 | 3.74% | 3.51% |
| 2003/04 | >2.4% | 2.40% |
| 2007/08 | >2.35% | 2.35% |
| 2010/11 | 2.15% | 1.38% |

Hence while the two lines in Fig. 2 may appear to remain parallel, there are additional subtle shifts in the gender ratio which arise from the slightly higher fertility rate increase for males.

This is illustrated in Fig. 3 where a corresponding step-up and down in the gender ratio aligns with the saw-tooth features in Fig. 2, except that Fig. 3 has been adjusted for the gestation period.

All such behavior aligns with similar patterns in deaths, medical admissions, emergency department attendances and NHS staff sickness absence, along with age-specific and case-mix changes [2-30,48]. Note the period in 1987 where the GR rises in response to the Chernobyl nuclear accident [1]. Hence, apart from the known effects of low levels of ionizing radiation on the GR [1,49-50], outbreaks of the proposed infectious agent appear to be the major factor regulating changes in the GR throughout 1980 to 2015.

Finally, it must be remembered that the analysis in this section is of the apparent trends for the whole of England and Wales. It is now known that these events occur at small-area level and then aggregate up to the larger national events [12-20]. The next section will attempt to shed further light on these events using small-area data.

## 3.2 Small-area Studies on Calendar Year Births (2001 to 2014)

This section examines some 8.97 million births over a 14-year period occurring in 171,045 OA in which a birth occurred (no births were reported in around 6% of OA).

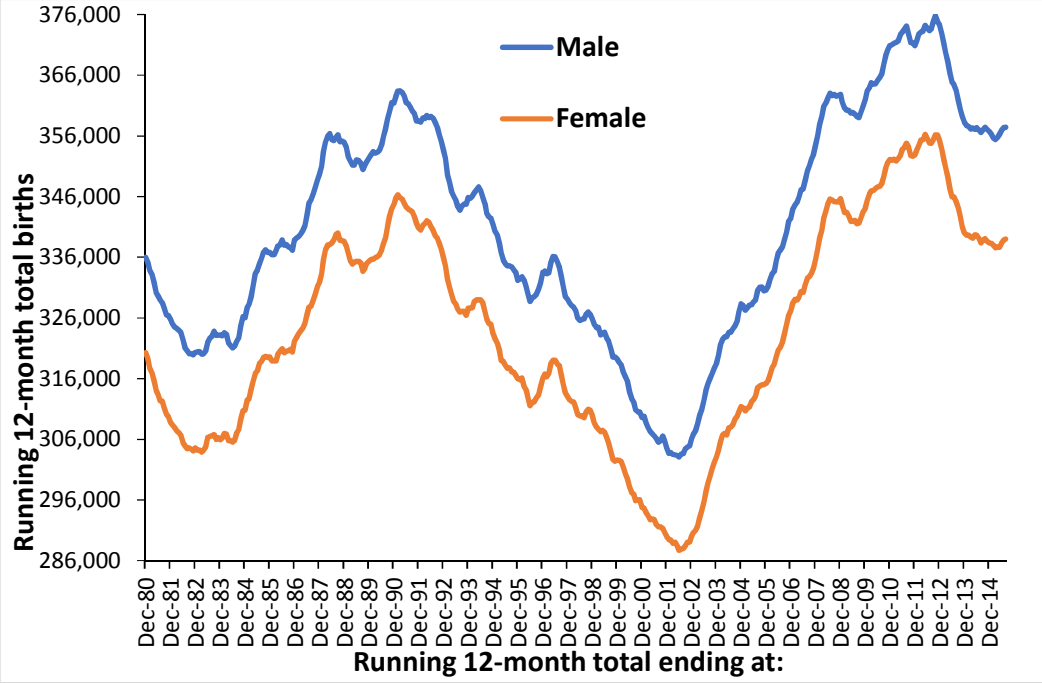


**Fig. 2. Trend in male and female births in England and Wales as a running (moving) 12-month total**

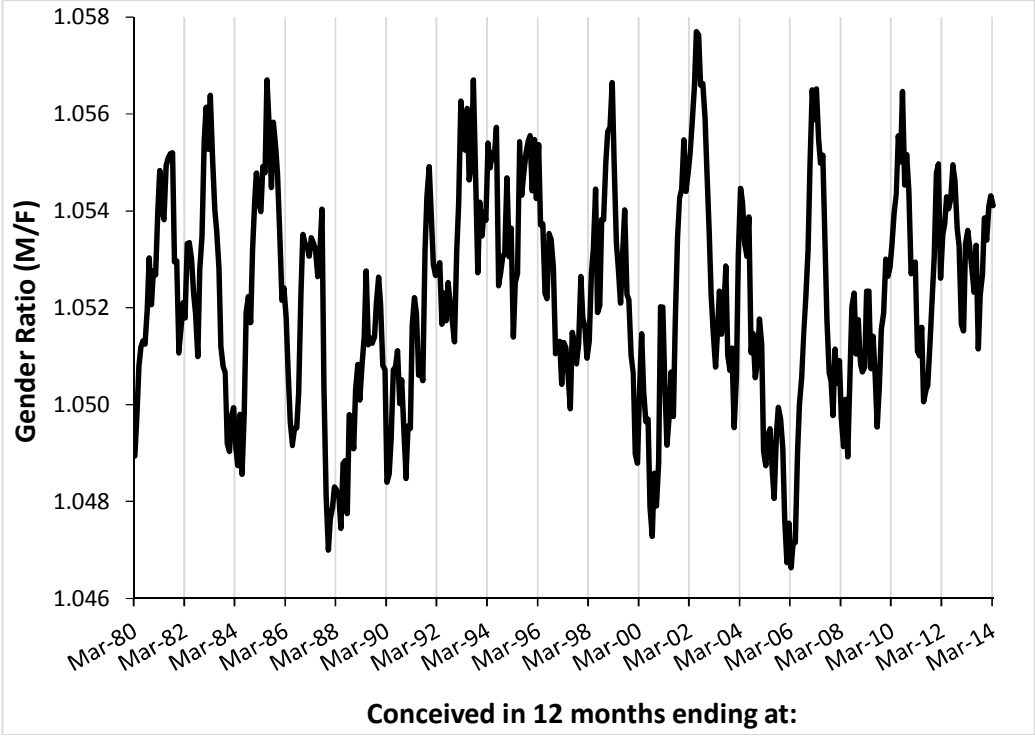


**Fig. 3. Changes in the gender ratio at conception in England and Wales**

If the infectious agent can achieve initiation at any point in the year, and to then remain active for a further 12 months, it follows that a series of year-to-year comparisons may fail to identify an outbreak which occurs toward the middle of the year. However, this key limitation is addressed by having access to both male and female births covering more than 171,000 OA over a 14-year period, i.e. covering seven potential outbreaks in each OA. Therefore, a large outbreak of the agent is likely to occur at least once, with initiation toward the start/end of a year in each OA. Also, the magnitude of events initiating closer to the end or start of a calendar year may be slightly under estimated, therefore, both calculated magnitude and frequency will be conservative.

The use of very small area data has the disadvantage that even annual numbers of births are small. However, given the previous small area studies using both deaths and medical admissions [12-20], and the wider international evidence for these events [8-11], it is still possible to look for statistically significant changes in births from one year to the next. This approach is greatly facilitated by transforming all differences into standard deviation (STDEV) equivalents based on the role of Poisson statistics in such whole number events. Rather than apply a strict dichotomous approach of significant/not significant, a more nuanced approach investigates counts of changes which exceed a +2 STDEV difference.

For example, Table 2 lists a count of all OA where the number of male or female births in each year compared to the previous exceeds certain Poisson thresholds. While >1 is not used in this study since it is likely to contain a degree of chance-based occurrences, it is of interest to note that the high years in the count of >1 (after making allowance for the nine-month lag due to gestation), are those where a national-level outbreak of the agent has been observed.

**Table 2. Count of output area where male or female births compared to the previous year exceed certain statistical thresholds (STDEV equivalents)**

| Year | Change between years exceeds STDEV | | | | | |
|---|---|---|---|---|---|---|
| | >1 | >2 | >3 | >4 | >5 | >6 |
| 2002 | 72,081 | 22,747 | 5,150 | 835 | 136 | 26 |
| 2003 | 76,812 | 25,001 | 5,661 | 926 | 145 | 17 |
| 2004 | 76,766 | 25,279 | 6,002 | 1,001 | 136 | 13 |
| 2005 | 75,994 | 24,911 | 5,657 | 921 | 135 | 14 |
| 2006 | 79,708 | 26,895 | 6,285 | 1,013 | 158 | 20 |
| 2007 | 80,291 | 27,767 | 6,674 | 1,162 | 144 | 11 |
| 2008 | 81,578 | 28,399 | 7,082 | 1,254 | 189 | 18 |
| 2009 | 79,282 | 27,423 | 6,891 | 1,254 | 184 | 23 |
| 2010 | 82,158 | 29,098 | 7,358 | 1,342 | 211 | 19 |
| 2011 | 80,191 | 28,708 | 7,440 | 1,410 | 243 | 36 |
| 2012 | 80,630 | 28,842 | 7,562 | 1,571 | 283 | 44 |
| 2013 | 75,028 | 25,691 | 6,684 | 1,291 | 265 | 54 |
| 2014 | 77,717 | 27,174 | 7,055 | 1,425 | 307 | 71 |

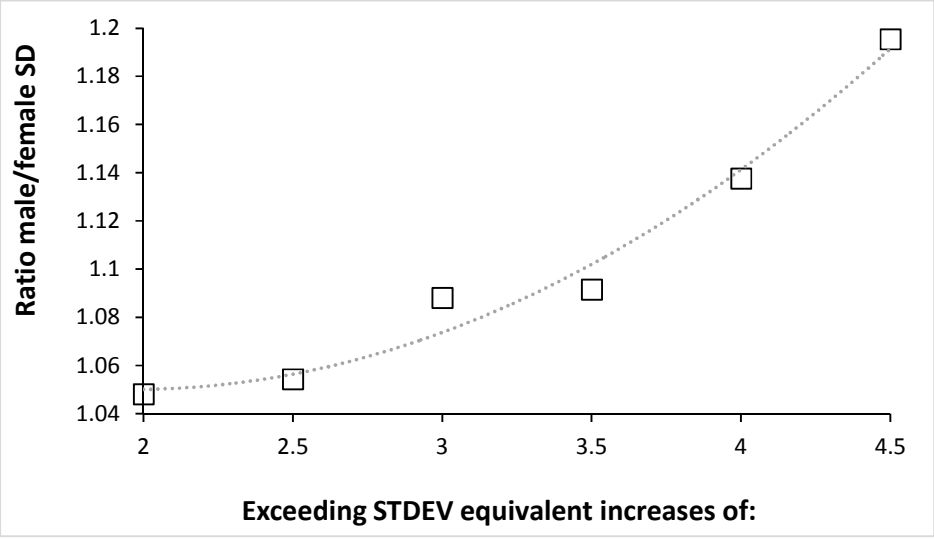


**Fig. 4. Ratio of inter year male to female standard deviation (2002 to 2014) associated with variation in the count of output areas exceeding STDEV equivalent changes in births**

From Figs. 2 and 3 and Table 1 the larger increase in male births during these events should lead to a higher calculated standard deviation across the years 2002 to 2014 for males compared to females. Fig. 4 therefore explores the ratio of male to female standard deviation of the counts of OA exceeding certain statistical thresholds. As can be seen male births show higher volatility (as measured by the SD) which increases as statistical significance (as STDEV equivalent) increases. The observed behavior at national level is therefore replicated at small area level.

Fig. 5 explores the maximum step-change in each OA observed over the period 2002 to 2014. As can be seen the percentage increase is slightly higher for males, and increases with reducing number of births. This same log-log behavior has been observed with deaths and medical admissions [10-20]. The striations in Fig. 5 arise from the fact that deaths are integer values. Each striation represents higher statistical significance.

Recall that Fig. 5 gives the maximum increase in each OA over the 14-year period, i.e. it is a measure of maximum potential which may only occur at a frequency of 1 in 14.

This log-log behavior has been explained by reference to transmission of the agent along social networks. In a single small social network, very large (potential) increases in the fertility rate for one female are possible if she places herself in the position where she could fall pregnant. As the size and number of social networks increase (more births per OA) there is the possibility of mixed outcomes within the various social networks both in terms of the time at which the individual is infected and subsequently falls pregnant, and of a range of increases in fertility up to the maximum possible (at a frequency of 1 in 14). This behavior can be replicated using a simulation [17], and roughly similar percentage increases are observed for both deaths and medical admissions [10-20].

Hence by the time the spatial unit contains an average of 100 births per annum the observed increase in the overall fertility rate for that whole spatial unit will be around +10% (range 2% to 25%). The implications of this finding to understanding demand surges and required capacity in maternity units is discussed in the next section.

### 3.3 Implications to Demand and Capacity in Maternity Units

Table 1 quantified step-changes in maternity demand arising from outbreaks of the agent at national level. However, small-area spread of the agent is known to produce highly granular effects in sub-national geographies, and this was quantified in Fig. 5. Fig. 6 supplements the national data (from Table 1) with those covering aggregates of smaller areas over a range of years. OA were added together in a random fashion to give total births around 1,000 and 10,000 per annum, and the magnitude of the step-increase was then calculated for these larger aggregates of OA. As can be seen a maternity unit dealing with 1,000 births per annum could experience a local surge in demand from 6% to 14%, while a unit dealing with 10,000 births would experience a 4% to 9% surge in demand. These surges, which can start at any point in the year, will endure for 12 months before reverting to baseline.

Up to the present these surges have gone largely undetected since they will lie concealed within calendar or financial year totals. In addition, absence of any mechanistic explanation will then lead to the effect being ignored as a blip.

Note that Fig. 6 also describes the effect of size on the increase in the local fertility rate arising from the outbreaks. Fig. 6 is merely a continuation of Fig. 5 which has already shown the maximum magnitude of the increase in fertility achievable in very small areas.

### 3.4 Role of Social Group

It is highly likely that the hygiene, sexual and socio-cultural behaviors of different social groups would render them more/less susceptible to infection with the proposed agent and subsequent fertility and gender alteration. These issues will be explored in this section using the Output Area Classification (OAC). Appendix A3 lists the counts of births in all OAC social groups in England and Wales along with number of OA in each social group, average values for deprivation, population density, and distance North, i.e. some social groups are more prevalent in the prosperous South of England while others are more frequent in Northern locations.

While Fig. 5 gave the maximum step-change in births in each OA (excluding changes less than +

2 STDEV equivalent), Fig. 7 explores the possibility that some social groups may contain higher proportions of OA with less than a 2 STDEV increase. Groups with a high proportion of not statistically significant changes are more likely to exhibit behaviors which limit the spread of the agent.

There is a clear gradient between social groups. Note that all social Groups 1 (Rural Tenants) and 6 (Suburbanites) lie in the right-hand tail, i.e. they tend to a high proportion of OAs with less than a 2 STDEV maximum increase. Social groups in the left-hand tail tend to live in the inner-city or cities where social groups are more tightly located, however, population density *per se* is not involved, i.e. it is the social and personal contacts which determine transmission.

Table A4 in the Appendix gives the maximum increase in births for each social group, along with the year in which the maximum increase occurred. Regarding year of maximum increase, it has been noted that males and females appear to act as separate compartments during these outbreaks, with either gender lagging behind the other [19]. Hence while the maximum male/female increase can occur in the same year, the maximum for each gender can occur years apart.

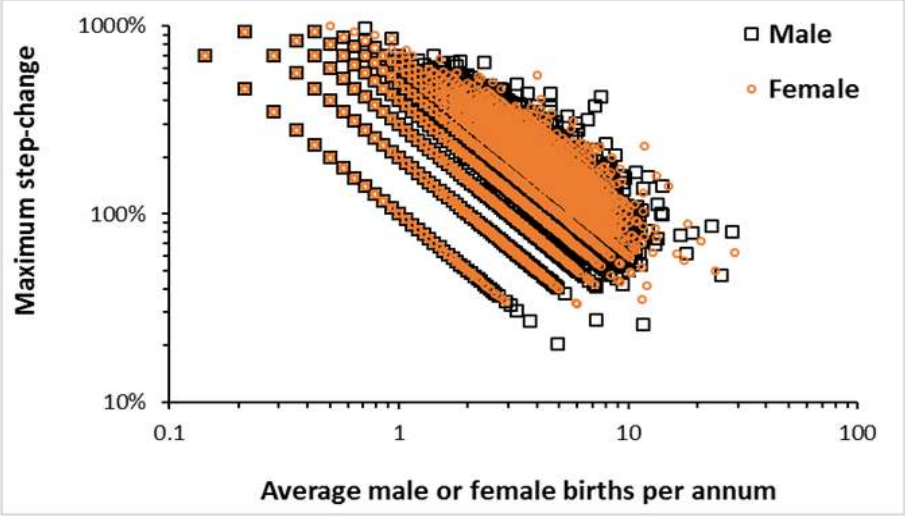


**Fig. 5. Maximum step-change in births in each OA (excluding OA below +2 STDEV)**

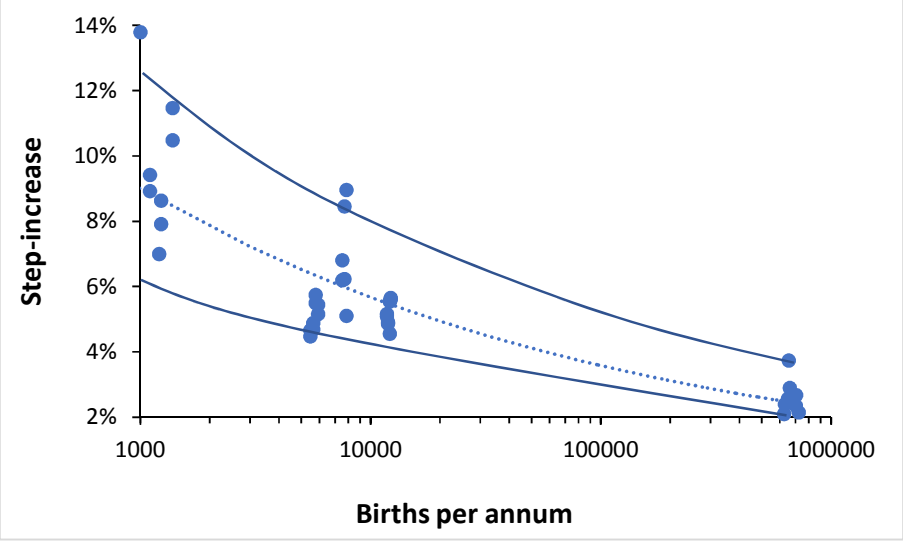


**Fig. 6. Effect of local outbreaks on surges in demand at maternity units**
*Data at national level (Table 1) is at the far right hand side*

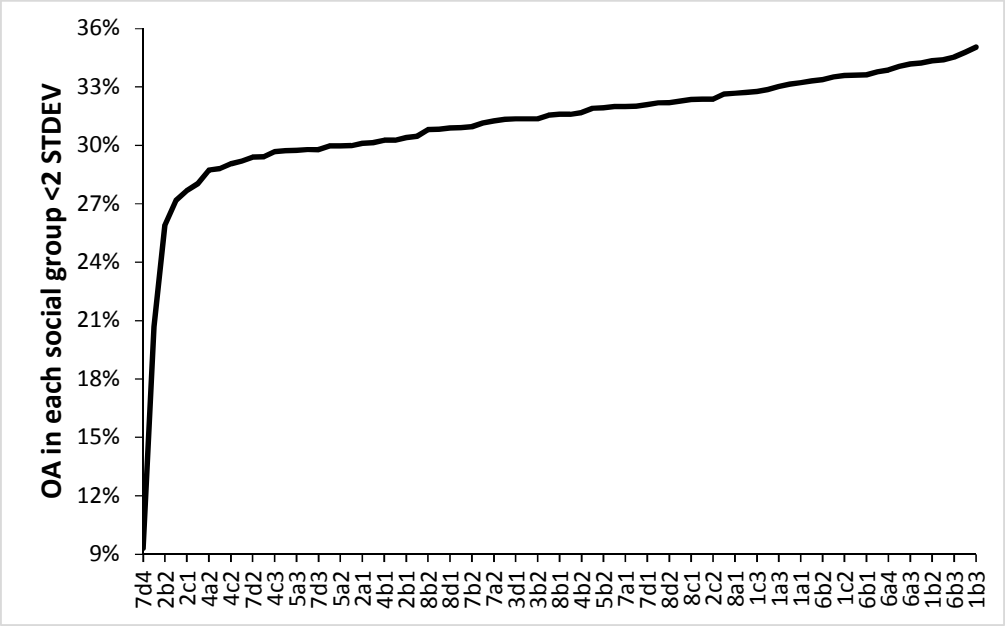


**Fig. 7. Proportion of output areas (OA) in each social group which have a maximum step-increase below 2 STDEV equivalents**

Social factors therefore play an important role in transmission of the agent.

### 3.5 Factors Affecting the Average GR

Data from Table A4 relating to the average GR in each social group is presented in Fig. 8 with GR ranging from 1.025 to 1.075 (excluding any social group with less than 900 male births). This can be compared to data at local government level in Appendix A1. Average GR at local government level ranges from 1.004 ± 0.021 in Bridgnorth (Shropshire) to 1.108 ± 0.032 in Maldon (Essex).

Most local government areas will be rich in particular social groups, however, the wider range in GR at local government area suggests that additional climatic or location-specific factors may be involved.

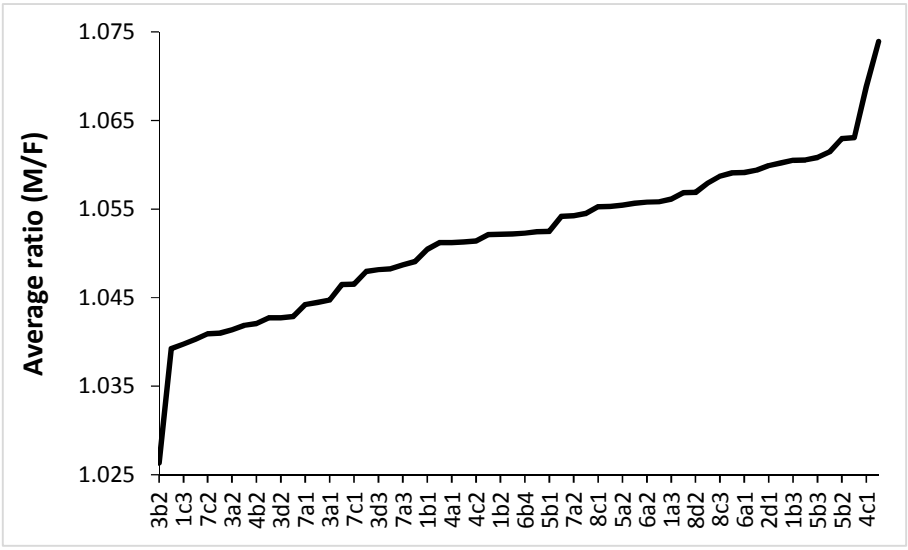


**Fig. 8. Average gender ratio (2001-2014) for various social groups**
*Social groups with less than 900 male births are excluded*

In this respect, Fig. 9 aggregates OAs by the Index of Multiple Deprivation (IMD) where least deprived areas (more affluent) have higher gender ratios. Note that only 1.6% and 0.2% of births occur above IMD 70 and 80 respectively, while 24.3% occur at IMD less than 10. The relationship is probably non-linear as is also the case for average IMD at local government level in Fig. A2 in the Appendix. While Table A3 demonstrated that social groups have different average values of IMD, both social group and specific OA deprivation may interact.

Data at local government level (Appendix A1) appears to support the notion that the GR is highest at very low population density, somewhat intermediate across other densities and then moving lower at high population density. Fig. 10 explores the possibility that OA population density may play a role. Note that 76% of births occur in the <100 persons per hectare band, while only 0.09% of births occur in the >1,000 persons per hectare bands.

There is a small gradient in GR with highest average GR at low population density, going through a minimum at around 500-1,000 persons per hectare. The GR for population density <50 persons per hectare is the same as <100.

The right-hand side of Fig. 10 is marked by abnormal values of GR and is difficult to interpret due to low numbers of births, i.e. only 3,986 births above 1,000 persons per hectare and 3,452 for the band 1,000 to 2,000. From Fig. A4 in the Appendix it is evident that a value of 1.1 can arise from chance, hence, in the absence of a larger data set we must conclude that there is a small gradient in the GR with population density, although this could arise due to the different social groups inhabiting rural versus town or city.

There was little evidence for the role of latitude on the GR, except in the most southern 100 km (1.059 compared to 1.052 in the rest of the country). The figure of 1.059 is reliable (>400,000 births).The most southern part of the UK (Cornwall) benefits from higher average temperatures and hours of sunlight due to the moderating effect of the gulf stream. However, it also experiences the highest levels of radon exposure in the UK, see https://www.gov.uk/government/collections/radon. Radon is a radioactive gas released from the breakdown of natural uranium in rocks and soil. Refer to Section 3.8 and Appendix A2 for a discussion of the role of low levels of radiation on the GR.

In conclusion, a combination of social, location (climatic, background radiation), racial and deprivation factors seemingly interact to determine the average GR gradients seen across the UK. The role of country of birth of the mother is addressed in Appendix A2.

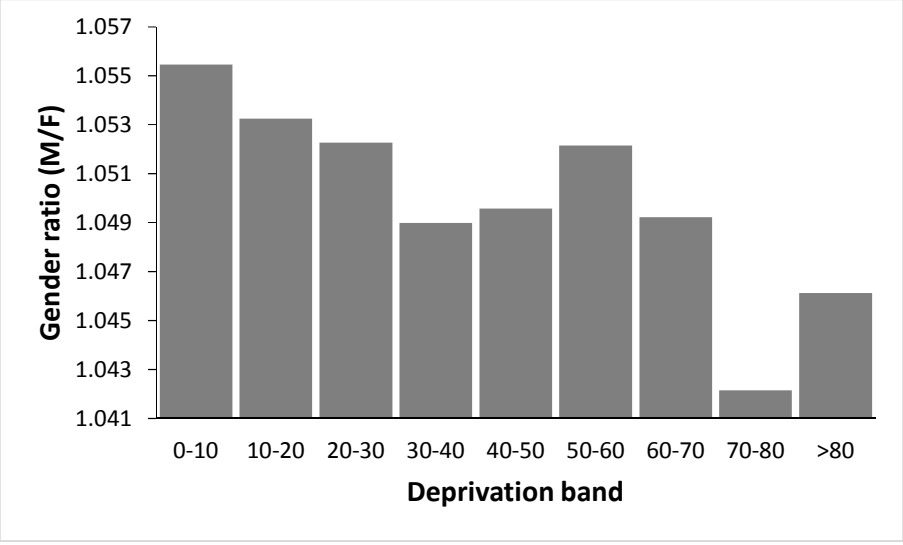


**Fig. 9. Average gender ratio (2001-2014) and the Index of Multiple Deprivation for output areas in England and Wales**

*The Index of Multiple Deprivation (IMD) ranges from 1 (least deprived) to 100 (most deprived). There is a linear correlation between IMD and income*

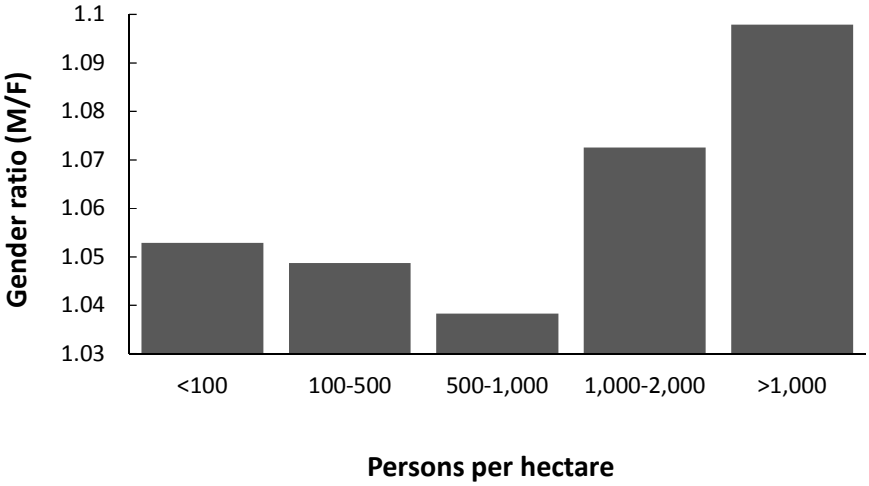


**Fig. 10. Effect of output area population density on the average gender ratio (2001-2014)**
*Due to the very small size of output areas the raw population density is a good approximation to the effective population density. Only 0.1% of births occur at >1,000 persons per hectare, and this is restricted to parts of London*

### 3.6 Factors Affecting Year-to-year Volatility in the GR

Both the frequency and magnitude of these outbreaks will influence the year-to-year variation in the GR, and will in some instances lift the average for the GR. Fig. A3 in the Appendix has already established that there are gradients in the volatility associated with different local government areas. Fig. 11 gives an example of this volatility for the seven largest social groups all containing more than 20,000 births per annum, while Fig. 12 shows the average year-to-year volatility in the GR for all social groups. Note that the year-to-year volatility is directly related to the standard deviation such that SD = 0.985 x average volatility.

Note that it is possible for certain social groups to be at a minimum of GR while others are at a maximum and this may modify the regional behavior of the outbreaks given the relative distributions of social groups between north and south (Table A3 in Appendix A3).

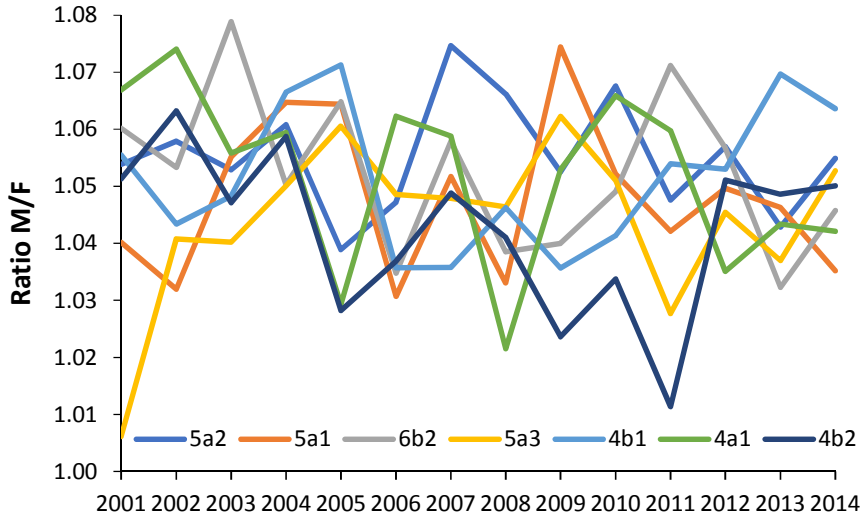


**Fig. 11. Variation in the GR over time in seven large social groups**

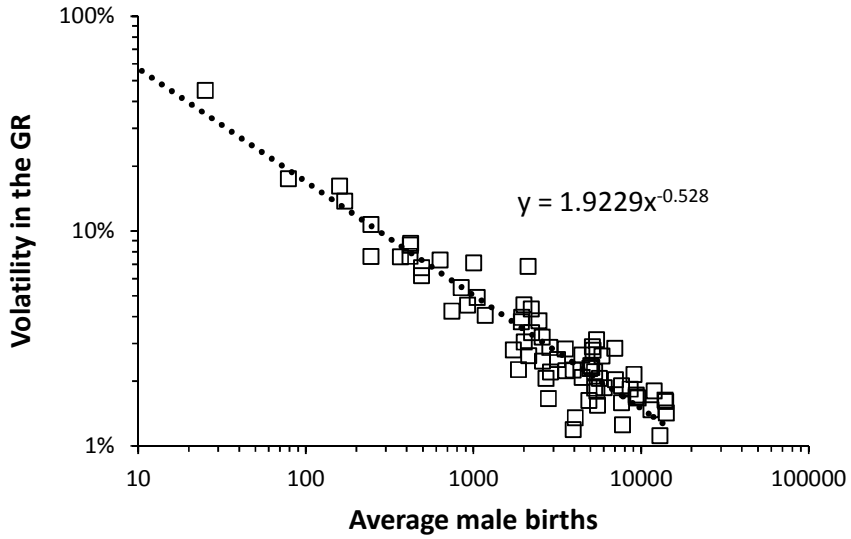


**Fig. 12. Average year-to-year volatility in the GR for all social groups**

From Fig. 11 some groups may be more volatile than others, and this is made clearer in Fig. 12 where groups lying below the trend line are less volatile and those above the trend line are more volatile. The group furthest above the trend line is 8b2 (Hard pressed rented terraces) which has average population density, higher deprivation and mainly live in the more northern parts of England. Furthest below are group 8c3 (Renting hard pressed aging workers). Hence there are probably gradients in volatility associated with different social groups which arise from both frequency and magnitude of the events.

All the above concurs with other studies indicating that the volatility in hospital admissions, deaths, cancer and other health care costs are all location specific [51-56].

## 3.7 Trends in Births by Social Group

Fig. 2 showed an overall pattern of births arising out of the WW II baby boom; however, different social groups should be expected to show social behaviors relating to number of children and age at first birth.

This is illustrated in Fig. 13 by reference to the largest social group in each Supergroup. Different groups reach the peak in births at different points in time. Those which peak later in time also show the highest increase in births.

The principle that different social groups are exhibiting different behaviors relating to births is therefore unequivocally established. The distinct health behavior of the different social groups has been recently demonstrated to affect both admission and case mix to critical care and hospital via the emergency department [57,58]. Appendix A4 provides additional detail.

The implications to section 3.3 relating to capacity in maternity units should be obvious. Having established the role of a series of presumed infectious outbreaks upon fertility and the gender ratio it is now necessary to investigate the biological basis for such effects.

## 3.8 Immune Regulation of Fertility and the GR

It has been estimated that the primary GR in humans may be as high as 1.7 [59], however, the reasons for this are more nuanced than first appears [60], but leaves room for a variety of factors to modulate the ratio upward and downward. It is also now realized that different types of assisted reproductive technologies lead to a variety of GRs ranging from 1.5 to 0.91 [61-63].

A comprehensive study of the GR from conception to birth has revealed that the GR declines in the first week after conception (excess male mortality), then increases for 10 to 15 weeks (excess female mortality), levels off at around 20 weeks, and then slowly declines after around 28 to 35 weeks (excess male mortality) [60]. By implication, the rise in the GR reported

during the proposed outbreaks must seemingly affect the fetus in the period 2 to 15 weeks after conception when female mortality is highest.

Fetal gender has also been demonstrated to induce differential cytokine production in peripheral blood mononuclear cells (PBMC) such that the female fetus is associated with higher LPS-stimulated PBMC production of IL-6 throughout pregnancy, higher TNF-αin early pregnancy, and IL-1βin mid- to late pregnancy [64]. However, no differences in serum cytokines were observed throughout pregnancy. It is clear that highly nuanced immune changes are occurring during pregnancy.

The study of immune involvement in fertility is a rapidly expanding field [65-67], with at least one journal dedicated entirely to the study of this topic. Male seminal fluid influences fertility, and can promote helpful or unhelpful immune responses in female reproductive tissues [66,68]. Male and female fertility is also regulated by a range of sexually transmitted pathogens [69-71].

Is there evidence that immune state also regulates the gender ratio? In this respect, higher levels of particulate air pollution (PM10), a known inflammatory agent [72], leads to an increased rate of female births [73]. The GR is known to be sensitive to the level of the mother's follicular testosterone which is modulated by stress levels [74,75], and this may explain why women in 'high stress' jobs are more likely to give birth to female babies (GR 0.68 in high stress to 1.17 in low stress) [76]. However, fathers with anxiety disorders are associated with more male babies (RR 1.76) [77], confirming studies that the seminal fluid can provoke inflammatory and other responses in female reproductive tissues [66,63].

In terms of immune involvement in the GR, the observation that very low levels of ionizing radiation lead to more male births is of vital importance [1,49,50] – see Appendix A2. It is now recognized that low (considered 'safe') levels of ionizing radiation alter the balance between Th1/Th2 immunity in humans [78]. The role of Th1/Th2 balance and related immune subsets is widely recognized in fertility [65,79,80]. Hence by extrapolation outbreaks of the proposed infectious agent are probably also altering Th1/Th2 balance. In this respect CMV is capable of altering Th1/Th2 balance and a host of other immune parameters [81-87]. CMV also responds to the altered Th1/Th2 balance induced by drugs or pregnancy [82,87], leading to a heightened immunosuppressive state [81-87], especially in pregnancy, leading to increased opportunity for other infections [88]. For example, infection with influenza in the sixth month of gestation leads to a higher incidence of Schizophrenia and possibly Parkinson's later in life [89,90].

A further area of interest is the ability of CMV to reprogram monocyte differentiation (65% of genes associated with M1 polarization are upregulated) toward a M1 pro-inflammatory macrophage [91]. This promotes increased

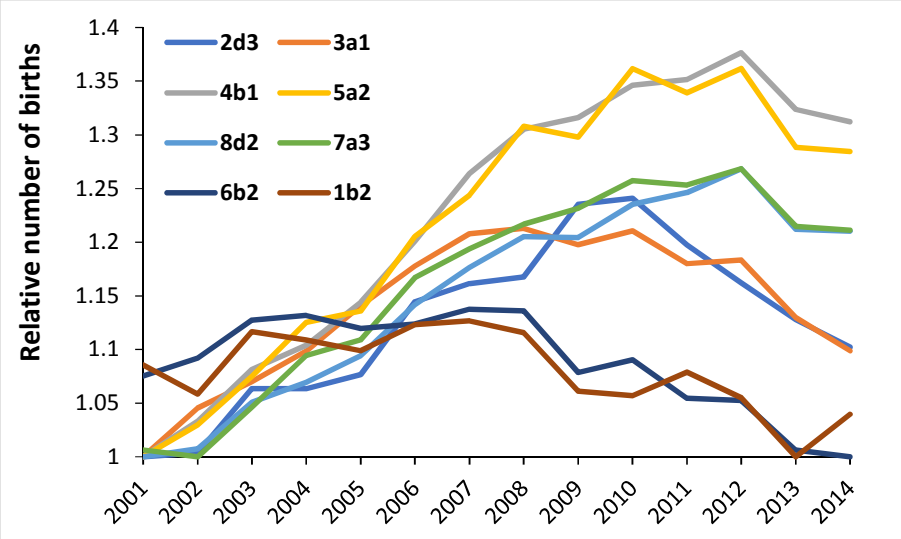


**Fig. 13. Change in births over time for different social groups relative to the minimum births**

monocyte mobility, adhesion to endothelial cells and trans-endothelial migration [91]. Coupled with the study on the effects of fetal gender on PBMCs [64] this generates the possibility for complex gender-specific responses. Indeed, tissue macrophages play an important role in all stages of pregnancy including uterine stromal remodeling before embryo implantation, angiogenesis, parturition, and post-partum uterine involution. M1/M2 dysregulation in the intrauterine environment is therefore involved in adverse pregnancy outcomes [92,93] – refer to section on stillbirth below.

Finally, CMV elicits new decidual NK (dNK) cell effector functions in that dNK cells become cytotoxic effectors after exposure to CMV-infected autologous decidual fibroblasts. This encourages intrauterine CMV infection [94].

CMV can therefore be said to be both immunosuppressive, immunomodulatory, oncogenic, oncomodulatory [5,6,9,27-30,43], and to also modify pregnancy outcomes. In this respect, different types of immune suppression have been observed to increase the susceptibility to different types of cancer [see discussion in 56], and outbreaks of the proposed pathogen have been linked to increases in the incidence of certain common cancers [56].

Of relevance to this study is the observation that infection with the agent alters the immune balance in such a way as to increase susceptibility to certain types of infection, and to increase symptom severity across a range of inflammation- and perhaps autoimmune-sensitive conditions [3,5,6,9,27-30,43].

### 3.9 Implications to Congenital Abnormalities and Stillbirths

Some 15% to 20% of pregnancies end in failure [95], while around 50% of spontaneous abortions and 55% of stillbirths arise from genetic abnormalities [95], the remaining proportion appear to arise from infection during pregnancy [96-98]. Given the ability of the agent to increase susceptibility to infection, infection during pregnancy is widely recognized to play a role in spontaneous abortion and stillbirth [88,99-101]. Secondary infection will only enhance inflammation [88]. Immune involvement in the gender ratio in spontaneous abortions is an additional possibility. Active inflammatory bowel disease during pregnancy may increase spontaneous abortion, stillbirth and congenital conditions [102], and women with depression (which is often associated with inflammation) suffer higher rates of fetal abnormalities (2.75-times), death (2-times), and pre-term labor (1.7-times) [103].

Fig. 14 therefore investigates the possibility that the presumed outbreaks are increasing the stillbirth rate. In Fig. 14 successive 12-month blocks of data are compared, hence, January to December 1993 versus January to December 1994 (first data point on the chart). A maximum value therefore indicates that the step-increase in the stillbirth rate occurred in January 1994, etc. Move forward one month and repeat the calculation.

In Fig. 14 it is not the value on the Y-axis which is of importance, but it is the saw-tooth behavior and the magnitude of the difference between trough and peak. The broader features centered around 2002 and 2008 represent periods where the small-area outbreaks show enhanced synchrony leading to a national scale outbreak. See Jones [104] for a description of the national level outbreaks and the effect on financial year total bed occupancy via the effect of the agent on acute illness requiring hospitalization.

As can be seen the stillbirth rate is indeed increased during the periods of a national-scale outbreak of the proposed agent, and during the periods of higher GR shown in Fig. 3.

It is important to confirm that this behavior is replicated in smaller areas and to this end, Appendix A5 lists 68 Clinical Commissioning Groups out of 216 (31%) which experienced a >2 STDEV step-like increase or decrease (after the event) in stillbirths in the period 2012 to 2014. Local outbreaks of the agent are therefore confirmed to affect the stillbirth rate as was observed for the gender ratio in Section 3.2.

A perusal of reports on both the British & Irish Network of Congenital Anomaly Researchers (www.binocar.org) and of the European Network of Population-based Registers for the Epidemiological Surveillance of Congenital Anomalies (www.eurocat-network.eu) reveals evidence of congenital anomaly events which endure for around 12-months before abating. A re-appraisal of data using month of conception in running (moving) 12-month totals/averages/rates is necessary.

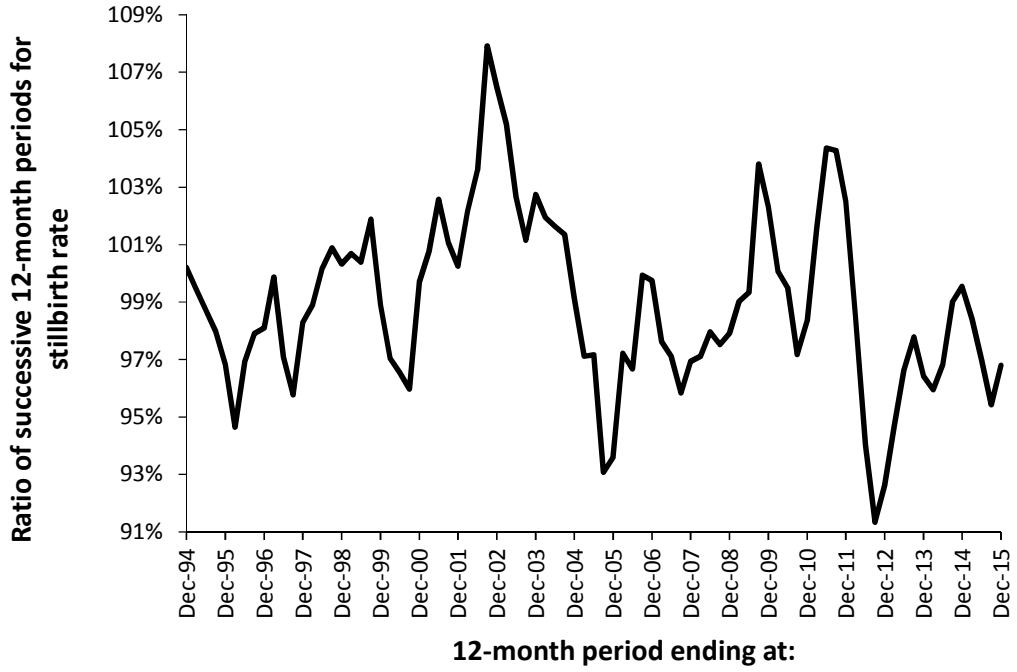


**Fig. 14. Comparison of successive 12-month periods for the stillbirth rate in England and Wales**

*Monthly data on births and stillbirths was obtained from the Office for National Statistics. Stillbirths were divided by births to obtain the stillbirth rate. Data covers the period after October 1992 when the definition of a stillbirth was changed from 28 to 24 weeks*

There is some evidence for CMV involvement in recurring pregnancy loss in that CMV IgG is 1.3-times more prevalent than in controls, and the IgG titer is 2.6-times higher [105]. If we assume that CMV may be involved, it is worth noting that the most serious neurological abnormalities for CMV infection occur in the first trimester [106], however additional vasculopathies also occur [107,108]. Another study noted that risk of abnormalities was highest for CMV infection in the preconception, periconception and first trimester periods [109]. In 2005/06 in Australia some 9% of still births were infected with CMV [110], while CMV was detected in 15% of over 20 week stillbirths [107]. All of this accords with the observation that highest female fetal demise occurs in the period 2 to 15 weeks after conception [60].

Based on this study, the most likely mechanism for the proposed pathogen (CMV??) is via immune manipulation by the agent leading to increased fertility but also higher female fetal loss, possibly compounded by secondary infection of the fetus by a range of additional pathogens.

To shed some light on the potential range of conditions affecting conception, pregnancy, neonates and congenital conditions a preliminary analysis was conducted using Hospital Episode Statistics (HES) data for England between 1998/99 and 2015/16. Table A6 in the Appendix provides a list of conditions which show increased occupied bed days during the presumed infectious outbreaks. The methods are detailed in Appendix A6. This preliminary list of conditions is most concerning and includes inflammation of the male genital organs, habitual spontaneous abortion and complication in artificial fertilization as expected from section 3.8. There are an additional list of conditions arising during pregnancy which include abnormalities, infections, placental disorders and embolism. Neonates are afflicted with a range of cardiovascular and other disorders and a range of congenital abnormalities (as discussed above) which necessitate increased hospitalization.

Urgent research is required to confirm the exact range of conditions sensitive to these outbreaks. The cost to society in human and financial terms is almost certainly truly prodigious.

### 3.10 Issues Specific to London

Due to the huge diversity in ethnicity and other social factors in London, it is recognized that the OAC for England and Wales does not fully reflect the nuances specific to London [111]. For this reason, London has its own OAC called the London Output Area Classification (LOAC) – see https://data.london.gov.uk/dataset/london-area-classification.

For example, the maximum increase in births between 2001and 2012 is 29% in London versus 22% outside London. Within London the maximum increase is 241% occurring at 2014 for LOAC group 2b2 (multicultural student neighborhoods), while the minimum increase of only 7% occurred at 2008 for LOAC group 6b1 (Multi-ethnic suburbia). Additional research using the LOAC is probably warranted.

### 3.11 Limitations of the Study

Any GR study must run the gauntlet of very large sample size (many years' data or very large areas) versus a need for precision. Given the desire to analyze relatively small areas, local government areas (1974-2010) or very small OA data (2001-2014), the studies had to cover relatively long time periods. Different etiological population factors have potentially changed during these periods. However, there was little evidence to suggest fundamental changes in the average GR over the time periods. It must also be recalled that the on/off (high/low) switching induced by the proposed outbreaks have been an unrecognized and highly influential factor in influencing any study calculating short-term GR.

Factors such as consanguinity can be inferred from the statistically high/low results in Appendix A2 of the GR for births in the UK associated with mothers born elsewhere in the world. However, such factors will be restricted to certain locations or social groups and are generally too small to affect the overall conclusions.

As a general conclusion deprivation (intrinsically linked to social group), and outbreaks of the proposed agent exert the strongest effects. Deprivation (associated with locations) remains surprisingly stable over time, however, outbreaks of the agent show high granularity and variably synchrony [4-20]. A reappraisal of previous studies is probably warranted. For example, it has been suggested by this author that an interaction between the proposed agent and the influenza strain responsible for the World War I 'Spanish Flu' may have caused the very large peak in the GR which occurred at that time, rather than the stress of WWI per se [112].

The possibility that even more complex patterns lie hidden in the data (as alluded to in Fig.1) cannot be excluded. Research in that direction must explore the possibility of links with stillbirth and congenital abnormalities.

Due to the limitations of data confidentiality this study has analyzed annual birth data for very small areas. Given the fact that mini-outbreaks of the agent are occurring continuously [19] a more detailed study using monthly data aggregated into running (moving) 12-month totals will give more precise information regarding the timing and magnitude of these outbreaks across different areas and social groups. However, this study has been able to establish that the basic principles regarding social behaviors and their interaction with the agent.

### 3.12 Further Research

International data on spontaneous abortion, stillbirth and congenital abnormalities needs to be re-analyzed using running (moving) 12-month totals/averages by month of conception. Issues regarding the role of infection in the mother or father need to be investigated.

This study needs to be replicated in an international context using monthly data, i.e. analysis at county level across the USA, or local government areas in other countries.

Wider roles for low levels of background radiation (including radon exposure) in the variation of the GR need to be investigated.

The authors own unpublished research suggests that there is a time cascade associated with infection by the agent with infection of the fetus occurring first, followed by a rise in medical hospital admissions, and finally by an increase in elderly deaths. Such time lags need to be quantified.

Due to the wider effects against deaths, medical admissions and sickness absence, studies involving more than just births are also recommended.

In 2015 an apparently rare interaction between influenza and the proposed agent led to higher

deaths in the elderly [20], especially those with Alzheimer's and dementia [30]. Given the know role of influenza in fetal death [113], levels of stillbirth and abnormalities for conceptions during the months of 2015 should be carefully investigated.

## 4. CONCLUSION

Over the past nine years, evidence for large scale outbreaks of an infectious agent has been steadily mounting. Curiously this has been ignored by Public Health agencies. A wide range of human health issues appear to be affected. Involvement of the agent in respiratory infection is probably far higher than realized [27], and the agent may even lie behind an unexplained trend to higher adult appendicitis seen in the UK [28]. My own unpublished studies show a large increase in female cardiovascular deaths during these outbreaks. The effects against fertility, the gender ratio and stillbirths reported in this study, and their potential relationship with congenital abnormalities is of grave concern.

This new type of infectious outbreak therefore falls within the category of a 'syndemic' in that infectious, social and environmental factors all interact to determine infectious potency [114].

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## ACKNOWLEDGEMENT

The helpful suggestions of David Goldeck are acknowledged with gratitude.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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## APPENDIX

### A1. Gender Ratio in UK Local Authorities and Regions (1974-2010)

The average GR in local authorities and regions across the UK for over 24 million births from 1974 to 2010 is presented in Fig. A1. As can be seen the average ranged from 1.0035 in Bridgnorth (Shropshire) to 1.108 in Maldon (Essex). Confidence intervals (95%) in the tails do not overlap.

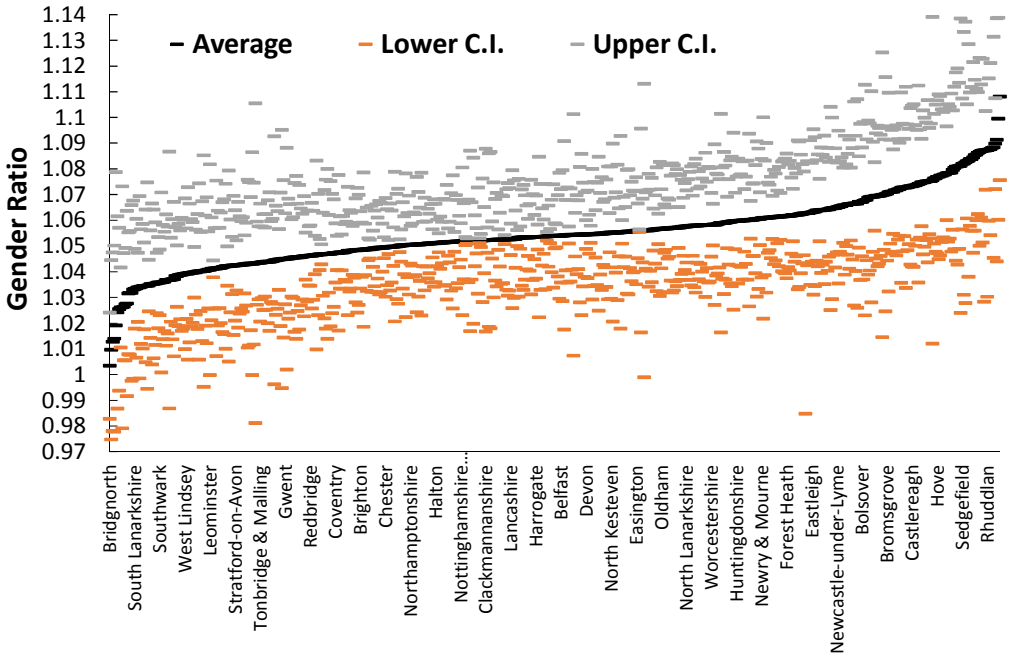


**Fig. A1. Average gender ratio for births in the English and Welsh local authorities (1974-2010)**

*Depending on local government boundary changes each authority/region contains between 15 to 31 years of data. All data from Office for National Statistics. C.I. = 95% confidence interval*

Local government population density appears to play a role in the average GR and ranges from 1.07 in sparsely populated rural areas down to 1.045 above 6,000 persons per square km in London (data not shown). However, this effect only appears to apply at the two extremes of population density. Hence more tranquil rural locations favor male births while more densely populated locations (presumably with higher levels of air pollution) seem to favor females. Although this generalization appears to be contradicted in a few OA in London as per Fig. 10, where gender selection by abortion cannot be excluded as a possibility.

Population deprivation (Fig. A2) also appears to play a role with low deprivation locations having a GR around 1.057 (males favored) while high deprivation locations have an average around 1.048. The gradient between low and high deprivation is far less than that seen for population density. Such findings are consistent with the known relationship between GR and mortality rates, where GR increases as adult mortality rate declines or GR declines as life expectancy at birth reduces [115]. Hence the relationships observed above.

As implied by the confidence intervals in Fig. A1 some locations experience greater year-to-year volatility in the GR than others. As would be expected the average volatility is directly related to the standard deviation and in this study average volatility = 1.1292 x SD (data not shown). This volatility will be a mixture of size-related and environment-related factors. The effect of size can be accounted for using Poisson statistics and Fig. A3 therefore investigates average year-to-year volatility after adjusting the raw average volatility to that at the equivalent of 1,000 births per annum, and with volatility adjusted (downward via square root of n years) for those locations where there was less than 35 years data. The 4-fold variation in volatility only confirms the proposal that the GR is sensitive to the external environment in complex ways. Also from Fig. A3, while London may have high population density and a lower GR, the level of environmental-induced volatility is relatively low.

The principle of location-specific volatility is well established, and has been shown to apply to deaths (hence end-of-life costs), total health care costs, cancer costs, other components of total costs, and hospital admissions and bed occupancy [51-56].

The year-to-year volatility in all aspects of human health is clearly intimately linked to the local environment.

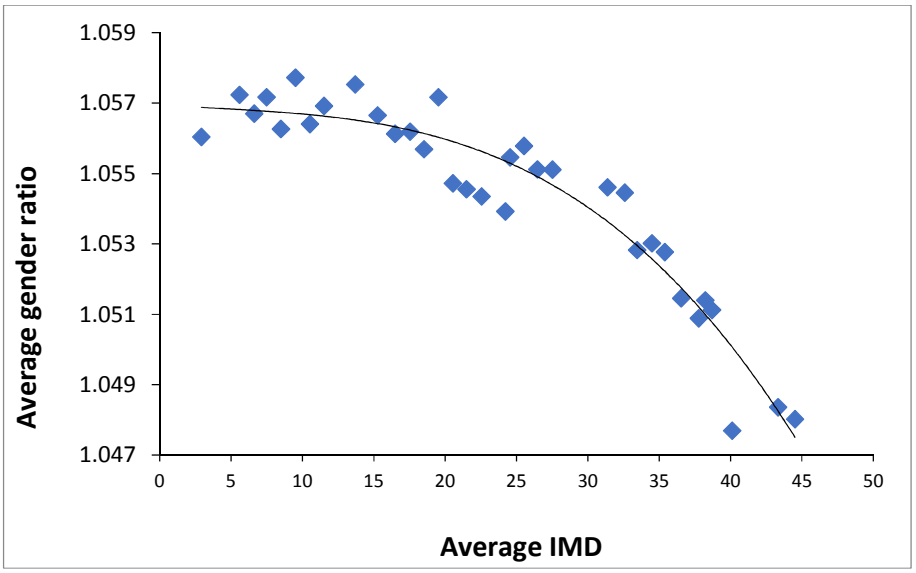


**Fig. A2. Effect of local authority average Index of Multiple Deprivation (IMD) on average GR**

*Local authority IMD was obtained from the Office for National Statistics. LAs were ranked by IMD and averages calculated for IMD bands*

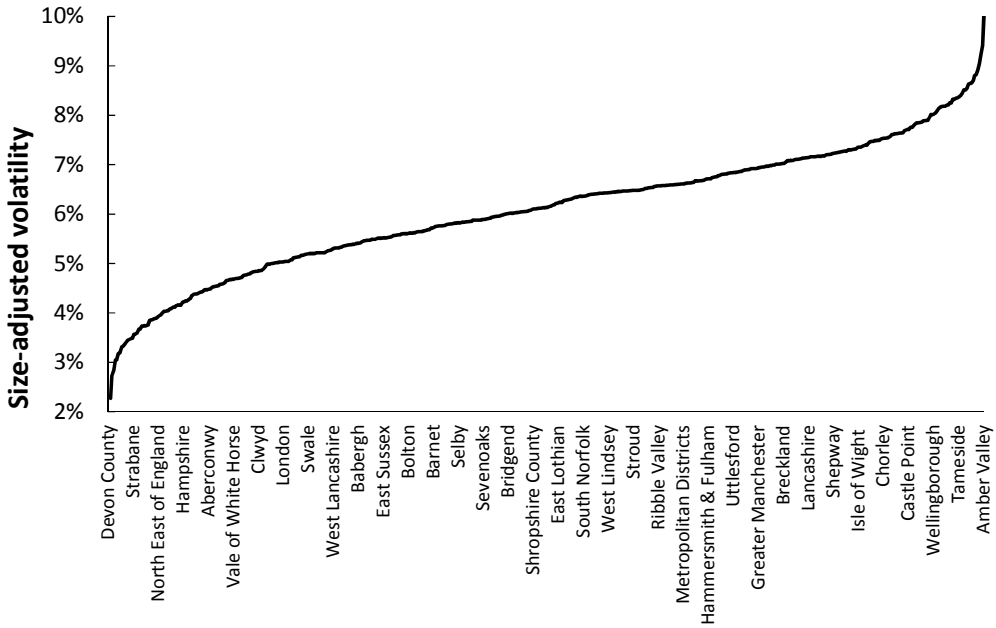


**Fig. A3. Average year-to-year volatility in the GR after adjusting the raw volatility for the effect of size**

*Adjustment assumed a Poisson (log-log) relationship between number of births and volatility, with all volatility adjusted to the equivalent at 1,000 births per annum, and to the equivalent with 35 years of data (in local authority areas with less than 35 years' data)*

In conclusion, a variety of environmental factors produce statistically significant differences in the GR. The year-to-year volatility in the GR is location specific presumably reflecting local weather and other patterns of (changes in) pollution and infection.

**A2. Gender Ratio in the UK by Place of Birth of the Mother (2007-2011)**

A Department of Health report into the gender ratio (GR) in the UK over the period 2007 to 2011 which calculated the GR of births in the UK for mothers born in 156 countries of the world (see Fig. A4) concluded that only one country had a GR significantly different to that of the UK average [44]. Fig. A4 illustrates the difficulty of determining the GR using small samples.

However, if we assume that the GR is subject to Poisson randomness it can be observed that in the 2007-2011 data 30.1% of countries have a GR higher than +1 standard deviation (SD) above the average (1.054 for England) when only 16% should occur by chance, and that 12.2% lie above +2 SD when only 2.32% should do so by chance. Likewise, 10.3% of countries lie below –2 SD when only 2.15% should do so due to chance.

The situation is clearly slightly more complex than the Department of Health report seeks to convey. The period 2007 to 2011 encompasses possibly three national outbreaks of the agent, with different nationalities most likely to be unequally distributed across the UK, and will have lived in the UK for different periods of time before conception.

Fig. A4 also contains additional data from a Department of Health report covering the years 2010 to 2014 (https://www.gov.uk/government/statistics/gender-ratios-at-birth-in-great-britain-2010-to-2014), plus recalculated GR based on both 2007-2011 plus 2010-2014. This additional analysis confirms the existence of higher than expected number of countries (of birth of the mother) above and below ±2 SD.

That the gender ratio for mothers from other countries should be different is entirely consistent with studies showing that persistent pathogens such as parasites and Toxoplasma gondii [116,117] play a role in regulating differences in the GR between countries. Pregnancy itself, i.e. previous births outside of the UK, leads to increased susceptibility to toxoplasmosis and listerosis, and increased illness severity and mortality from influenza and varicella [96].

Hence the GR for births in the UK should show the higher variation exhibited in the data, however, sample size prevents us from determining exactly how wide the range in GR may be expected to be.

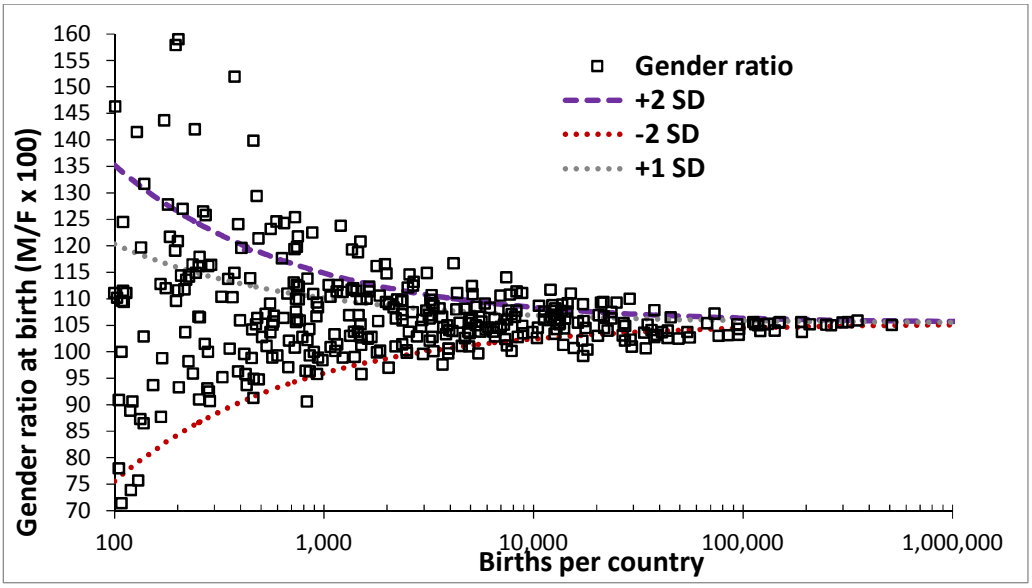


**Fig. A4. Gender ratio for births in the UK between 2007 and 2011 for mothers born in different countries**

*Contains additional data for births between 2010 to 2014, and 2007-2011 combined with 2010-2014*

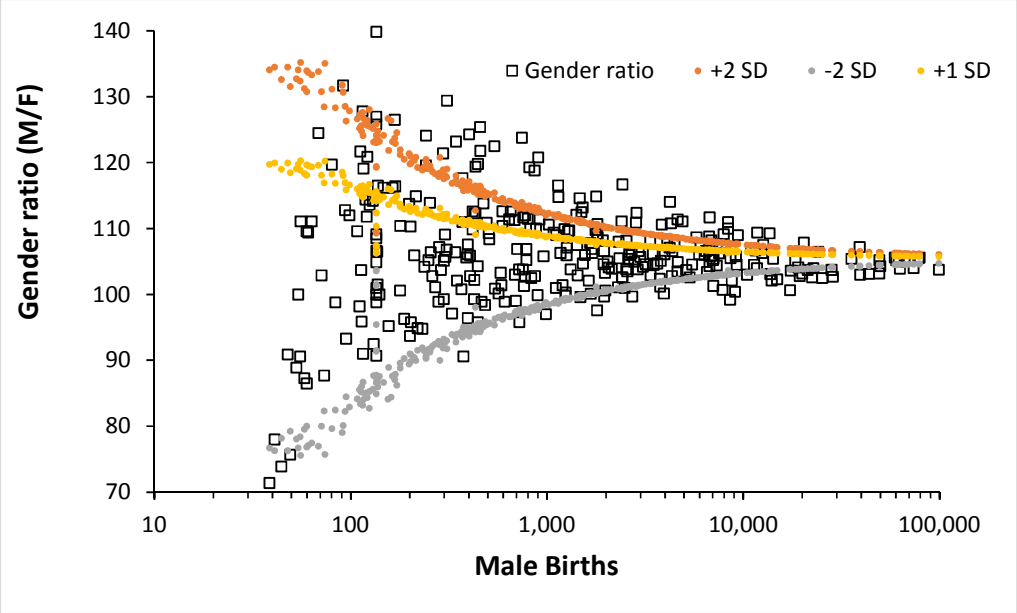


**Fig. A5. As per Fig. A4 but using male births on the X-axis**

A role for low levels of nuclear radiation in high GR has been recognized for some years [49,50]. Given the pattern of spread of the radioactive cloud from Chernobyl it is of interest to note that mothers born in Central Asia (Kazakhstan, etc) have a combined high GR of 1.162, while Belarus, Bulgaria, Moldova, Slovakia have a combined GR of 1.093, i.e. exposure of the mother leads to a measure of sustained modification of the GR. This effect is most likely to occur due to consumption of contaminated food [49], prior to arriving in the UK where the birth(s) eventually occur.

Earlier studies relating to higher GR in Cuba (probably due to radioactive contaminated food imported from Russia and former USSR states) [49] are also confirmed in that mothers born in Cuba have a combined GR (2007-2014) of 1.294 for babies subsequently born in the UK which exceeds the 95% confidence interval.

## A3. Details of Social Groups Available in the OAC for England and Wales

**Table A3. Details of social groups**

| Social group | Super-group | Group | Sub-group | Number of OA | Total births (2001-2014) | Average values | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Persons per hectare | IMD | Km North |
| 1a1 | Rural Residents | Farming Communities | Rural Workers and Families | 464 | 13,351 | 1.3 | 18 | 300 |
| 1a2 | Rural Residents | Farming Communities | Established Farming Communities | 2,406 | 70,539 | 1.2 | 13 | 280 |
| 1a3 | Rural Residents | Farming Communities | Agricultural Communities | 1,784 | 46,986 | 0.4 | 17 | 290 |
| 1a4 | Rural Residents | Farming Communities | Older Farming Communities | 985 | 20,263 | 8 | 15 | 270 |
| 1b1 | Rural Residents | Rural Tenants | Rural Life | 3,906 | 149,806 | 10 | 15 | 300 |
| 1b2 | Rural Residents | Rural Tenants | Rural White-Collar Workers | 4,314 | 159,321 | 2.7 | 12 | 250 |
| 1b3 | Rural Residents | Rural Tenants | Ageing Rural Flat Tenants | 2,213 | 70,076 | 10 | 16 | 260 |
| 1c1 | Rural Residents | Ageing Rural Dwellers | Rural Employment and Retirees | 720 | 23,081 | 1.6 | 16 | 260 |
| 1c2 | Rural Residents | Ageing Rural Dwellers | Renting Rural Retirement | 892 | 32,191 | 9 | 16 | 280 |
| 1c3 | Rural Residents | Ageing Rural Dwellers | Detached Rural Retirement | 952 | 25,301 | 5 | 13 | 240 |
| 2a1 | Cosmopolitans | Students Around Campus | Student Communal Living | 384 | 11,239 | 89 | 21 | 290 |
| 2a2 | Cosmopolitans | Students Around Campus | Student Digs | 435 | 10,068 | 139 | 20 | 340 |
| 2a3 | Cosmopolitans | Students Around Campus | Students and Professionals | 1,262 | 54,608 | 105 | 20 | 260 |
| 2b1 | Cosmopolitans | Inner-City Students | Students and Commuters | 86 | 2,059 | 208 | 25 | 260 |
| 2b2 | Cosmopolitans | Inner-City Students | Multicultural Student Neighbourhoods | 1,064 | 27,031 | 286 | 26 | 270 |
| 2c1 | Cosmopolitans | Comfortable Cosmopolitans | Migrant Families | 1,382 | 60,235 | 92 | 26 | 210 |
| 2c2 | Cosmopolitans | Comfortable Cosmopolitans | Migrant Commuters | 122 | 4,296 | 147 | 35 | 220 |
| 2c3 | Cosmopolitans | Comfortable Cosmopolitans | Professional Service Cosmopolitans | 225 | 6,596 | 144 | 17 | 210 |
| 2d1 | Cosmopolitans | Aspiring and Affluent | Urban Cultural Mix | 974 | 52,770 | 86 | 14 | 190 |
| 2d2 | Cosmopolitans | Aspiring and Affluent | Highly-Qualified Quaternary Workers | 1,229 | 58,355 | 199 | 18 | 180 |
| 2d3 | Cosmopolitans | Aspiring and Affluent | EU White-Collar Workers | 1,340 | 86,081 | 130 | 15 | 180 |
| 3a1 | Ethnicity Central | Ethnic Family Life | Established Renting Families | 1,933 | 164,617 | 124 | 42 | 220 |
| 3a2 | Ethnicity Central | Ethnic Family Life | Young Families and Students | 1,524 | 140,493 | 129 | 35 | 220 |
| 3b1 | Ethnicity Central | Endeavouring Ethnic Mix | Striving Service Workers | 1,371 | 110,708 | 250 | 39 | 180 |
| 3b2 | Ethnicity Central | Endeavouring Ethnic Mix | Bangladeshi Mixed Employment | 654 | 55,163 | 270 | 40 | 180 |
| 3b3 | Ethnicity Central | Endeavouring Ethnic Mix | Multi-Ethnic Professional Service Workers | 906 | 52,859 | 229 | 32 | 190 |
| 3c1 | Ethnicity Central | Ethnic Dynamics | Constrained Neighbourhoods | 971 | 67,455 | 154 | 47 | 270 |
| 3c2 | Ethnicity Central | Ethnic Dynamics | Constrained Commuters | 15 | 711 | 319 | 38 | 300 |
| 3d1 | Ethnicity Central | Aspirational Techies | New EU Tech Workers | 1,272 | 78,425 | 161 | 28 | 180 |
| 3d2 | Ethnicity Central | Aspirational Techies | Established Tech Workers | 1,085 | 76,649 | 114 | 23 | 190 |
| 3d3 | Ethnicity Central | Aspirational Techies | Old EU Tech Workers | 1,409 | 96,509 | 110 | 25 | 180 |
| 4a1 | Multicultural Metropolitans | Rented Family Living | Social Renting Young Families | 4,407 | 326,268 | 61 | 38 | 280 |
| 4a2 | Multicultural Metropolitans | Rented Family Living | Private Renting New Arrivals | 3,292 | 246,464 | 75 | 29 | 270 |
| 4a3 | Multicultural Metropolitans | Rented Family Living | Commuters with Young Families | 2,913 | 212,421 | 80 | 27 | 200 |

| Social group | Super-group | Group | Sub-group | Number of OA | Total births (2001-2014) | Average values | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Persons per hectare | IMD | Km North |
| 4b1 | Multicultural Metropolitans | Challenged Asian Terraces | Asian Terraces and Flats | 3,490 | 349,197 | 119 | 35 | 240 |
| 4b2 | Multicultural Metropolitans | Challenged Asian Terraces | Pakistani Communities | 2,565 | 313,720 | 112 | 45 | 360 |
| 4c1 | Multicultural Metropolitans | Asian Traits | Achieving Minorities | 2,276 | 139,692 | 59 | 20 | 270 |
| 4c2 | Multicultural Metropolitans | Asian Traits | Multicultural New Arrivals | 1,802 | 135,073 | 80 | 21 | 190 |
| 4c3 | Multicultural Metropolitans | Asian Traits | Inner City Ethnic Mix | 2,258 | 144,036 | 66 | 16 | 210 |
| 5a1 | Urbanites | Urban Professionals and Families | White Professionals | 6,680 | 383,645 | 48 | 14 | 290 |
| 5a2 | Urbanites | Urban Professionals and Families | Multi-Ethnic Professionals with Families | 6,018 | 385,725 | 51 | 12 | 230 |
| 5a3 | Urbanites | Urban Professionals and Families | Families in Terraces and Flats | 5,685 | 355,023 | 71 | 19 | 260 |
| 5b1 | Urbanites | Ageing Urban Living | Delayed Retirement | 3,687 | 148,350 | 36 | 11 | 220 |
| 5b2 | Urbanites | Ageing Urban Living | Communal Retirement | 3,446 | 143,092 | 33 | 16 | 250 |
| 5b3 | Urbanites | Ageing Urban Living | Self-Sufficient Retirement | 6,420 | 253,865 | 31 | 14 | 250 |
| 6a1 | Suburbanites | Suburban Achievers | Indian Tech Achievers | 3,079 | 120,601 | 30 | 7 | 260 |
| 6a2 | Suburbanites | Suburban Achievers | Comfortable Suburbia | 2,406 | 107,206 | 28 | 7 | 290 |
| 6a3 | Suburbanites | Suburban Achievers | Detached Retirement Living | 5,065 | 121,453 | 22 | 8 | 280 |
| 6a4 | Suburbanites | Suburban Achievers | Ageing in Suburbia | 3,233 | 96,699 | 20 | 8 | 230 |
| 6b1 | Suburbanites | Semi-Detached Suburbia | Multi-Ethnic Suburbia | 3,115 | 139,088 | 47 | 12 | 280 |
| 6b2 | Suburbanites | Semi-Detached Suburbia | White Suburban Communities | 7,946 | 379,018 | 36 | 11 | 300 |
| 6b3 | Suburbanites | Semi-Detached Suburbia | Semi-Detached Ageing | 6,482 | 207,980 | 38 | 12 | 350 |
| 6b4 | Suburbanites | Semi-Detached Suburbia | Older Workers and Retirement | 3,897 | 133,123 | 33 | 12 | 300 |
| 7a1 | Constrained City Dwellers | Challenged Diversity | Transitional Eastern European | 1,150 | 74,241 | 61 | 43 | 310 |
| 7a2 | Constrained City Dwellers | Challenged Diversity | Hampered Aspiration | 2,559 | 136,756 | 67 | 35 | 300 |
| 7a3 | Constrained City Dwellers | Challenged Diversity | Multi-Ethnic Hardship | 3,696 | 235,338 | 64 | 42 | 290 |
| 7b1 | Constrained City Dwellers | Constrained Flat Dwellers | Eastern European Communities | 168 | 11,273 | 118 | 50 | 270 |
| 7b2 | Constrained City Dwellers | Constrained Flat Dwellers | Deprived Neighbourhoods | 267 | 11,632 | 130 | 53 | 350 |
| 7b3 | Constrained City Dwellers | Constrained Flat Dwellers | Endeavouring Flat Dwellers | 118 | 4,662 | 90 | 38 | 290 |
| 7c1 | Constrained City Dwellers | White Communities | Challenged Transitionaries | 692 | 28,717 | 60 | 36 | 380 |
| 7c2 | Constrained City Dwellers | White Communities | Constrained Young Families | 1,058 | 60,711 | 63 | 50 | 370 |
| 7c3 | Constrained City Dwellers | White Communities | Outer City Hardship | 1,231 | 50,429 | 47 | 33 | 330 |
| 7d1 | Constrained City Dwellers | Ageing City Dwellers | Ageing Communities and Families | 854 | 17,164 | 47 | 23 | 270 |
| 7d2 | Constrained City Dwellers | Ageing City Dwellers | Retired Independent City Dwellers | 449 | 6,674 | 75 | 40 | 340 |
| 7d3 | Constrained City Dwellers | Ageing City Dwellers | Retired Communal City Dwellers | 479 | 13,288 | 47 | 31 | 310 |
| 7d4 | Constrained City Dwellers | Ageing City Dwellers | Retired City Hardship | 22 | 89 | 103 | 37 | 290 |
| 8a1 | Hard-Pressed Living | Industrious Communities | Industrious Transitions | 5,146 | 255,011 | 39 | 20 | 310 |
| 8a2 | Hard-Pressed Living | Industrious Communities | Industrious Hardship | 3,268 | 154,296 | 41 | 31 | 390 |
| 8b1 | Hard-Pressed Living | Challenged Terraced Workers | Deprived Blue-Collar Terraces | 3,127 | 189,607 | 74 | 29 | 370 |
| 8b2 | Hard-Pressed Living | Challenged Terraced Workers | Hard-Pressed Rented Terraces | 1,131 | 57,562 | 58 | 37 | 390 |
| 8c1 | Hard-Pressed Living | Hard-Pressed Ageing Workers | Ageing Industrious Workers | 4,277 | 191,401 | 36 | 22 | 290 |
| 8c2 | Hard-Pressed Living | Hard-Pressed Ageing Workers | Ageing Rural Industry Workers | 1,651 | 77,981 | 34 | 24 | 270 |

| Social group | Super-group | Group | Sub-group | Number of OA | Total births (2001-2014) | Average values | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Persons per hectare | IMD | Km North |
| 8c3 | Hard-Pressed Living | Hard-Pressed Ageing Workers | Renting Hard-Pressed Workers | 2,290 | 106,959 | 47 | 32 | 350 |
| 8d1 | Hard-Pressed Living | Migration and Churn | Young Hard-Pressed Families | 2,807 | 208,177 | 60 | 49 | 390 |
| 8d2 | Hard-Pressed Living | Migration and Churn | Hard-Pressed Ethnic Mix | 4,181 | 260,864 | 57 | 34 | 280 |
| 8d3 | Hard-Pressed Living | Migration and Churn | Hard-Pressed European Settlers | 1,994 | 147,458 | 58 | 36 | 310 |
| All | All | All | All | 171,045 | 8,969,871 | 67 | 22 | 280 |

### A4. Average Gender Ratio (M/F), Maximum Increase in Births, and Year in Which the Maximum Increase Occurred

The column labelled 'Poisson' gives a +2 STDEV increase calculated from Poisson Statistics.

**Table A4. Average gender ratio, maximum step-increase in births and year in which the maximum occurred**

| Social group | Average births per annum | | Average GR (M/F) | Maximum increase (%) | | | Maximum increase (STDEV) | | Maximum year | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Female | Male | | Female | Male | Poisson | Female | Male | Female | Male |
| 1a1 | 465 | 488 | 1.050 | 10% | 8% | 9% | 2.1 | 1.9 | 2004 | 2009 |
| 1a2 | 2,470 | 2,569 | 1.040 | 4% | 3% | 4% | 1.9 | 1.4 | 2003 | 2003 |
| 1a3 | 1,632 | 1,724 | 1.056 | 4% | 8% | 5% | 1.6 | 3.4 | 2003 | 2002 |
| 1a4 | 706 | 741 | 1.049 | 6% | 4% | 7% | 1.6 | 1.1 | 2011 | 2004 |
| 1b1 | 5,219 | 5,482 | 1.050 | 5% | 2% | 3% | 3.6 | 1.4 | 2003 | 2002 |
| 1b2 | 5,546 | 5,835 | 1.052 | 5% | 5% | 3% | 4.1 | 4.1 | 2003 | 2003 |
| 1b3 | 2,429 | 2,576 | 1.061 | 6% | 5% | 4% | 3.1 | 2.7 | 2006 | 2014 |
| 1c1 | 807 | 842 | 1.044 | 6% | 5% | 7% | 1.8 | 1.6 | 2007 | 2014 |
| 1c2 | 1,126 | 1,174 | 1.043 | 10% | 10% | 6% | 3.2 | 3.3 | 2011 | 2007 |
| 1c3 | 886 | 921 | 1.040 | 10% | 1% | 7% | 3.0 | 0.4 | 2014 | 2012 |
| 2a1 | 385 | 417 | 1.083 | 15% | 11% | 10% | 2.9 | 2.3 | 2004 | 2009 |
| 2a2 | 353 | 367 | 1.039 | 16% | 11% | 10% | 3.0 | 2.1 | 2008 | 2010 |
| 2a3 | 1,893 | 2,008 | 1.061 | 7% | 14% | 4% | 3.1 | 6.2 | 2004 | 2008 |
| 2b1 | 69 | 79 | 1.145 | 31% | 37% | 23% | 2.5 | 3.3 | 2012 | 2008 |
| 2b2 | 931 | 1,000 | 1.074 | 20% | 17% | 6% | 6.0 | 5.4 | 2006 | 2010 |
| 2c1 | 2,086 | 2,217 | 1.063 | 14% | 13% | 4% | 6.3 | 6.2 | 2006 | 2003 |
| 2c2 | 148 | 159 | 1.070 | 33% | 16% | 16% | 4.0 | 2.1 | 2003 | 2007 |
| 2c3 | 227 | 244 | 1.074 | 14% | 15% | 13% | 2.1 | 2.4 | 2003 | 2007 |
| 2d1 | 1,830 | 1,939 | 1.060 | 13% | 12% | 5% | 5.4 | 5.2 | 2010 | 2006 |
| 2d2 | 2,035 | 2,133 | 1.048 | 11% | 9% | 4% | 4.8 | 4.3 | 2010 | 2010 |
| 2d3 | 2,986 | 3,163 | 1.059 | 7% | 9% | 4% | 4.0 | 4.8 | 2003 | 2006 |
| 3a1 | 5,751 | 6,008 | 1.045 | 7% | 5% | 3% | 5.2 | 3.7 | 2002 | 2007 |
| 3a2 | 4,916 | 5,119 | 1.041 | 8% | 10% | 3% | 5.9 | 6.9 | 2006 | 2007 |

| Social group | Average births per annum | | Average GR (M/F) | Maximum increase (%) | | | Maximum increase (STDEV) | | Maximum year | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Female | Male | | Female | Male | Poisson | Female | Male | Female | Male |
| 3b1 | 3,864 | 4,044 | 1.046 | 7% | 5% | 3% | 4.2 | 3.4 | 2003 | 2003 |
| 3b2 | 1,945 | 1,996 | 1.026 | 8% | 5% | 4% | 3.5 | 2.1 | 2004 | 2004 |
| 3b3 | 1,852 | 1,924 | 1.039 | 7% | 9% | 5% | 3.0 | 4.1 | 2006 | 2010 |
| 3c1 | 2,360 | 2,459 | 1.042 | 11% | 11% | 4% | 5.2 | 5.6 | 2005 | 2004 |
| 3c2 | 26 | 25 | 0.975 | 35% | 64% | 40% | 1.8 | 3.2 | 2008 | 2010 |
| 3d1 | 2,730 | 2,872 | 1.052 | 4% | 5% | 4% | 2.2 | 2.6 | 2004 | 2009 |
| 3d2 | 2,680 | 2,795 | 1.043 | 9% | 13% | 4% | 4.9 | 6.8 | 2010 | 2010 |
| 3d3 | 3,366 | 3,528 | 1.048 | 6% | 8% | 3% | 3.4 | 4.8 | 2003 | 2003 |
| 4a1 | 11,361 | 11,943 | 1.051 | 6% | 5% | 2% | 6.5 | 6.0 | 2003 | 2007 |
| 4a2 | 8,555 | 9,050 | 1.058 | 10% | 8% | 2% | 8.8 | 8.0 | 2006 | 2007 |
| 4a3 | 7,427 | 7,746 | 1.043 | 6% | 6% | 2% | 5.0 | 5.3 | 2006 | 2006 |
| 4b1 | 12,160 | 12,783 | 1.051 | 6% | 5% | 2% | 6.9 | 5.8 | 2006 | 2007 |
| 4b2 | 10,974 | 11,435 | 1.042 | 3% | 3% | 2% | 3.0 | 3.3 | 2005 | 2002 |
| 4c1 | 4,823 | 5,155 | 1.069 | 6% | 5% | 3% | 4.2 | 3.6 | 2006 | 2007 |
| 4c2 | 4,703 | 4,945 | 1.051 | 9% | 7% | 3% | 6.1 | 4.6 | 2007 | 2006 |
| 4c3 | 5,013 | 5,275 | 1.052 | 9% | 6% | 3% | 6.1 | 4.3 | 2007 | 2006 |
| 5a1 | 13,381 | 14,022 | 1.048 | 6% | 4% | 2% | 7.1 | 5.1 | 2008 | 2008 |
| 5a2 | 13,404 | 14,148 | 1.055 | 6% | 6% | 2% | 6.6 | 7.2 | 2008 | 2006 |
| 5a3 | 12,404 | 12,955 | 1.044 | 7% | 7% | 2% | 7.4 | 7.4 | 2008 | 2008 |
| 5b1 | 5,163 | 5,434 | 1.052 | 8% | 5% | 3% | 5.4 | 3.9 | 2006 | 2012 |
| 5b2 | 4,955 | 5,266 | 1.063 | 4% | 6% | 3% | 3.0 | 4.1 | 2003 | 2006 |
| 5b3 | 8,799 | 9,334 | 1.061 | 4% | 5% | 2% | 3.6 | 4.8 | 2003 | 2007 |
| 6a1 | 4,184 | 4,431 | 1.059 | 6% | 6% | 3% | 4.1 | 4.2 | 2006 | 2007 |
| 6a2 | 3,725 | 3,933 | 1.056 | 5% | 5% | 3% | 3.3 | 2.8 | 2003 | 2006 |
| 6a3 | 4,223 | 4,452 | 1.054 | 3% | 4% | 3% | 2.2 | 2.5 | 2006 | 2012 |
| 6a4 | 3,358 | 3,549 | 1.057 | 5% | 5% | 3% | 3.1 | 3.1 | 2007 | 2007 |
| 6b1 | 4,868 | 5,067 | 1.041 | 3% | 5% | 3% | 2.3 | 3.8 | 2007 | 2014 |
| 6b2 | 13,191 | 13,882 | 1.052 | 2% | 4% | 2% | 2.3 | 5.3 | 2003 | 2003 |
| 6b3 | 7,228 | 7,628 | 1.055 | 4% | 3% | 2% | 3.8 | 2.9 | 2012 | 2004 |
| 6b4 | 4,633 | 4,876 | 1.052 | 4% | 8% | 3% | 3.1 | 5.3 | 2014 | 2004 |
| 7a1 | 2,594 | 2,709 | 1.044 | 10% | 9% | 4% | 4.9 | 4.9 | 2004 | 2003 |
| 7a2 | 4,755 | 5,013 | 1.054 | 5% | 8% | 3% | 3.2 | 5.5 | 2010 | 2008 |
| 7a3 | 8,205 | 8,605 | 1.049 | 6% | 4% | 2% | 5.4 | 3.8 | 2006 | 2006 |
| 7b1 | 385 | 420 | 1.090 | 12% | 15% | 10% | 2.4 | 3.0 | 2006 | 2003 |
| 7b2 | 409 | 422 | 1.030 | 12% | 9% | 10% | 2.4 | 1.8 | 2006 | 2003 |
| 7b3 | 163 | 170 | 1.047 | 24% | 19% | 15% | 3.1 | 2.5 | 2012 | 2003 |
| 7c1 | 1,002 | 1,049 | 1.047 | 14% | 10% | 6% | 4.5 | 3.2 | 2003 | 2010 |
| 7c2 | 2,125 | 2,212 | 1.041 | 13% | 4% | 4% | 6.1 | 2.0 | 2010 | 2004 |
| 7c3 | 1,748 | 1,854 | 1.060 | 6% | 7% | 5% | 2.7 | 3.1 | 2010 | 2003 |

| Social group | Average births per annum | | Average GR (M/F) | Maximum increase (%) | | | Maximum increase (STDEV) | | Maximum year | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Female | Male | | Female | Male | Poisson | Female | Male | Female | Male |
| 7d1 | 594 | 632 | 1.063 | 14% | 19% | 8% | 3.3 | 4.9 | 2012 | 2010 |
| 7d2 | 233 | 244 | 1.048 | 24% | 14% | 13% | 3.7 | 2.1 | 2004 | 2003 |
| 7d3 | 459 | 490 | 1.067 | 13% | 9% | 9% | 2.8 | 1.9 | 2006 | 2009 |
| 7d4 | 3 | 4 | 1.225 | 140% | 171% | 107% | 2.4 | 3.2 | 2003 | 2013 |
| 8a1 | 8,866 | 9,349 | 1.054 | 5% | 6% | 2% | 5.0 | 5.7 | 2006 | 2004 |
| 8a2 | 5,379 | 5,643 | 1.049 | 7% | 6% | 3% | 5.1 | 4.2 | 2003 | 2008 |
| 8b1 | 6,588 | 6,956 | 1.056 | 6% | 4% | 2% | 4.7 | 3.2 | 2010 | 2010 |
| 8b2 | 1,997 | 2,115 | 1.059 | 7% | 13% | 4% | 3.2 | 6.2 | 2010 | 2006 |
| 8c1 | 6,652 | 7,020 | 1.055 | 4% | 6% | 2% | 3.5 | 4.7 | 2006 | 2003 |
| 8c2 | 2,715 | 2,855 | 1.051 | 5% | 8% | 4% | 2.7 | 4.5 | 2007 | 2008 |
| 8c3 | 3,711 | 3,929 | 1.059 | 6% | 8% | 3% | 3.8 | 4.7 | 2003 | 2003 |
| 8d1 | 7,234 | 7,636 | 1.056 | 4% | 5% | 2% | 3.6 | 4.6 | 2003 | 2004 |
| 8d2 | 9,059 | 9,574 | 1.057 | 5% | 3% | 2% | 4.6 | 3.4 | 2006 | 2006 |
| 8d3 | 5,109 | 5,423 | 1.061 | 7% | 6% | 3% | 4.8 | 4.6 | 2004 | 2004 |

**A5. Stillbirths in English Clinical Commissioning Groups or Welsh Area Health Boards (2012 to 2014)**

Data provided by Office for National Statistics. Value of the step-down is also provided as a second estimate of any potential step-change.

**Table A5. Year-to-year variation in the number of stillbirths as STDEV equivalents**

| CCG | Average births p.a. | Stillbirths per 1,000 birth | 2012 step-down | 2013 | | 2014 step-up |
|---|---|---|---|---|---|---|
| | | | | Step-up | Step-down | |
| Brent | 5,082 | 6.23 | 4.8 | | | |
| Redbridge | 4,548 | 6.30 | | 2.0 | 4.4 | |
| South Worcestershire | 2,958 | 3.83 | | 4.3 | 4.2 | |
| Corby | 1,000 | 7.64 | 4.3 | | | |
| Ashford | 1,470 | 5.21 | 4.1 | | | |
| Somerset | 5,458 | 3.85 | 3.8 | | | 2.4 |
| Nottingham City | 4,220 | 5.29 | | | | 3.7 |
| Wiltshire | 5,103 | 4.05 | 3.7 | | | |
| Chiltern | 3,574 | 4.85 | | 2.0 | | 3.5 |
| Greenwich | 4,373 | 7.39 | | 2.8 | 3.5 | |
| Telford and Wrekin | 2,101 | 4.28 | | | 3.4 | |
| Aylesbury Vale | 2,297 | 4.64 | 3.3 | | | |
| Horsham and Mid Sussex | 2,266 | 3.53 | | | | 3.3 |
| Leicester City | 5,109 | 6.46 | 3.3 | | | |
| North Tyneside | 2,224 | 3.90 | | 2.3 | 3.3 | |
| Wyre Forest | 1,039 | 4.17 | | | | 3.2 |
| Enfield | 4,813 | 4.36 | 3.2 | | | |
| Nottingham North and East | 1,634 | 4.08 | | | 3.1 | |
| Windsor, Ascot and Maidenhead | 1,623 | 5.75 | 3.1 | | | |
| South Reading | 1,883 | 6.37 | 3.0 | | | |
| Southwark | 4,646 | 5.24 | 2.9 | | | |
| Cambridgeshire and Peterborough | 10,724 | 3.48 | | | | 2.9 |
| South Gloucestershire | 3,035 | 4.39 | 2.9 | | | |
| East and North Hertfordshire | 6,559 | 4.07 | 2.9 | | | |
| Southampton | 3,264 | 5.11 | 2.9 | | | |
| Luton | 3,446 | 5.51 | 2.8 | | | |
| Great Yarmouth and Waveney | 2,275 | 4.98 | 2.8 | | | |
| Croydon | 5,555 | 4.80 | 2.8 | | | |
| Sunderland | 2,910 | 4.47 | | 2.7 | | |
| Central London (Westminster) | 1,807 | 4.24 | | 2.7 | 2.4 | |
| Waltham Forest | 4,585 | 5.23 | 2.6 | | | |
| South Warwickshire | 2,537 | 3.15 | | | | 2.5 |
| Barnet | 5,177 | 4.18 | 2.5 | | | |
| Surrey Heath | 1,057 | 5.36 | | 2.4 | | |
| Bromley | 3,905 | 4.44 | | | 2.4 | |
| Southend | 2,209 | 3.47 | | | 2.4 | |
| Hammersmith and Fulham | 2,446 | 4.77 | | | 2.4 | |
| Stafford and Surrounds | 1,355 | 3.20 | | | 2.4 | |
| Southport and Formby | 1,001 | 4.33 | | | | 2.4 |
| Fareham and Gosport | 1,988 | 4.02 | 2.4 | | | |
| Fylde & Wyre | 1,424 | 3.04 | | 2.4 | 2.1 | |
| Calderdale | 2,540 | 4.46 | 2.3 | | | |
| North Derbyshire | 2,486 | 4.56 | 2.3 | | | |
| North & West Reading | 1,204 | 4.71 | | | | 2.3 |
| Greater Huddersfield | 2,840 | 5.52 | | | | 2.3 |
| High Weald Lewes Havens | 1,478 | 3.61 | 2.2 | | | |
| Swindon | 2,967 | 3.15 | | | 2.2 | |
| Cwm Taf University Health Board | 3,403 | 5.19 | 2.2 | | | |
| Warwickshire North | 2,148 | 2.48 | 2.2 | | | |
| North Staffordshire | 1,988 | 3.02 | | | | 2.2 |
| Wandsworth | 5,047 | 3.24 | | | 2.2 | |

| CCG | Average births p.a. | Stillbirths per 1,000 birth | 2012 step-down | 2013 | | 2014 step-up |
|---|---|---|---|---|---|---|
| | | | | Step-up | Step-down | |
| East Surrey | 2,215 | 4.52 | | 2.2 | | |
| Hartlepool and Stockton-on-Tees | 3,364 | 5.55 | | | 2.2 | |
| Central Manchester | 2,889 | 6.23 | 2.1 | | | |
| North Hampshire | 2,581 | 2.84 | 2.1 | | | |
| East Leicestershire and Rutland | 3,166 | 2.95 | 2.1 | | | 2.1 |
| Castle Point and Rochford | 1,542 | 2.16 | | | 2.1 | |
| Wakefield | 3,987 | 4.60 | 2.1 | | | |
| Newark & Sherwood | 1,213 | 2.47 | | | 2.1 | |
| South Kent Coast | 2,145 | 4.20 | 2.0 | | | |
| Oldham | 3,209 | 5.61 | | | 2.0 | |
| Sheffield | 6,527 | 4.70 | | | | 2.0 |
| Trafford | 2,734 | 3.66 | 2.0 | | | |
| Wolverhampton | 3,412 | 5.47 | | | | 2.0 |
| West Essex | 3,602 | 2.68 | | 2.0 | | |
| Leeds West | 3,918 | 4.17 | | | 2.0 | |
| West London | 2,640 | 4.42 | | | | 2.0 |
| Sandwell and West Birmingham | 7,672 | 6.13 | 2.0 | | | |

### A6. Conditions Complicating Reproduction, Pregnancy, Neonates and Congenital Disorders Wich Rise During the Presumed Infectious Outbreaks

Data provided relating to occupied bed days is from Hospital Episode Statistics (HES) data obtained from NHS Digital.

To determine this list of conditions a count of occupied bed days by condition was obtained for each financial year between 1998/99 and 2015/16. This includes both elective and emergency admissions. The ICD-10 codes were changed at the start of 2012/13 to reflect updates to the ICD-10 classification. Bed days were used due to the observation that bed occupancy increases due to the presumed outbreaks due to a mix of increased admissions and increased length of stay (due to acuity). Paired comparison between years was used to detect conditions sensitive to the outbreaks. Increase 1 was calculated before the change to the ICD-10 codes by comparing years with a large national outbreak 2003/04+2004/05+2008/09+2009/10 versus years without the outbreaks 199899 to 2000/01+2007/08+2010/11+2011/12 [104]. After the change in ICD-10 codes Increase 2 was calculated based on years with the outbreak 2014/15+2015/16 which were compared to years largely without 2012/13 and 2013/14. Annual bed days are given as an indicator of relative size. An estimate of the standard deviation (SD) was derived as the square root of bed days divided by bed days. Experience shows that this approximation works reasonably well, although it is likely to be an over-estimate.

**Table A6. Congenital, neonatal, reproduction and pregnancy disorders which increase during the presumed infectious outbreaks**

| ICD-10 | Description | Bed days | Increase 1 | Increase 2 | SD |
|---|---|---|---|---|---|
| N45 | Orchitis and epididymitis | 15,827 | 7% | 7% | 1% |
| N49 | Inflammatory disorders of male genital organs NEC | 10,680 | 14% | 6% | 1% |
| N96 | Habitual aborter | 25 | 38% | 33% | 20% |
| N98 | Complications associated with artificial fertilization | 2,481 | 14% | 1% | 2% |
| O07 | Failed attempted abortion | 200 | 6% | 8% | 7% |
| O11 | Pre-exist hypertensive disorder with superimposed proteinurea | 2,123 | 9% | 12% | 2% |
| O24 | Diabetes mellitus in pregnancy | 37,080 | 1% | 15% | 1% |
| O25 | Malnutrition in pregnancy | 120 | 14% | >100% | 9% |
| O28 | Abnormal findings on antenatal screening of mother | 2,287 | 24% | 88% | 2% |
| O35 | Mat care for known or suspect fetal abnormality and damage | 5,223 | 15% | 22% | 1% |
| O42 | Premature rupture of membranes | 69,582 | 14% | 1% | 0% |
| O43 | Placental disorders | 2,902 | 3% | 8% | 2% |
| O61 | Failed induction of labour | 15,503 | 9% | 10% | 1% |

| ICD-10 | Description | Bed days | Increase 1 | Increase 2 | SD |
|---|---|---|---|---|---|
| O86 | Other puerperal infections | 11,380 | 5% | 7% | 1% |
| O88 | Obstetric embolism | 1,387 | 3% | 5% | 3% |
| O90 | Complications of the puerperium NEC | 8,107 | 12% | 3% | 1% |
| O98 | Maternal infections/parasitic diseases preg/childbirth/pu | 5,173 | 22% | 9% | 1% |
| O99 | Other maternal diseases complicating pregnancy | 45,789 | 2% | 5% | 0% |
| P00 | Fetus and newborn affected mat conds unrel present preg | 28 | 43% | 20% | 19% |
| P07 | Disorders relating to short gestation and low birth weight | 573,077 | 8% | 6% | 0% |
| P10 | Intracranial laceration and haemorrhage due to birth injury | 274 | >100% | 19% | 6% |
| P12 | Birth injury to scalp | 5,665 | 3% | 5% | 1% |
| P29 | Cardiovascular disorders originating in the perinatal period | 12,102 | 3% | 15% | 1% |
| P53 | Haemorrhagic disease of fetus and newborn | 22 | 66% | 28% | 21% |
| P60 | Disseminated intravascular coagulation of fetus and newborn | 45 | 37% | 51% | 15% |
| P61 | Other perinatal haematological disorders | 3,357 | 14% | 10% | 2% |
| P72 | Other transitory neonatal endocrine disorders | 299 | 23% | 66% | 6% |
| P78 | Other perinatal digestive system disorders | 9,061 | 8% | 6% | 1% |
| P83 | Other conditions of integument specific to fetus and newborn | 9,853 | 5% | 2% | 1% |
| P91 | Other disturbances of cerebral status of newborn | 10,519 | 1% | 18% | 1% |
| Q11 | Anophthalmos, microphthalmos and macrophthalmos | 53 | 1% | 19% | 14% |
| Q15 | Other congenital malformations of eye | 178 | 9% | 99% | 8% |
| Q16 | Congenital malformations of ear causing impairment of hearing | 58 | 1% | 36% | 13% |
| Q22 | Congenital malformations of pulmonary and tricuspid valve | 6,364 | 5% | 18% | 1% |
| Q23 | Congenital malformations of aortic and mitral valves | 13,746 | 5% | 6% | 1% |
| Q38 | Other congenital malformations of tongue, mouth and pharynx | 8,971 | 11% | 18% | 1% |
| Q41 | Congenital absence atresia and stenosis of small intestines | 5,333 | 15% | 3% | 1% |
| Q45 | Other congenital malformations of digestive system | 392 | 61% | 56% | 5% |
| Q56 | Indeterminate sex and pseudohermaphroditism | 241 | 13% | 32% | 6% |
| Q67 | Cong musculoskeletal deformities of head, face, spine and chest | 2,687 | 3% | 3% | 2% |
| Q79 | Congenital malformations of the musculoskeletal system NEC | 18,387 | 17% | 3% | 1% |
| Q82 | Other congenital malformations of skin | 1,660 | 27% | 10% | 2% |
| Q97 | Other sex chromosome abnormalities female phenotype NEC | 27 | 6% | 61% | 19% |



*Peer-review history:*
*The peer review history for this paper can be accessed here:*
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