# Multi-factorial influences on sex ratio: a spatio-temporal investigation of endocrine disruptor pollution and neighborhood stress

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Background: It is suggested the declining male birth proportion in some industrialized countries is linked to ubiquitous endocrine disruptor exposure. Stress and advanced parental age are determinants which frequently present positive findings. Multi-factorial influences on population sex ratio are rarely explored or tested in research.

Objectives: To test the hypothesis that dual factors of pollution and population stress affects sex proportion at birth through geographical analysis of Central Scotland.

Methods: The study incorporates the use of Geographical Information Systems (GIS) tools to overlay modeled point source endocrine disruptor air emissions with "small-area" data on multiple deprivation (a proxy measurement of stress) and birth sex. Historical review of regional sex ratio trends presents additional data on sex ratio in Scotland to consider.

Results: There was no overall concentration in Central Scotland of low sex ratio neighborhoods with areas where endocrine disruptor air pollution and deprivation or economic stress were high. Historical regional trends in Scotland (from 1973), however, do show significantly lower sex ratio values for populations where industrial air pollution is highest (i.e. Eastern Central Scotland).

Conclusions: Use of small area data sets and pollution inventories is a potential new method of inquiry for reproductive environmental and health protection monitoring and has produced interesting findings.

Keywords: Sex ratio, Male births, Endocrine disruption, Reproductive health, Air pollution, Multiple deprivation, Neighborhood stress, Maternal age

## Introduction

It has been suggested that the declining proportion of male births in some Western industrialized countries post-World War II may be attributed to human exposure to endocrine disrupting compounds.[1,2] This hypothesis sits alongside other reproductive epidemiological trends that have been linked to endocrine disruption and pollution, including: the rising incidence of testicular cancer and declining sperm quality for men;[3,4] earlier sexual development in adolescents;[5] and the increasing occurrence of crytorchidism in male newborns.[6] Some of these reported trends could also be a result of social determinants that reflect lifestyles in Western countries, such as poor nutrition and sedentary behavior.[7]

The secondary sex ratio is the ratio between male to female births per 100 or 1000 live births. The male birth proportion marker is calculated by dividing male births into total live births and can be used to describe demographic trends in countries and regions.[8,9] For the purposes of this paper, the term "sex ratio" refers to both of these calculations and "sex proportion at birth" (male births/total births) is the unit of analysis in the spatio-temporal investigation. The primary sex ratio is the ratio of males to females at the time of conception and the secondary sex ratio is the ratio at birth. Various reports have demonstrated proportionally greater male fetal death rates, resulting in the adjustment of the primary sex ratio downwards to the secondary sex ratio.[10–12]

Motivation for measurement and analysis of the human sex ratio arises from multiple hypotheses across social biology;[13–15] environmental, medical and behavioral science;[16–19] demography;[20,21] and epidemiology.[22,23] It has been suggested that because the sex ratio can easily be calculated, there has been an over-proliferation of such research with highly speculative

hypotheses built from sex ratio alteration reports.[24] However, the sex ratio offers an alternative "response variable" for many environmental toxicology and epidemiological study designs. For example, there are clear ethical difficulties in recording adverse reproductive health events, such as pregnancy loss, in small geographical areas. Furthermore, a snapshot of sex ratio imbalance in a population may be instructive for new paradigms of biology, whereby teratogenic exposures are possibly linked to the later on-set of disease in the life course.[25]

Scientists have identified persistent organic pollutants, particularly chronic exposure to polychlorinated bi-phenyls (PCBs) and acute releases of dioxins, as likely to be linked to human sex ratio alteration. For PCBs, research suggests the effects are bi-phasic whereby the sex ratio increase occurs with acute exposure and declines with persistent and chronic exposure.[26–28] Bio-measurement of toxin serum levels add validity to findings, though this is qualified by the lack of any STROBE assessment of particular bio-markers.[29] The use of bio-measurement is particularly instructive in studies designed with other reproductive parameters such as sperm quality. Analysis of socio-economic and health-related confounders and obtaining serum samples almost immediately upon exposure can also add validity to investigations. The direct recruitment of cohorts with acute dioxin exposure from the Seveso industrial accident permitted robust results showing significant downward sex ratio alteration, particularly among young men in a comprehensive follow-up study.[19,30] The triple investigation of sperm production, 1,2-dibromo-3-chloropropane (DBCP) levels (previously used as a soil fumigant) and low secondary sex ratio, as well as a case–control study of testicular cancer incidence and reduced sex ratio, add further weight to the environmental hypothesis on reduced male births.[31,32] However, well-designed toxicological investigations of PCBs in breast milk and maternal lead pollution exposure found no effect on sex ratio.[33,34] These non-significant results may reflect different endocrine disrupting properties for particular compounds or congeners, or altering effects on sex ratio may be dependent on dose, timing, or male or female exposure. Studies adopting mapping techniques and geographical analysis, including estimates of pesticide exposure, air pollution, and multiple source pollution, have produced mixed results with skewing of sex ratios upwards, downwards, and within normal confidence limits.[35–37] Such studies present significant methodological challenges in modeling or measuring environmental exposure which usually include surrogate data, particularly given the geographic and temporal variation and composition of multiple and potentially interacting pollutants.

Substantial evidence from large demographic ecological studies suggests that advancing parental age contributes to a lowering of sex ratio.[20,21,38–42] Stress may also alter the secondary sex ratio, with declines in the proportion of male births during and after acutely hazardous events.[43–48] The greater vulnerability of the male fetus to spontaneous loss in pregnancy has been consistently demonstrated and may be a factor in the decline in sex ratios.[10,12] In a recent UK cohort study, advanced maternal age was independently associated with greater risk of miscarriage in the first trimester of pregnancy.[49] There is also evidence that women with older male partners are more susceptible to early pregnancy loss.[50,51] Maternal endocrine changes and stressor responses linked to adverse birth outcomes, including fetal mortality, have received much attention in peri-natal epidemiology. Furthermore, exposure to stress during pregnancy as a result of living in deprived urban areas with elevated crime and physical degradation has been examined in a number of studies focusing on birth outcomes.[52–54]

Many analyses have been conducted on socio-economic status and sex ratio that test the adaptive Trivers–Willard hypothesis that proposes, with natural selection, the "strongest" and wealthiest parents are more likely to sire sons owing to their reproductive advantage over daughters i.e. producing more grandchildren. Results from such types of studies, however, are contradictory with methodological weaknesses attached to using occupation and educational levels as singular de-facto measurements of socio-economic status.[55]

Determination of the secondary sex ratio is multifaceted with evidence suggesting environmental pollution, population stress, and parental age as likely influential factors. Yet there is a paucity of research on sex ratios that investigates the environmental, health-related, and socio-economic influences. Frequently, individual studies tend to be "locked" in a single discipline approach though exceptions are some well-designed environmental epidemiological studies that include adjustments for confounders. The aim of this study is to test the hypothesis that endocrine disruptor pollution combined with population stress influences the proportion of sex at birth in Scotland. The authors utilized Geographical Information Systems (GIS) to combine data on point source endocrine disruptor pollution emissions, area-based data-sets of socio-economic and public health indicators, and compatible area measurement of sex proportion at birth. Starting in 2003, pollution data from Scotland are available in the Scottish Pollutant Release Inventory. All registered emitters are mandated to report total emissions (in kg) of individual pollutants at a site address. Extensive socio-economic and health–related area-based data collected at the neighborhood level

are also available. Scottish birth registration records are available starting in the year 1855 with some regional areas retaining consistent boundaries from 1973 and neighborhood data also available from 2001. The extent and consistency of birth sex ratio data in Scotland thus permits broad analysis over historical time periods and regions complementing the neighborhood multi-factorial approach.

## Methods

The study was divided into three stages: (1) a review of temporal and regional trends in the secondary sex ratio in Scotland; (2) a stratified analysis of sex ratios and levels of multiple deprivation for small areas, i.e. datazones, in Scotland; and (3) a GIS spatial analysis of datazone sex ratios with modeled endocrine disruptor exposure for Central Scotland combined with the levels of multiple deprivation.

### Data sources

For stage (1), data were sourced from the General Register Office (GRO), which compiles birth statistics from local registrars in Scotland. Births by sex from 1855 to 2010 were obtained from the GRO and GRO statisticians provided birth totals by health board area from 1973 to 2010. The "Advanced Reporter" database at Scottish Neighborhood Statistics (SNS) (http://www.sns.gov.uk) was utilized for stages (2) and (3). Data were constructed from multiple sources, including the Scottish Index of Multiple Deprivation (SIMD) and geo-coding from Information Services Division (NHS Scotland). The smallest area abstracted in SNS is the datazone level, which was selected as the major geographical unit of reference for stages (2) and (3). Datazones comprise 6505 areas in Scotland formed by amalgamating census enumeration districts to establish distinctive neighborhood zones with populations ranging from 600 to 1000 persons. Homogeneity of birth data sets was achieved for all stages, as the GRO (Scotland) geo-codes and reports the sex at birth for Scottish Neighborhood Statistics data zones. The Scottish Pollutant Release Inventory (SPRI), produced by the Scottish Environmental Protection Authority (SEPA), was the primary data source for modeled endocrine disruptor pollution in stage (3). The interactive database contains annual declarations in kilograms for separate pollutants by registered emitters, principally industrial companies, or landfill/waste water operators. Data are tabulated for the years 2002 and 2004–2010 and searchable according to local authority area, pollution media type (air, land, water, wastewater), and specific pollutant.

With the exception of non-compliance with birth registration in some rural areas in the late nineteenth century, the GRO (Scotland) statistics are robust and accurate.[56] We used the SIMD for the year 2006 to create the stratified and spatial analyses categorical values ("vigintiles" — divide the distribution of individuals into twenty groups of equal frequency). SIMD is an area-based composite index of deprivation with "equalizing" of varied forms of data on income, employment, education, crime, access, and housing. Deprivation indices have been widely used in Scotland as geographical measurements of poverty, undergoing numerous methodological and data refinements since the 1980s.[57] SIMD was produced according to the rank of datazones from 1 to 6505 and also *vigintiles* — group 1 with most deprivation to 20 for the lowest deprivation. Stratification was performed by cross-tabulating and aggregating the datazones by SIMD viginitile with total male births and total births. This allowed us to calculate secondary sex ratios for each level of deprivation (1–20). All statistical analyses were performed using SPSS version 19.

### Statistical methods

Significance testing was performed by hypothesis testing of two proportions (*z*-test). The two proportions tested were: (1) SIMD vigintile/regional (health board area) sex ratios; and (2) "control" samples of other regional sex ratios in the UK. Male births and total births in the Yorkshire & Humber region were selected as the control region for cumulative health board sex ratios (1973–2010) and for the 20 levels of multiple deprivation. This region was selected as the control due to the roughly equivalent birth totals per year (approx. 30 000), comparable post-war downward trend in sex ratio and similar industrial geography of heavy industry concentrated in urban areas contrasted by expansive rural catchments. Where sex ratios for five separate years of health board areas in Scotland were compared, cumulative birth figures from an earlier national period in Scotland (1974–1979) were used as the control sample. Independence between the two proportions is thus achieved, as time periods are not commensurate. The null hypothesis was that regional sex ratio, or sex ratio for an area-measured deprivation level, is no different than the sex ratio for a similar region or earlier national calculation.

### Spatial analysis

The spatial analysis was confined to a central region of Scotland consisting of six areas (Falkirk, South Lanarkshire, North Lanarkshire, Stirling, Fife, Clackmannanshire) covering 1640 datazones (Fig. 2). Central Scotland is the most industrial area in the country with historically high levels of pollution from old industries, but also with rural areas with low pollution. It contains major sites of industrial pollution in Scotland, such as the Grangemouth INEOS complex and Longannet coal-fired power station, as well as large tracts of contaminated and remediated

land, a legacy of Scotland's heavy manufacturing industry. There is also socio--economic diversity with both urban and rural localities and deprived and non-deprived areas.

Mapping of potential multi-factorial influences on local sex ratios involves creating a projection of modeled endocrine disruptor air pollution emissions from SPRI registered emitter sites over datazone areas in Central Scotland. All datazones were assigned multiple deprivation levels. Significantly low sex ratios ($P<0.1$) in these small-areas are also shown. A simplified modeling of endocrine disruptor air pollution emissions was achieved using the following methodology:

1. Identification of endocrine disruptors on the SPRI Pollutant Search list. Cross-referencing with the Endocrine Disruption Exchange — *List of Potential Endocrine Disruptors* with SPRI Pollutant List.
2. Systematic search of SPRI for air pollutant releases of identified endocrine disruptors for each year from 2002 to 2010 (no records 2003) by six local authorities. Recording of cumulative total emissions (kg) for each site listed.
3. Grid reference obtained for each SPRI emission site using address and postcode from search results and http://www.gridreferencefinder.com. The $X$ and $Y$ co-ordinates were plotted using ArcMap.
4. Simplified modeling of source air pollution by approximating from (1) Met Office wind-roses and (2) air quality scenarios from environmental impact reports on Grangemouth Renewable Plant (2012) and Dunbar Energy from Waste Facility (2008). Three polygons were created using ArcGIS of wind-rose directions (degrees) and predicted distance of pollutants (meters) for SPRI emission sites in (1) Falkirk and Clackmannanshire, (2) Stirling, North Lanarkshire and South Lanarkshire, and (3) Fife.
5. Projection of air pollution polygons layered onto the Central Region datazone layer.

The SPRI emissions data utilized are from declarations made by industrial operators. The SEPA sets wide, flexible criteria for determining the pollutant releases for emitters in SPRI, suggesting some results may be imprecise. Occasional over-estimation errors have also been traced in SPRI, though ostensibly emission values are likely to easily gradate endocrine disruptor pollution between sites.[58] Significances for low datazone sex ratios were calculated by hypothesis testing of two proportions with the second comparator proportion being the national Scotland sex ratio for the same period (2002–2010).

## Results

Figure 1 shows the historical secondary sex ratio linear trend in Scotland from 1865 to 2010. There is a statistically significant downward shift in national birth sex ratio observed starting in 1960 ($R^2=0.243$, $P<0.01$). There is a peak birth sex ratio of 0.519 in 1973. The pattern of declining sex proportions between 1855 and 1905 was similar to the trend of declining sex ratios observed for the period 1970–2010, though birth registration around this time was not reliable. The change in the sex ratio between 1905 and 1973 reflects a similar pattern as in other industrial countries. An explanation offered for this trend is that improvements in obstetrics and mid-wifery have led to lower rates of still births.[2] As fetal mortality disproportionately affects male babies, the sex ratio has climbed over this long period. The cumulative secondary sex ratios for health regions in Scotland from 1973 to 2010 (Tables 1 and 2) provide a regional breakdown, which is in temporal alignment with the declining national male birth proportion period. The figures show significant upward skewing of the sex ratio for the Highland region and lower sex ratios for the Borders and Forth Valley. Although the Forth Valley difference in male birth proportion is not significant ($Z$ score: 1.152), it is potentially noteworthy given that the region's total births constitute over five percent of the national figure.

Table 2 provides "two proportions" testing on health region birth totals for five separate years where Scotland's sex ratio was below 0.510. The three statistically lowest birth sex ratio regions are shown in Table 2. The Forth Valley Health Board area is identified as one of these three lowest regions in four of the 5 years of low national sex ratio. For 2008, the sex ratio value for Forth Valley is statistically significant ($P<0.05$) when compared to the control sample of Scotland's national ratio from 1974 to 1979. From the years 1973–2010, the Forth Valley region contributes to the downward trajectory of the national sex ratio. The larger Lothian region had the lowest sex proportion at birth for all regions in 2001and had a significantly lower sex ratio in 2010 compared with the earlier control sample ($P<0.01$).

In the stratified analysis of sex ratio and SIMD vigintiles (Table 3), there is no step-by-step change in sex proportion from lower to higher deprivation categories. There is a significantly elevated male birth/total birth proportion of 0.5235 for the highest vigintile, the least deprived and wealthiest sub-group of the Scottish population ($P<0.01$). This upwards skewing also occurs for the second most deprived group with a sex ratio of 0.5185 ($P<0.05$). Furthermore, significantly reduced male birth proportion was calculated for vigintiles 13 ($P<0.05$) and 17 ($P<0.05$).

Figure 3 shows the spatial distribution of modeled endocrine disruptor air pollutants, low skewed sex ratio datazones and datazone SIMD levels for the mid area of the Central Region, which encompasses North Lanarkshire, Falkirk, southern Stirling, western Fife, and the northern area of South Lanarkshire. The air pollution polygons reflect the likely dispersal of pollutants based on local windroses
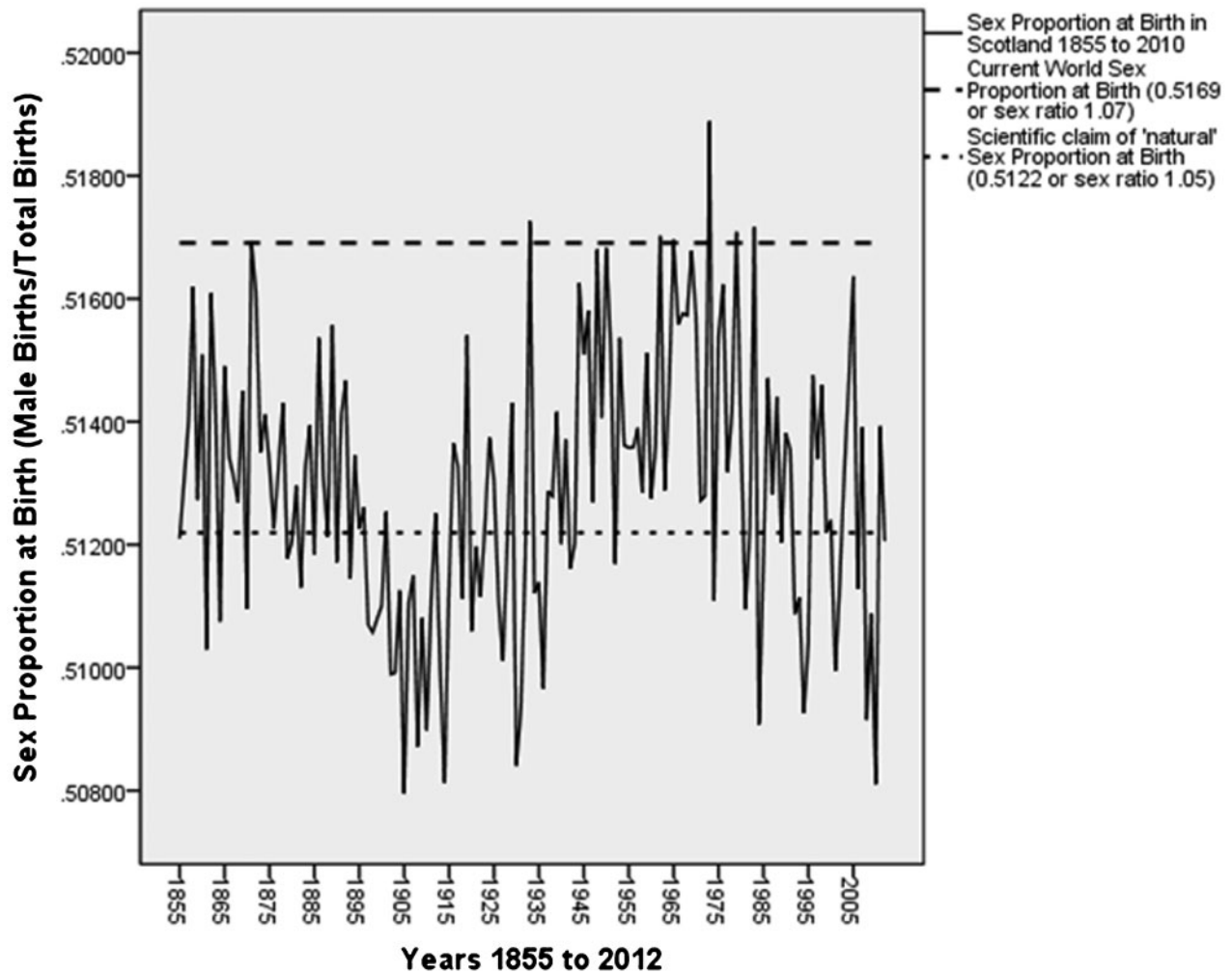
**Figure 1  Sex proportion at birth in Scotland: 1855–2010. Data source: General Register Office for Scotland 2010 (accessed through http://www.groscotland.gov.uk/statistics/births/births-time-series-data.html).**

and other modeling data. They are gradated according to the cumulative annual (2002, 2004–2010) releases in kilograms recorded on SPRI. Low sex ratio datazones are identified based on cumulative male and total births records from 2001 to 2010, with significance at the low tail of the 90% confidence interval. Multiple deprivation measurement of datazones is by five levels based on equal intervals of vigintile categories (1–4, 5–8, 9–12, 13–16, and 17–20).

The maps display a concentration of low skewed sex ratio datazones for some urban and central rural areas within the region. The map does not show a general spatial concentration of endocrine disruptor air pollution with small areas of low sex ratio or for high levels of multiple deprivation and pollution. However, there are some localities with low sex ratio markers that overlap or are proximate to the polygon models of endocrine disruptor air pollution. Of note are; (1) low sex ratio figures for neighborhoods in the Falkirk local authority area, in Grangemouth close to the industrial complex and Bonnybridge (West of Falkirk) replicating results from an earlier study with

1980s data and (2) the large datazone to the east of Rutherglen, which registers a large number of births with an excess of 230 females per 188 males (birth sex ratio=0.45, *P*=0.010).[59]

## Discussion

A spatio-temporal analysis of sex proportion at birth and secondary data on pollution and deprivation reveal important regional differences, which may contribute to Scotland's declining male birth proportion over the last 40 years. Results also show an upwards skewing in the sex ratio among the least deprived and wealthiest populations. We found no combined effect for pollution and socio-economic status, as there was not a consistent concentration of low sex ratio neighborhoods with endocrine disruptor air pollution and deprivation.

For the low "male birth proportion" regions of Forth Valley and Lothian, it is noteworthy that SEPA stated in their 2008 National Air Quality Report that "the majority of Scotland's industrial oxides of nitrogen are generated in east central Scotland."[60] The current study also found that the

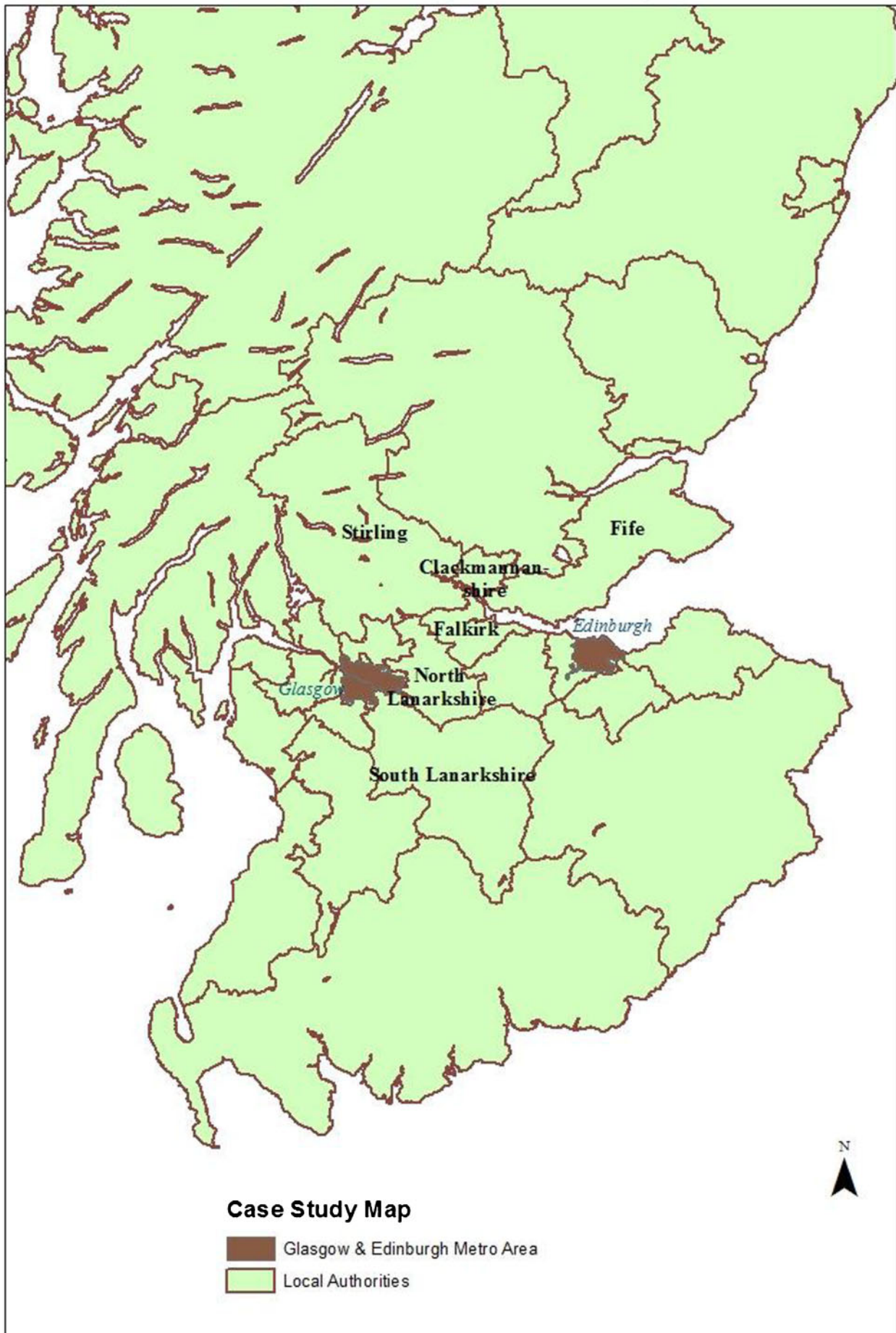**Central Region Case Study: 6 Local Authority Areas**



**Figure 2   Central region case study: 6 local authority areas.**

**Table 1 Large sample significance testing of sex proportion at birth by health region, 1973–2010**

| Health board region | Male births | Total births | Sex proportion at birth | Z score | Two-tail significance test |
|---|---|---|---|---|---|
| Ayrshire + Arran | 83 308 | 162 732 | 0.5119 | 0.4842 | 0.6282 |
| Borders | 21 015 | 41 372 | 0.5080 | 1.8561 | 0.0634 |
| Dumfries + Galloway | 30 505 | 59 640 | 0.5115 | 0.5159 | 0.6059 |
| Fife | 79 231 | 154 753 | 0.5120 | 0.4354 | 0.6632 |
| Forth Valley | 62 268 | 121 888 | 0.5109 | 1.1522 | 0.2492 |
| Grampian | 116 390 | 226 240 | 0.5144 | 1.7244 | 0.0846 |
| Greater Glasgow + Clyde | 300 875 | 586 978 | 0.5126 | 0.0383 | 0.9694 |
| Highland (incl. A + B) | 67 503 | 130 407 | 0.5177 | 3.5705 | 0.0004* |
| Lanarkshire | 136 182 | 265 541 | 0.5128 | 0.2854 | 0.7754 |
| Lothian | 173 421 | 338 582 | 0.5122 | 0.3883 | 0.6978 |
| Orkney, Shetland, and Western Isles | 15 738 | 30 946 | 0.5086 | 1.3953 | 0.1629 |
| Tayside | | | | | |

Note: ''Control'' and second largest sample=Yorkshire & Humber 1974–2010 male births/total births (1 185 114/2 312 167).
*Significant at the 0.01 level.

largest air pollution emitters in Scotland are located in the Forth Valley and Lothian regions. Scotland's only air quality management area for industrial pollution is in Grangemouth in the Forth Valley region, the location of a large manufacturing industrial complex and refinery. The identification of these regional birth sex ratio trends tentatively suggests a possible environmental link to the national male birth proportion adjustment. Localized incidences of a downward sex ratio skewing coupled with high exposure to endocrine disruptor pollution (as shown in Fig. 3) add to this evidence. The 90% significance levels for the neighborhood concentration of low sex ratios however, mean caution must be exercised in drawing such a link. Importantly though, by analyzing data across geographical areas, both

regional (Forth Valley) and local (datazones), the methodological limitations of the ''modifiable areal unit'' problem is partly averted.

A limitation of the stage (3) analyses is that estimating exposure to pollutants in populations with geographical area-based data is in effect a ''moving target.'' The normal movement of persons and households in and out of neighborhoods and regional areas means that assuming transference of pollution and reproductive effects for a given locality is not straightforward. In Scotland, approximately 13% of all households were classified as 'moving households' in the 2001 Census. However, in North Lanarkshire, South Lanarkshire, Falkirk, Clackmannanshire, and Fife, council area populations are less mobile, with percentages below the national figure.[61] We thus

**Table 2 Large sample significance testing of sex proportion at birth by health region for five 'downward' years of national birth sex ratio**

| National/health authority | Male births | Female births | Total births | Sex proportion at birth | Z score | Two-tail significance test |
|---|---|---|---|---|---|---|
| Scotland | 33 144 | 31 962 | 65 106 | 0.5091 | 2.5752 | 0.01** |
| Ayrshire + Arran | 2401 | 2401 | 4802 | 0.5000 | 2.0001 | 0.0455* |
| Tayside | 2411 | 2390 | 4801 | 0.5022 | 1.6987 | 0.0894 |
| Highland | 1932 | 1900 | 3832 | 0.5042 | 1.2745 | 0.2025 |
| Year 1994 | | | | | | |
| Scotland | 31 399 | 30 257 | 61 656 | 0.5093 | 2.4306 | 0.0151** |
| Fife | 2028 | 2082 | 4110 | 0.4934 | 2.6901 | 0.0071** |
| Forth Valley | 1615 | 1594 | 3209 | 0.5033 | 1.2691 | 0.2044 |
| Lanarkshire | 3506 | 3409 | 6915 | 0.5070 | 1.2377 | 0.2158 |
| Year 2001 | | | | | | |
| Scotland | 26 786 | 25 741 | 52 527 | 0.5099 | 1.9705 | 0.0488* |
| Lothian | 4208 | 4123 | 8331 | 0.5051 | 1.7016 | 0.0888 |
| Forth Valley | 1414 | 1403 | 2817 | 0.5020 | 1.3291 | 0.1838 |
| Borders | 529 | 537 | 1066 | 0.4962 | 1.1911 | 0.2336 |
| Year 2008 | | | | | | |
| Scotland | 30 570 | 29 471 | 60 041 | 0.5092 | 2.4526 | 0.0142** |
| Forth Valley | 1711 | 1743 | 3454 | 0.4954 | 2.2413 | 0.025* |
| Borders | 558 | 580 | 1138 | 0.4903 | 1.6291 | 0.1033 |
| Grampian | 3193 | 3130 | 6323 | 0.5050 | 1.5050 | 0.1323 |
| Year 2010 | | | | | | |
| Scotland | 29 872 | 28 919 | 58 791 | 0.5081 | 2.9042 | 0.0037** |
| Lothian | 4921 | 4903 | 9824 | 0.5009 | 2.6639 | 0.0077** |
| Grampian | 3158 | 3096 | 6254 | 0.5050 | 1.5008 | 0.1334 |
| Forth Valley | 1672 | 1658 | 3330 | 0.5021 | 1.4270 | 0.1536 |

Note: ''Control'' and second largest sample for Z score=male births/total births for Scotland from 1974 to 1979 (204 745/397 934).
*Significant at the 0.05 level.
**Significant at the 0.01 level.

hypothesize that mobilization of the population was minimal and that the study populations have likely been living in the study sites and exposed to endocrine disruptors for enough of their reproductive life to potentially impact the primary and secondary sex ratios. Further, the English control region, although similar in several respects in terms of population size, range of industrial activity, and urban/rural settings, is also not identical to Scotland. The available environmental data relate to specific point sources with possible under or over-estimates of releases, and not all endocrine disruptor releases were measured or recorded. Biological monitoring or modeling of exposures is not available.

Area-based measurement can also be imprecise as not all persons residing in an area display the characteristics shown by the indicator, i.e. individuals experiencing deprivation can live in non-deprived areas. There is also a difficulty in temporally aligning all the indicators from the data sets. For example, the SPRI begins in 2002 and no releases were published for 2003. Despite these shortcomings, area-based measurement is predominantly how public health and socio-economic data are constructed in Scotland. Meanwhile, in Sweden, individually tabulated medical and demographic data sets permit comprehensive ecological studies.[47,62] Given the global extent of reproductive health changes observed, countries with different approaches to public health data collection must also be documented. A crucial advantage of utilizing geographical area-based measurement is that it facilitates a *comprehensive* inquiry, both spatially and temporally, of secondary sex ratio change in national and regional populations, rather than by acute events or selected cohort groups.

It is also feasible that confounding, in the form of other pollutants that are not recorded as endocrine disruptors, may be present in the spatial analysis. Recent research undertaken in the Teplice area of the Czech Republic on potential male reproductive effects from exposure to heavy concentrations of sulfur-polluted air is instructive.[63] Damage to the chromatin of sperm initially mediated through environmental chemicals and then transferred genetically though the paternal line an additional hypothesis for consideration on the sex ratio question. Environmentally mediated genetic damage to sperm has been proffered as an alternative explanation to the endocrine disruptor hypothesis for rises in testicular cancers and declines in sperm quality.[64] Exposure to pollutants not identified as endocrine disruptors may therefore compromise some of the spatial concentrations of pollution and low sex ratio flagged in this study. In common with both hypotheses, however, the mediation of chronic long-term exposure of pollution, potentially over generations, and including mixing of low doses of chemicals, requires additional scientific research. Further, the inclusion of secondary sex ratio monitoring with new methods of environmental assessment, on cumulative impacts from pollution, is also worthy of consideration.[65,66] It is noteworthy that in the context of long standing proliferation of industrial pollution in the Central Region, the Lanarkshire and Forth Valley health regions display the highest crude rates (9.9 and 8.8) of cancer of the testis (per 100 000 person-years at risk) in Scotland for the 2004–2008 period.

Furthermore, studies also suggest that increasing male age is associated with greater sperm DNA fragmentation as well as greater probability of a

**Table 3   Large Sample Significance Testing of Sex Proportion at Birth 2001 to 2009 by Datazone SIMD Vigintile**

| Vigintile | Deprivation | Male births | Total births | Sex proportion at birth | Z score | Two-tail significance test |
|---|---|---|---|---|---|---|
| 1 | Most deprived | 17 529 | 34 272 | 0.5115 | 0.3297 | 0.7417 |
| 2 | | 16 736 | 32 278 | 0.5185 | 2.1355 | 0.0327* |
| 3 | | 15 081 | 29 401 | 0.5129 | 0.1862 | 0.8523 |
| 4 | | 13 636 | 26 695 | 0.5108 | 0.5035 | 0.6146 |
| 5 | | 13 208 | 25 865 | 0.5107 | 0.5449 | 0.5858 |
| 6 | | 13 087 | 25 535 | 0.5125 | 0.0399 | 0.9682 |
| 7 | | 12 685 | 24 983 | 0.5077 | 1.4345 | 0.1514 |
| 8 | | 12 245 | 23 787 | 0.5148 | 0.7228 | 0.4698 |
| 9 | | 11 880 | 23 133 | 0.5136 | 0.3480 | 0.7278 |
| 10 | | 12 130 | 23 593 | 0.5141 | 0.5269 | 0.5982 |
| 11 | | 11 943 | 23 379 | 0.5108 | 0.4618 | 0.6442 |
| 12 | | 11 245 | 21 856 | 0.5145 | 0.6148 | 0.5387 |
| 13 | | 10 830 | 21 422 | 0.5056 | 1.9614 | 0.0498* |
| 14 | | 12 004 | 23 361 | 0.5138 | 0.4383 | 0.6612 |
| 15 | | 12 490 | 24 180 | 0.5165 | 1.2663 | 0.2054 |
| 16 | | 11 963 | 23 529 | 0.5084 | 1.1863 | 0.2355 |
| 17 | | 11 138 | 22 041 | 0.5053 | 2.0537 | 0.04* |
| 18 | | 12 416 | 24 285 | 0.5113 | 0.3424 | 0.732 |
| 19 | | 11 211 | 22 129 | 0.5066 | 1.6816 | 0.0926 |
| 20 | Least deprived | 11 206 | 21 404 | 0.5235 | 3.2078 | 0.0013** |

Note: "Control" and second largest sample=male births/total births for Yorkshire & Humber 2001–2009 (281 708/549 798).
*Significant at the 0.05 level.
**Significant at the 0.01 level.

Central Scotland - Cumulative Endocrine Disruptor Pollution (2002, 2004-2010), SIMD (2006) Vigintile and Low Secondary Sex Ratios (2002 to 2010) by Datazone
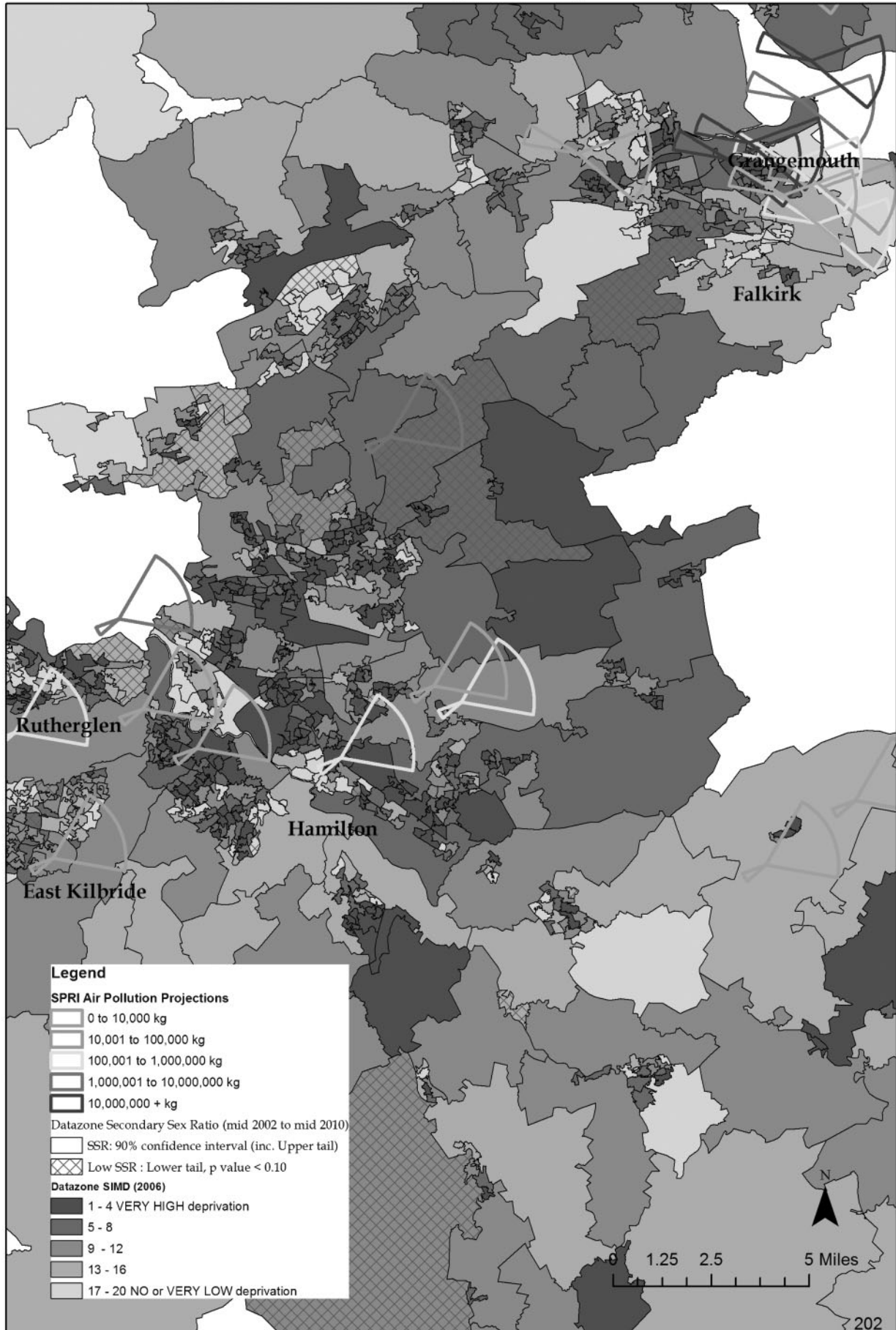


**Figure 3** **Central Scotland: cumulative endocrine disruptor pollution (2002, 2004–2010). SIMD (2006) vigintile and low secondary sex ratios (2002–2010) by datazone.**

partner's miscarriage.[50,51] With the social trend of delayed fatherhood for many men in industrialized countries, increasing paternal age as a contributing factor to the declining male birth proportion is another reasonable hypothesis. Future environmental studies of sex ratio skewing following post-hazardous events and/or heavily polluted areas should consider parental age and stress as confounding factors.

With regard to multiple deprivation, the "spike" in sex ratio for the wealthiest SIMD group would initially seem to reinforce the evolutionary psychological theory of Trivers–Willard described earlier. However, it is contradicted by the stratified results for deprivation and the sex ratio not displaying a gradated trend across the other 19 groups. Furthermore, there was a significant increase in the sex ratio for highly deprived group (vigintile 2). The pollution and SIMD mapping show no evidence of a combined "environmental deprivation" effect on secondary sex ratio. Genomic imprinting during embryogenesis before clinically recognized pregnancy may be a key reproductive process to examine.[67] Adoption and advancement of reproductive medicine and technologies in Western countries may also be linked. There is anecdotal evidence of richer American couples purchasing pre-implantation genetic diagnosis to balance females in families, though empirical research does not indicate any bias towards either daughters or sons among couples.[68,69] In the UK, non-medical sex selection is illegal but may occur. The ethical debate on pre-implantation genetic diagnosis and sperm sorting practices is ongoing.[70]

Relevant and available socio-economic and public health, pollution inventory emissions, and birth sex ratios data sets in Scotland were brought together using GIS. Their analysis provides further tentative evidence for the hypothesis that declines in male birth proportion in some industrialized countries are possibly linked to chronic exposure to pollution by endocrine disrupting compounds. The historical and regional trends and localized skewing of sex ratios found in this study are in line with other studies linking male birth proportion decline with air pollution. The findings have implications for the availability, frequency, and range of future environmental pollution monitoring. They further highlight the importance of continuity and consistency in such sets for meaningful time series analysis to inform health protection policy, especially of vulnerable populations exposed to a range of environmental and socio-economic conditions that may affect ratios. This study provides a foundation for further work to examine the possible relationships between social, economic and environmental factors in a diverse demographic setting with regard to sex proportions. Advanced geo-statistical analyses can be used to help

shed light both on public health issues linked to reproductive health and the significance of particular exposures to pollution and the related effectiveness of environmental regulations in protecting reproductive health.

## Disclaimer statements

## Acknowledgements

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