Multidisciplinary Insights into Health Care Financial Risk

and Hospital Surge Capacity, Part 2:

High Population Density is Associated with Enhanced Year-to-Year Volatility in Many Aspects of Poor Health Including Health Care Worker Sickness Absence

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Abstract

The weighted population density for 349 English local government areas, and the raw population density for a further 58 areas from Northern Ireland and Scotland, were used to demonstrate the role of high population density in the volatility associated with year-to-year total deaths and of excess winter mortality (EWM). Volatility in EWM was measured as the standard deviation over a 20-year period while for total deaths looked at the absolute value of the year-to-year difference expressed as standard deviation equivalents. The volatility in EWM for the most densely populated areas was almost double that of least populated areas. This reached a plateau when weighted population density exceeded 8,000 persons per square Km. For total deaths, the year-to-year average difference was around 35% higher when population density exceeded 7,000 persons per square Km. Death culminates a six-month period of increasing admission to acute hospital which can account for 55% of a person's lifetime use of a hospital bed. Hence the volatility in death is a good measure of volatile costs and capacity pressures. Volatility in costs will follow the year-to-year pattern while hospital capacity pressures will tend to follow the EWM pattern, although with time lags. Population density acts to facilitate the spread of infectious agents, which increasingly arrive via international air travel. Population density is also associated with air pollution which acts to increase systemic inflammation in the population, thereby rendering them more susceptible to infection and adverse outcomes. Dysregulation of the inflammatory response to infection in the elderly implies that infection(s) with otherwise seemingly 'trivial' pathogens can then lead to surges in admissions and deaths which are then reported as a variety of (secondary) diagnoses. Unexplained patterns in average length of stay and the gender ratio for admissions for common conditions, which have previously been ignored, support this explanation. Similar unusual trends in the volatility associated with sickness absence among health care workers are also observed.

Key Points
- Population density is a proxy for air pollution and person-to-person contact, both of which enhance the transmission of infectious diseases
- Highest population density was associated with the highest volatility in year-to-year deaths and of Excess Winter Mortality (EWM)
- Transmissible infections work via the inflammatory immune response to promote acute illness and death in a variety of respiratory and pre-existing conditions, i.e., they often act as the trigger for final demise
- Human pathogens are now known to interact in complex ways
- Multiple infections are far more common than realized
- Unexplained trends and spikes in hospital average length of stay and the ratio of male to female admissions seemingly arise from the network of such infectious outbreaks
- Unusual volatility in sickness absence rates among health care workers is also related to population density
- The higher volatility associated with population density implies that costs associated with the population of large cities will be more volatile than for least populated areas, i.e., there is higher financial risk and greater opportunity for insurance revenue to be out of sync with insurance costs
- The foundations for the health insurance underwriting cycle appear to lie in the time patterns arising from this complex and ever-changing infectious landscape
- For the hospitals situated in large cities, this will manifest in more volatility in winter capacity pressures. However, this will be partly mitigated by larger hospital size necessitated in the more densely populated areas

Introduction

Earlier studies have shown that the year-to-year volatility in deaths, admissions and healthcare costs is both size and location specific, i.e., after adjusting for size some locations have intrinsically higher financial risk than others (Jones 2010a,b, 2012a-h, 2013a-c). This was assumed to be due to location-specific environmental factors including infectious outbreaks.

This study will first outline the fundamental biological/medical basis as to why some locations should show higher cost/capacity volatility. It will then give the corroborating evidence of a role for small-area population density, explore wider health care parameters showing unexplained volatility, and then conclude with the areas for further research.

Overview of infectious outbreaks

Modern society exists in a cocktail of infectious agents. In 2005, over 1,400 species of human pathogens had been identified (Woolhouse and Gowtage-Sequeria 2005). Of the human viruses alone, in 2012 it was estimated that between 89 to 265 new species remained to be identified (Woolhouse et al 2012). A study published in 2012 involving over 26,000 clinical samples specifically looking at bacteria identified 95 novel taxa, 111 novel genera, and 673 novel species (Schlaberg et al 2012). The figure of >1,400 species had suddenly jumped to >2,000 species in one leap.

A disturbing number of new species of bacteria causing human infection are emerging from those previously considered to be non-pathogenic (Sekowska and Gospodarek-Komkowska 2019). A search of the term "new species in clinical samples" in Google Scholar restricted to papers published since 2016 yields hundreds of results.

In England, only 60 of these >1,400 species are 'notifiable' to Public Health Agencies (Public Health England 2020). High volume air travel and airports distribute these agents with disturbing ease (Kumala 2017, Pequeno et al 2020). Indeed, 1,400 species is the tip of the iceberg, since each species will have multiple strains and sub-types. Testing for atypical pathogens in something as common as pneumonia varies considerably between countries and hospitals (Gramegna et al 2018).

Indeed, outbreaks of different strains of the same species, i.e. the two coronaviruses SARS and COVID-19 can show markedly different spatiotemporal (space-time) patterns of infectious spread (Zhang et al 2020).

Accurate diagnosis of cause and effect is not simple. Up to 200 different species of virus can cause symptoms of the common cold (National Institutes for Health 2009). Rhinovirus, the most common cause of the cold, has 99 distinct types. This vast array of species/types/variants gives ample scope for health professionals to dismiss the potential implications of exactly why someone is feeling 'unwell'. The don't worry, its only a virus syndrome. Indeed, while most pathogens are of little consequence to younger adults, the same cannot be said for the elderly.

No pathogen operates in splendid isolation and an increasing number of interactions between pathogens and between the intestinal microbiota are being identified (Brundage 2006, Xie et al 2020, Zuo et al 2020). In addition, humans accumulate a variety of persistent pathogens throughout their lifetime (Noppert et al 2019), called the 'pathogen burden', which has been implicated in the progress and severity of several diseases (Mundkur et al 2012, Sharma et al 2016). Active co-infection with multiple pathogens (different species and different strains of the same species) is far more common than appreciated (Seinost et al

1999, Rippee-Brooks et al 2020). This cocktail of infections has been linked to human mortality (O'Sullivan et al 2020).

Vaccination can diminish the impact of health services and a national rotavirus vaccination program in Finland led to large reduction in bed occupancy for acute gastroenteritis (Hartwig et al 2014).

For example, Americans make 2.3 billion recreational journeys within the U.S. each year, they make a further 93 million journeys to other countries, while 80 million international visitors arrive each year (Condor Ferries 2020). The opportunities to import and transmit pathogens are vast. The specifics of how population density and other environmental factors interact will now be briefly covered.

Population density and air pollution

The spread of measles epidemics is profoundly influenced by population density (Tarwater and Martin 2001). As population density increases so also do the contact rates between individuals, however, this saturates at high density (Hu et al 2013). These authors noted that "in crowds with unusually large densities, e.g., transportation terminals, stadiums, or mass gatherings, the lack of organized social contact structure deviates the physical contacts towards a special case of the spatial contact model" (Hu et al 2013). Hence persons living in large cities will experience a mix of two types of exposure.

Population density has been linked with the spread of COVID-19 in both the USA and the UK (Jones 2020), in Europe (Johnson 2020), Brazil (Pequeno et al 2020), Japan (Hirata et al 2020), and Algeria (Kadi and Khelfaoui 2020). Note that the best studies used weighted or lived population density rather than raw or standard population density (Johnson 2020). The latter can give misleading results. However, population density is also associated with air pollution which increases as a power-law function of population density (Lamsal et al 2013).

Air pollution acts to increase the potency of respiratory infections including COVID-19 (Domingo and Rovera 2020). A high air pollution index was associated with an 80% increased risk of SARS fatality (Cui et al 2003). Airborne particulate matter (PM 2.5 and PM10) has been implicated in the spread of COVID-19 and its morbidity and mortality (Comunian et al 2020, Setti et al 2020, Wang et al 2020, Wu et al 2020, Tung et al 2021). Ambient NO2 increases systemic inflammation in COPD patients (Dadvand et al 2014), pollutants (PM2.5 and black carbon) also increase inflammation in Type 2 diabetes (O'Neill et al 2007). Another study demonstrated that different pollutants affected different inflammatory markers (Bind 2012). Long-term exposure to PM2.5 is also associated with risk of Alzheimer's and other dementias (Wang et al 2020), and combinations of air pollutants increase cognitive decline in adults (Chen et al 2021).

Seasonality in deaths and the effect of temperature

Deaths generally peak during the winter months, and in England and Wales, reach a minimum in August, and a maximum in January (around 60% higher than the daily minimum) (Jones 2013c). The winter peak is due to a mixture of cold, mainly due to physiological changes upon exposure of the respiratory tract to cold air (Mourtzoukou and Falagas 2007), seasonal gene expression (Shi et al 2009, Dopico et al 2015, Goldinger et al 2015), and lower levels of Vitamin D leading to impaired innate and adaptive immunity (Baggerly et al 2015, Aranow 2011), especially in the elderly (Meehan 2014, Kuwabara et al 2020), which be sensitive to cloud-free hours of sunlight during the summer (Garland et al 2016). In combination, these promote susceptibility to, and circulation of, winter infectious (typically respiratory) agents (Fleming et al 2005, Fleming and Elliot 2008).

Temperature is a well-recognized factor in the mortality rates for different diseases (Chen et al 2018, Bareca et al 2012). The effect of cold and heat on mortality has been characterized by a comprehensive Dutch study (latitude of Netherlands is 52.34 which is roughly the midlands of England) which showed that mortality reached a minimum around 17 ^{O}C but requires a +10 or -22 ^{O}C deviation from 17 ^{O}C to elevate daily mortality by 14% (Ekamper et al 2009). Hence it requires an extended period of unusual cold (relative to average at that time of the year) to make a large impact on deaths. The mortality risk of extreme cold lasts longer than that from extreme heat (Chen et al 2018), and the shape of the temperature-mortality profile varies considerably between countries, as does the temperature for minimum mortality (Gasparinni et al 2015).

In addition, one study has demonstrated that rates of consultation for inflammation-related diseases also varies with temperature. Low temperatures were associated with higher consultations for all types of inflammatory conditions, while high temperatures were only associated with gastroenteritis (Wang et al 2020). Cold air acts to increase inflammation in the lung (Larsson et al 1998). Interestingly, faster spread of COVID-19 in Brazil was associated with lower temperature (Pequeno et al 2020). The association of low temperature with inflammation is important since inflammation is identified as a risk for infection, followed by infection-induced additional inflammation.

Role of infections and inflammation

Infection is usually followed by a 'protective' inflammatory response which can become dysregulated, especially in the elderly, with lethal consequences (Levi et al 2003, Bauer and Wetzka 2020, Channappanavar and Perlman 2020). With over 1,400 species of human pathogens, there is ample scope for local infectious outbreaks of unknown origin (Woolhouse and Gowtage-Sequeria 2005). The vast majority of these are not 'notifiable' pathogens and so will remain largely unreported and un-investigated.

Regarding influenza-like illness (ILI) one study identified that in addition to influenza(s) there are at least eight common viruses causing ILI (Taylor et al 2017). In another study, 44% of ILI respiratory swabs yielded multiple viruses (Dierig et al 2014). ILI can also be caused by bacteria, fungi, and parasites.

As mentioned above, the ensuing inflammatory response after initial infection becomes less regulated in the elderly (Boyd and Orihuela 2011). In the lung, this can lead to secondary bacterial pneumonia or direct damage to the lung by the inflammatory response (Jabr 2017). Around 30% of Influenza deaths arise from the effects of inflammation on pre-existing conditions outside of the lungs (Jabr 2017).

Few would realize that obesity is itself a serious inflammatory 'disease' (Karczewski et al 2018), which predisposes the obese to a higher risk of infection and poor outcomes from infection (Fernandes and Manuel 2017). Somewhat perversely some infections can also promote obesity (Akheruzzaman et al 2019). Elevated levels of C-reactive protein (CRP), which is a measure of inflammation, are associated with international travellers attending the ED due to overseas acquired illness (Herbinger et al 2016), and in detecting persons with viral and atypical bacterial infections (Duran et al 2016). However, chronic elevated CRP is also associated with disease progression and as an early biomarker of inflammatory disease onset (Luan and Yao 2018). Numerous industrial, household, and agricultural chemicals promote chronic inflammation (Furman et al 2019). Hence it should come as no surprise that reasonably common conditions such as appendicitis *in adults* follow local trends influenced by air pollution (as an example of chronic inflammation) and common infections (Jones 2015).

Age immunoscenescence and inflammaging

Aging is associated with both immunoscenescence and chronic low-grade inflammation called inflammaging (Fulop et al 2018, Thomas et al 2020). The immune response to vaccination wanes with age especially in those who are infirm (Ciabattiani et al 2018). For these reasons, the elderly are more prone to disease and more specifically infectious disease (Ebihara 2011, Batista et al 2020). Prescription of multiple drugs in old age (polypharmacy) further erodes the immune response with diminished vaccine effectiveness (Agarwal et al 2018).

The last year of life

Healthcare demand depends far more on proximity to death than age. A score based on self-reported health rose from 3.46 at 15 years prior to death to 4.43 at one year prior to death (Stenholm et al 2016). Cognitive ability and wellbeing decline slowly with age but becomes more rapid 3-5 years prior to death (Stenholm et al 2016, Cohen-Mansfield et al 2018). Failure to account for nearness to death wrongly attributes decline to age per se (Rabbitt et al 2008), hence the sound bite "it's all due to the aging population". This is called the constant risk fallacy (Nicholl 2007).

The last year of life sees a transition from independence to requiring increasing help with the normal activities of life. For example, one study showed that 20% of persons in the last year of life had 6 limitations in the activities of daily living (ADLs) while only 6% of persons had 6 ADLs in the year prior to the last year of life. Some 63% of persons had no ADLs in the year before the last but 58% had 1 or more ADLs in the last year of life (Kalbarczyk-Steclik and Nicinska 2015). This decline is compressed in cancer patients (Kalbarczyk-Steclik and Nicinska 2015, Stenholm et al 2016). Admissions to hospital in the last year of life can account for 55% of lifetime bed occupancy (Hanlon et al 1998), and this occurs with increasing frequency in the last six months of life – irrespective of age (Larsson et al 2008, Thorn et al 2016, Jones et al 2016). It is of interest to note that a composite score based on common blood biochemical tests shows a sudden shift to a higher (worse) score in the months prior to death (Jones et al 2016). This appears to be linked to the progressive increase in admissions in the last six months of life.

A functional aging index combined with frailty can predict entry into care and mortality (Finkel et al 2019). Elderly patients (aged 65+) with community-acquired pneumonia who were frail had a 2.9-times higher risk of death within one year of hospital discharge (Luo et al 2020).

A U.S. study conducted between 1998 and 2010 showed that the prevalence of pain, depression, periodic confusion, dyspnea, incontinence, severe fatigue, and anorexia all increased over time (Singer et al 2015). Many of these can be related to inflammation and infection so it could be possible that the susceptibility to infectious outbreaks is increasing with time. As it were, those in the last year of life are waiting for any agent capable of precipitating final demise.

Results

Year-to-year variation in total deaths, U.S. States

Table 1 shows the top 15 U.S. states with the highest year-to-year volatility in deaths, relative to the state with the lowest volatility (Wyoming and Vermont, relative volatility = 1). These are mostly the states with highest weighted population density.

Table 1: Top 15 U.S. states with highest year-to-year relative volatility in the rolling 12-month total of deaths, 2007 to 2019.

| State	Relative volatility
Florida	5.65
Texas	5.19
California	4.41
North Carolina	4.27
Ohio	4.05
Pennsylvania	3.89
Arizona	3.62
Georgia	3.58
Virginia	3.38
New York	3.24
Indiana	3.22
Massachusetts	3.19
Illinois	3.19
Maryland	3.10
New Jersey	3.04

Figure 1 compares the rolling year-on-year volatility in deaths between Florida (highest relative volatility) and Vermont (lowest). The chart starts at the difference between the sum of deaths during 2007 compared to 2008, move forward one month and repeat the calculation.

Due to their difference in number of deaths, a 1 standard deviation difference due to Poisson- based chance equals ± 1.3% in Vermont but just ± 0.2% in Florida (Koehrsen 2019). Hence while the chart shows roughly similar percentage changes, the effect of size dramatically increases the relative volatility for Florida compared to Vermont. Hence the use of size-adjusted volatility throughout this study. However, note the differences in shape and timing, and the peculiar absence of influenza-only features. In a rolling 12-month chart a 'spike' in deaths due to influenza shows up as a rectangular-shaped feature with a base which is roughly 12-months wide. This is because the spike in deaths enters the rolling 12-month total, stays there for 12-months, and then drops out of the rolling total. The significance of some of these trends will be discussed in Part 3 of this series.

While Public Health agencies seek to promote the simple 'word bite' story that major surges in deaths are due to influenza, the data in Figure 1 does not support such a simple explanation. Hence while influenza is important, it is not exclusively so and cannot explain the more nuanced trends over time, and between states. As explained above no pathogen operates in splendid isolation.

The problem with analysis at state level (above) is the huge size of the USA. For example, England has a surface area of 50,350 square miles, of which 21% is urban development. This is roughly the same size as Arkansas, Alabama, and North Carolina. On the other hand, Texas is 5-times the size of England (Wikipedia 2020a,b). From Poisson statistics, we need a spatial area with 500 to 1000 deaths per annum to achieve a degree of reliability that the differences are not due to chance (Koehrsen 2019). Local authority areas in the UK fit these criteria and have associated widely different weighted population densities.

Figure 1: Rolling year-to-year change in total deaths for Vermont and Florida based on a rolling 12-month sum of monthly data from January 2007 to March 2019. Utah and the USA have been added to illustrate wider trends.
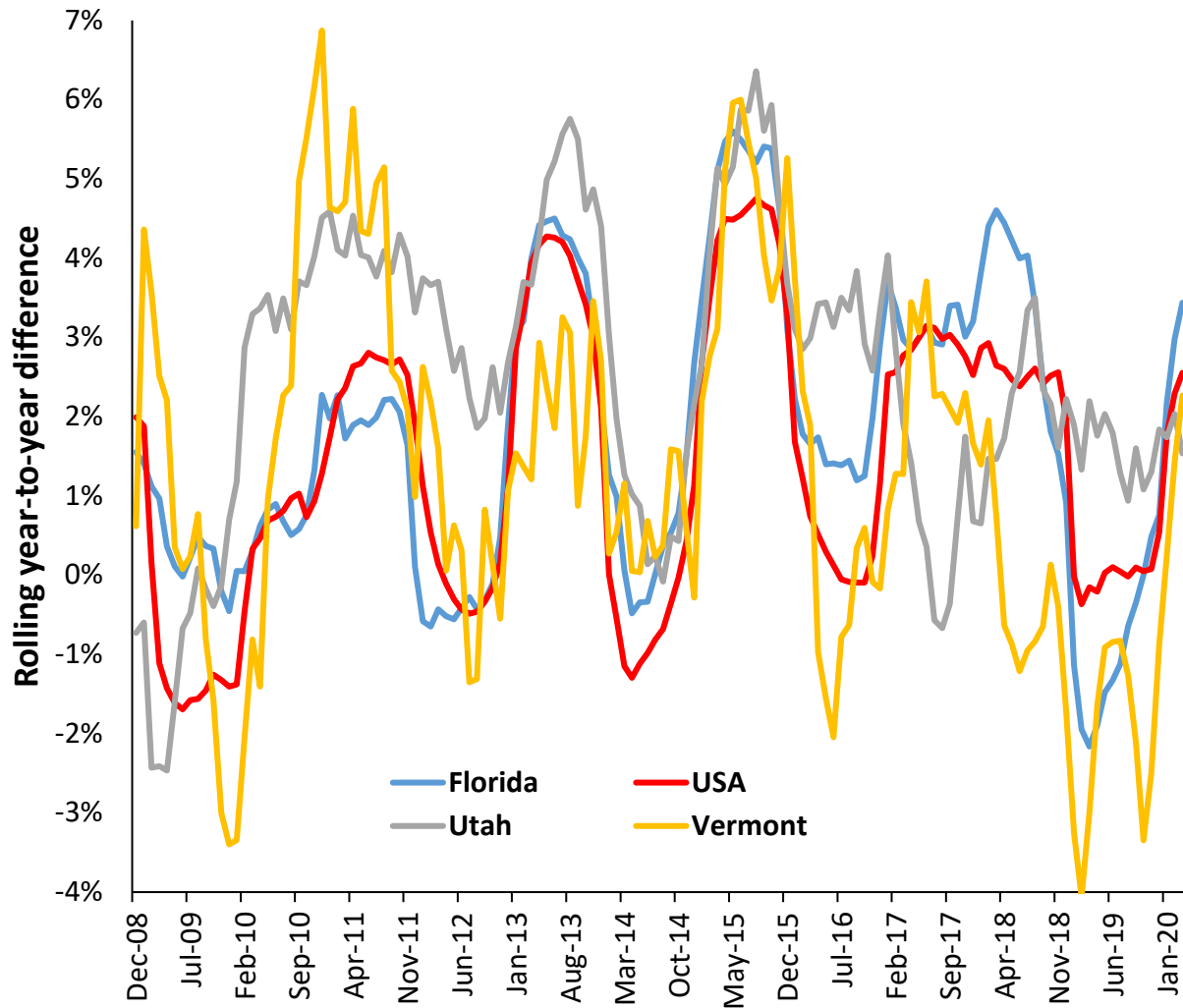

Year-to-year variation in total deaths, 349 English Local Authorities

Year-to-year variation in total deaths was plotted versus weighted population density for each local authority in England and Wales as shown in Figure 2. As can be seen, the average year-to-year volatility increases with weighted population density and appears to reach a maximum (saturates) around a population density of 7,000 per square Km (18,000 per square mile). A linear relationship may apply, although the high scatter after averaging using 10 consecutive local authorities indicate that other factors also influence the volatility. These could include weather patterns and social behaviours. The relative number of nursing home beds in each local authority will make a significant contribution to the volatility see in Figures 2 to 5 (Jonker et al 2013).

While average volatility is a useful measure, the standard deviation (STDEV) around the average is a better measure of the volatility in costs and capacity relating to the last year of life. This is shown in Figure 3.

Figure 2: Average year-to-year difference (volatility) in deaths for English and Welsh local authorities, 2001 to 2020, versus weighted population density. Each point is the average of 10 local authorities ranked by weighted population density, but data is selected at 100 increments of weighted population density.

Weighted population density per square Km
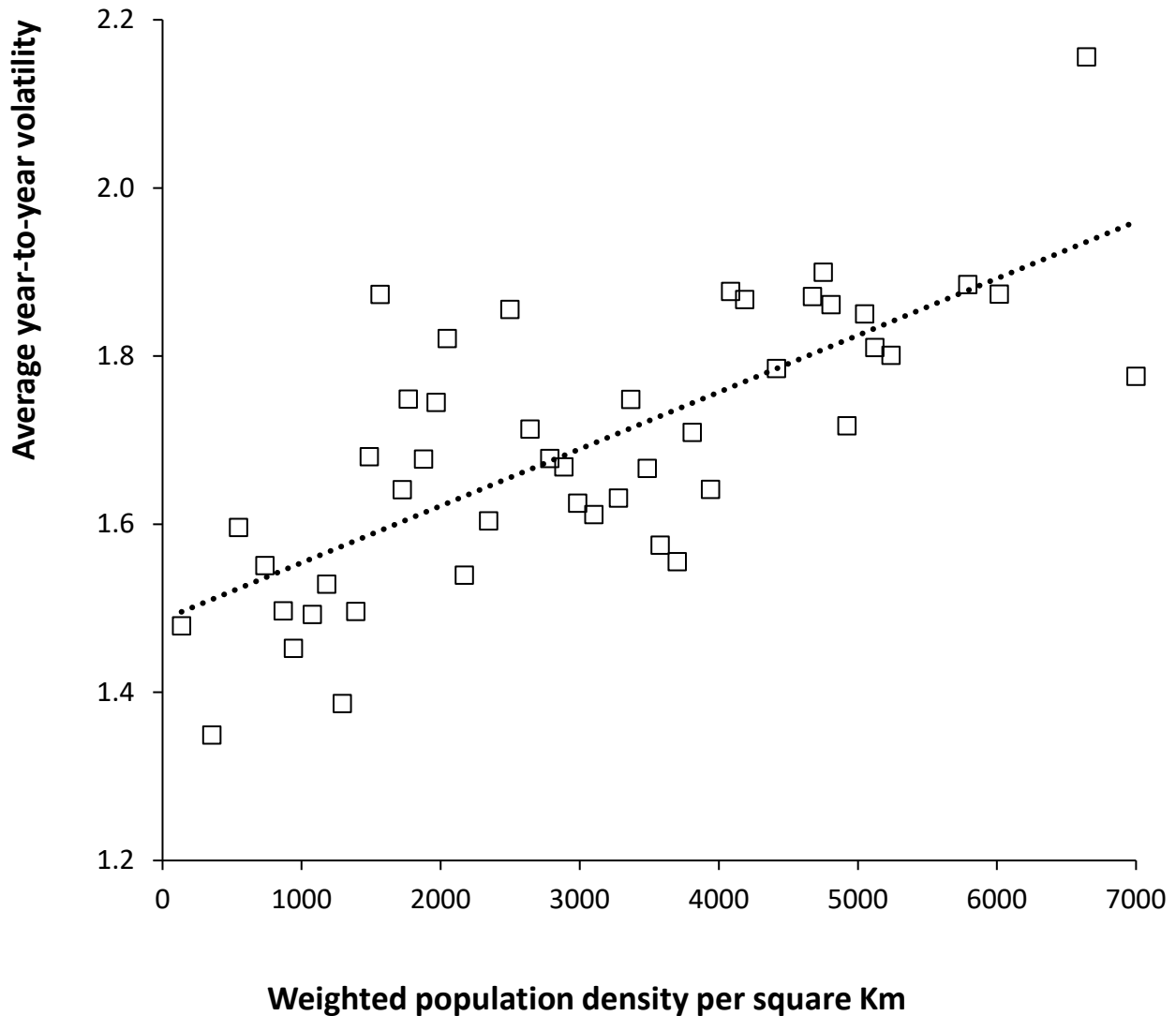
As can be seen in Figure 3 a non-linear relationship may be possible up to a maximum (saturation) somewhere around 8,000 per square Km (21,000 persons per square mile). Many local authorities in London exceed this upper limit with 21,362 per square Km in Tower Hamlets, 20,430 in Westminster, i.e., up to 52,000 per square mile.

However, the key point has been established that population density is a key variable in volatility for costs and capacity associated with end-of-life. Also, that this relationship reaches a maximum (saturates) as predicted from theory (Hu et al 2013). Scatter in the relationship indicates that additional factors are involved at a local level. Recall that equal population density does not imply equal levels of air pollution.

Figure 3: Standard deviation (STDEV) associated with the year-to-year differences in total deaths, as per Figure 2.

$$y = 1E\text{-}08x^2 + 1E\text{-}05x + 1.2103$$
$$R^2 = 0.8655$$

STDEV of year-to-year differences

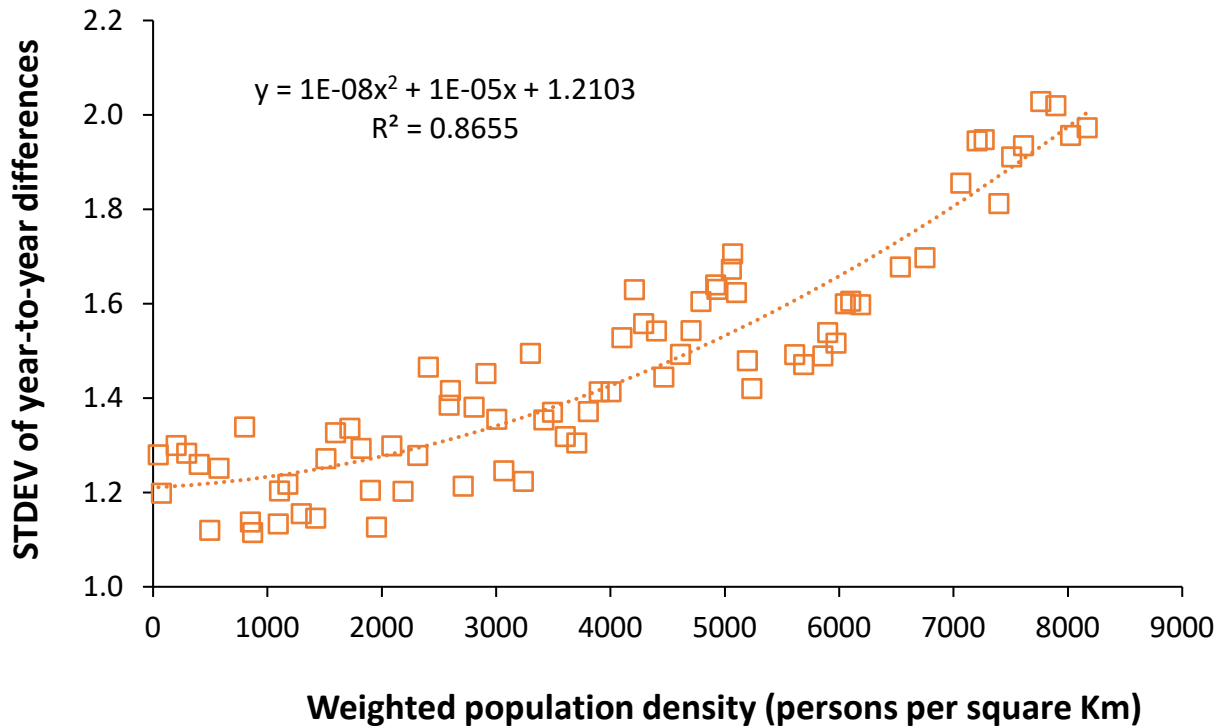Weighted population density (persons per square Km)

Figure 4: Relationship between raw population density and the adjusted standard deviation (STDEV) associated with year-to-year deaths in 58 Scottish and Northern Ireland local authorities, 2001 to 2020.

STDEV relative to expected for size

Raw population density per square Km

Year to year variation in total deaths in 58 Scottish and Northern Ireland local authorities

Population density in Scotland and Northern Ireland is far lower than that in England. At the time of this study, small area population densities for these countries were not available and so unweighted (raw) population density has been used.

Figure 4 shows the relationship between the standard deviation in year-to-year deaths, after adjusting for the effect of size on the standard deviation (as above) and raw population density. Each point is an average of five local authorities. On this occasion, the standard deviation has been calculated relative to that expected for size (number of deaths). Recall that raw population density significantly underestimated the weighted population density (Decision Science News 2017). Volatility is around 20% higher at around 3,500 per square Km. However, even within the limitations of this data, the relationship between population density and volatility is still clear.

Volatility in Excess Winter Mortality

Since higher deaths occur during the winter months a measure called excess winter mortality (EWM) has been developed which compares average deaths in the four 'winter' months with the eight 'non-winter' months (Healy 2003). A study conducted in the South West Region of England between 1994 and 1998 at electoral ward level did not detect any association between Townsend deprivation score or population density and the average winter mortality (Lawlor et al 2002). This study did not note a strong association between average EWM and population density. This is because EWM is largely driven by multiple factors, the most important seeming to be indoor temperature (National Institute of Care Excellence 2009, Hamilton et al 2017, Ogbebor et al 2018, Thai et al 2019). These other factors would act to obscure any relationship. However, no one seems to have investigated the year-to-year volatility in EWM and any relationship with population density.

The standard deviation associated with raw EWM needs to be adjusted for size (number of deaths) since there will be greater statistical scatter associated with the smallest local authorities. This adjustment was made by fitting a power-law relationship to the raw data of STDEV in EWM versus average deaths in each local authority. STDEV was adjusted to the equivalent at 1,000 deaths per annum which is roughly the average size for local authorities. Each point is an average of 10 local authorities as above.

Figure 5 shows the resulting relationship between the standard deviation associated with EWM and population density. A non-linear relationship appears to apply up to a maximum (saturation) at around 8,000 per square Km. As above, volatility is roughly double in the most densely populated areas as that observed in least densely populated areas. A third-order polynomial has been used to explore the shape of the possible relationship. Multiple issues are involved in EWM (National Institute of Care Excellence 2009), however, while a full understanding of the causes may be unclear its impact upon capacity and costs is clear. To my knowledge, this is the first large study of volatility in EWM using 20 years of data covering 349 local authorities with weighted population density.

In conclusion, for deaths (end-of-life) both the average volatility and the standard deviation around the average show dependence on population density with implications to capacity and cost volatility. Any relationship with the average EWM is obscured by the multiple factors affecting the average, however, the standard deviation (Volatility) shows a clear relationship.

Figure 5: Standard deviation (STDEV) associated with Excess Winter Mortality (EWM) in English and Welsh local authorities (2000/01 to 2019/20)
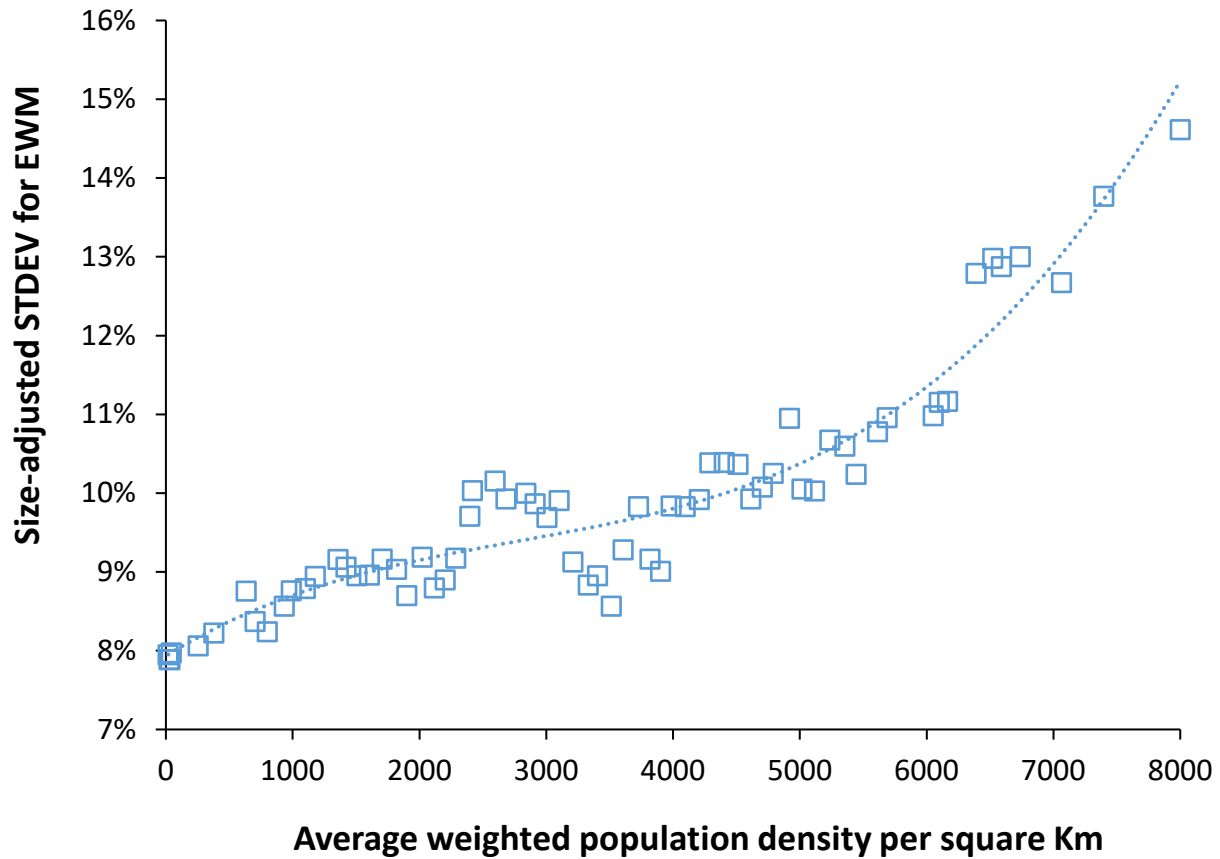
Based on the proposal that mini-infectious outbreaks are occurring in different locations data relating to admissions from the English NHS will be used to explore if parameters such as length of stay and the gender ratio of admissions show unexplained year-to-year volatility. Finally, volatility in health care worker sickness absence across English regions will be explored.

Appendix 1 gives a wider discussion of the role of place in the volatility associated with weighted population density.

Length of stay shows 'unexplained' undulations

Hospital average length of stay (LOS) has been a traditional measure of hospital efficiency which is presumed to be under the direct control of hospital managers (Buttigieg et al 2018). However, if we accept the hypothesis that multiple infectious outbreaks lie behind surges in admissions and deaths for many common conditions, then it should follow that LOS should likewise show 'unexplained' peaks and undulations. See Part 4 of this series for further evidence and analysis.

Figure 6 shows evidence for such peaks and undulations for the average LOS in the medical group of specialties between 2005/06 and 2019/20. This is a large data set with 4.9 million admissions in 2005/06 rising to 8.5 million in 2019/20, i.e., changes in LOS are not due to sampling error in small samples. Rapid reduction in LOS over time prior to 2005/06 has meant that this period has been excluded from the

analysis. Over this period the underlying trend to lower LOS (average of 5.8 days in 2005/06 falling to 3.5 days in 2018/19 and 2019/20) was fitted to a polynomial equation and the difference between trend and actual calculated.

Figure 6: Deviation of financial year average length of stay for the medical group of specialties from the underlying trend for England, 2005/06 to 2019/20. The medical group includes all medical specialties, clinical specialties, haematology, oncology, rehabilitation, and palliative care.
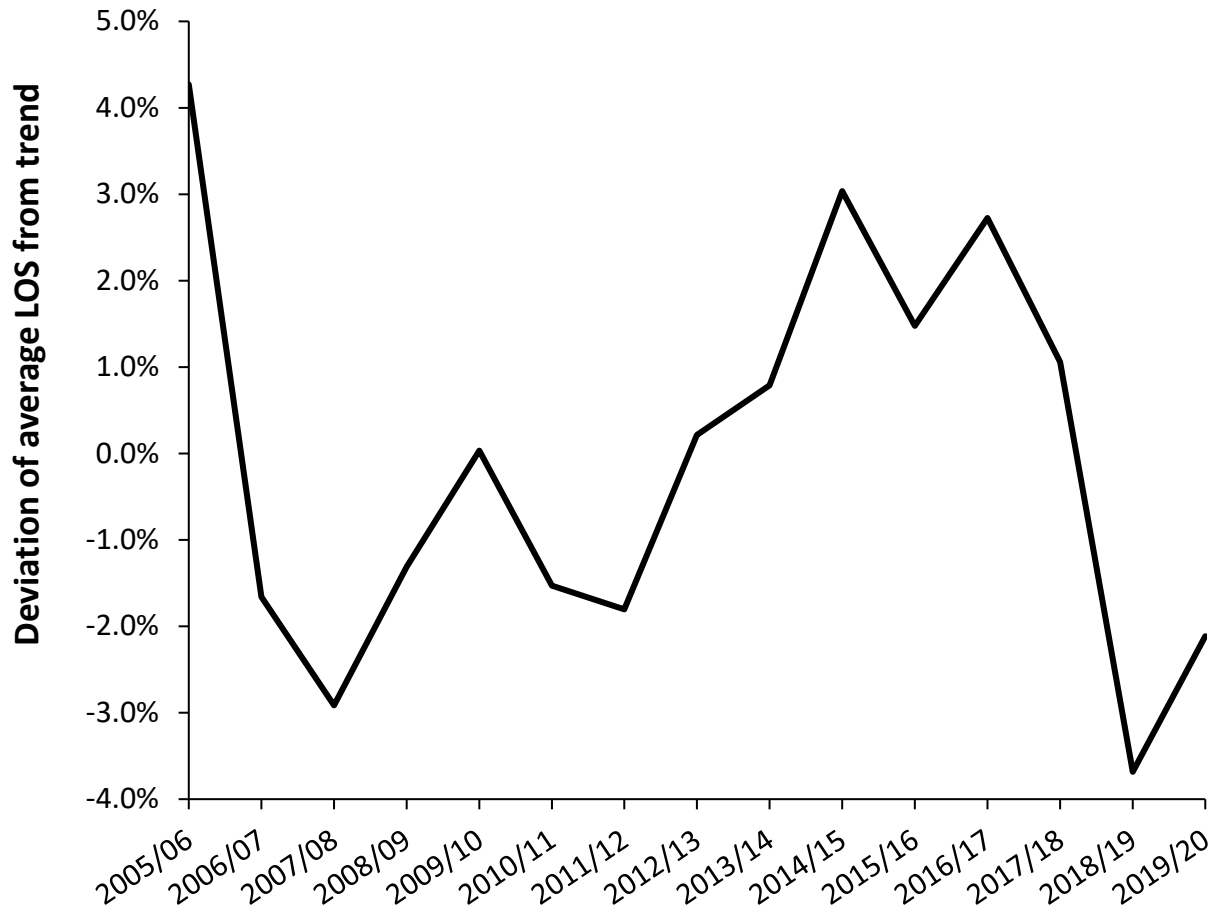
The medical group includes all the medical specialties, haematology, oncology, and various clinical specialties. The expected 'unexplained' trends emerge which are the combined result of subtle changes in case mix and patient illness severity arising from the multitude of infectious outbreaks which will have occurred across England over this period.

While this is not conclusive proof of the proposed cause, it nevertheless suggests that more detailed investigation is warranted.

Curious trends and fluctuations in the gender ratio for admissions

The immune system in women has fundamental differences to it than in men, in that women must be able to avoid immune rejection of the foetus during pregnancy (Aghaeepour et al 2017). Interestingly, these immune changes are sensitive to the prevailing burden of infectious agents, i.e., location-specific (Hove et al 2020).

Table 2: Top 15 specialties where the proportion of male admissions shows higher than expected variation (STDEV). England 1998/99 to 2019/20

Specialty	Average male admissions	STDEV
All Specialties	7,166,888	2.21
Medical Oncology	95,397	1.63
Nursing	10,658	1.59
Allied Health Professional	5,633	1.56
General surgery	817,509	1.55
Clinical oncology (radiotherapy)	134,139	1.54
Mental illness	65,067	1.47
Urology	513,585	1.47
Tropical Medicine	506	1.31
Forensic psychiatry	2,200	1.28
General medicine	1,316,796	1.25
Accident & Emergency (A&E)	220,847	1.22
General Practice (mainly elderly)	31,794	1.16
Plastic surgery	123,989	1.08
General pathology	835	1.04
Rehabilitation	13,959	1.03

Table 3: ICD-10 chapters (body systems) where the proportion of male admissions shows higher than expected variation, England 1998/99 to 2019/20

ICD-10 Chapter	Description	Average male admissions	STDEV
A	Mainly bacterial	105,358	2.52
R	Signs & Symptoms	845,902	2.21
S	Injuries & fractures	347,468	2.05
J	Respiratory	580,129	1.83
N	Genitourinary	404,707	1.79
K	Digestive	921,397	1.51
Z	Health Services	488,230	1.41
C	Cancers	694,212	1.38
I	Circulatory	730,816	1.13
D	Blood forming	283,055	1.10
F	Mental & behavioural	124,760	1.06
B	Virus, fungi, protozoa	63,538	0.97
H	Ear & mastoid	284,874	0.96
M	Musculoskeletal	451,518	0.81
E	Endocrine & metabolic	128,155	0.80
P	Neonatal	131,446	0.72
T	Burns, poisoning, etc	182,450	0.61
G	Nervous	161,028	0.55
L	Skin & subcutaneous	173,277	0.53
Q	Congenital	65,423	0.48

The genders differ in their response to and susceptibility to many diseases and infectious agents (Canadian Women's Health Network 2012, Klein and Roberts (eds) 2015), which extends to differential infection with strains of the same pathogen (Long et al 2000). This author is not aware of any study which has followed the ratio of male to female admissions over time, however, given the differential susceptibility of the genders to inflammation and infection it would be expected that certain specialties may be more susceptible to the infectious landscape proposed in this study. This is an entirely neglected area of investigation (Jones 2011, 2012, 2013) and the unexplained trends have probably been dismissed as 'statistical' scatter or 'poor' coding. Tables 2 and 3 shows that this is indeed the case for both specialties and diagnoses within body systems. The gender ratio in this study is expressed as the percentage of male admissions.

Figure 7: Trend in the proportion of male admissions for diagnosis R69 (unknown and unspecified causes of morbidity and mortality) in England between 1998/99 and 2019/20. The standard deviation due to chance alone varies from ± 0.03% to 0.05% depending on the year, i.e., chance variation can be categorically excluded
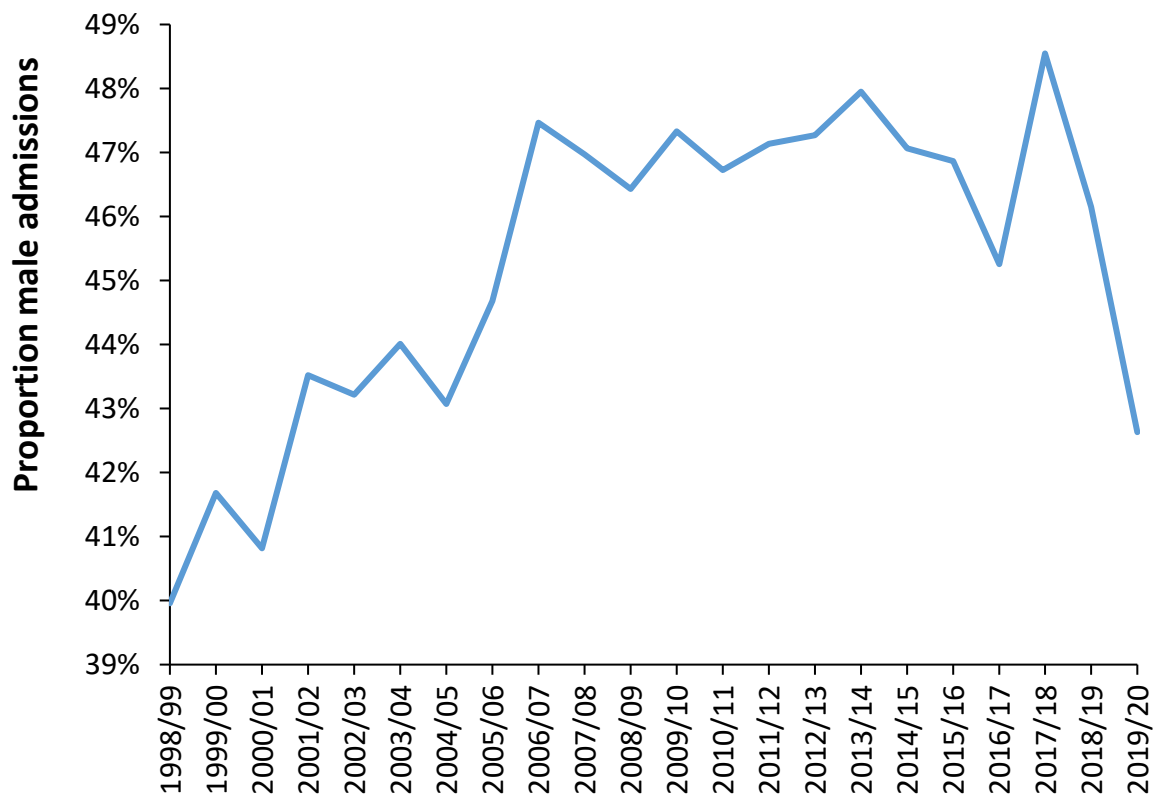
The specialties in Table 2 mainly involve medical care or surgery to remedy the outcomes of medical disease processes. Specialty A&E is mainly medical assessment. The presence of mental health specialties is entirely consistent with the known relationships between immune function and mental health (Anisman et al 2019), and the fact that some pathogens are either neurotropic or associated with neuropsychiatric disorders (Tucci et al 2017, Munjal et al 2017, Ciurkiewizc et al 2020).

I have previously documented unusual trends in admissions for injuries and fractures as per Table 3, and the explanation lies in the fact that the inflammatory response to an infection will generally accompany headache and an associated increase in clumsiness; hence, an increase in falls, injuries and fractures. Most of these admissions are for the elderly as a medical admission, but more serious fractures are to trauma and orthopaedics. Note the difference between Chapters A and B in Table 3 which cover different groups of pathogens.

The entire list of ICD-10 chapters has been included in Table 3 (except Childbirth) to show the wide range in volatility between chapters. The situation at specialty level can be replicated for individual diagnoses and diagnosis R69 (unknown and unspecified causes of morbidity and mortality) is shown in Figure 7. Diagnosis R69 is a highly relevant diagnosis since it is indicative of "we know you are ill enough to get admitted but we don't know what is wrong with you". This is the type of diagnosis that would be expected to arise from the subtleties of undocumented infectious outbreaks and their medical consequences (as seen in Chapter R in Table 3).

In the U.S. commercial pressure to maximize income would mean that R69 would generally be up coded by conducting more investigations to find something 'wrong' with the patient. The general ambiguity resulting from multiple infections and inflammation would then be lost.

As a final comment, it is my belief that the current system of diagnostic coding is unable to reflect the nuances of multi-organism infection, inflammation, and immune function in the need for admission among the elderly.

Considering the above, it should come as no surprise to note that the gender ratio at birth also shows unexplained volatility (Jones 2017).

Having investigated the presence of curious patterns in LOS for admissions and the gender ratio of admissions, the issue of sickness absence rates among health care workers can now be explored.

Sickness absence in health care workers

Health care workers are directly exposed to patients and therefore are a high-risk group for the acquisition of a wide range of infections. If the proposed mechanism of infectious exacerbation of existing illness is correct, then the year-to-year volatility in sickness absence among health care workers should go from less volatile in the least densely populated region through to most volatile in the most densely populated region.

This relationship is confirmed in Figure 8 where the South West of England (Cornwall, Devon, Dorset, Somerset, Wiltshire, etc) is the least densely populated, followed by the East of England (Norfolk, Suffolk, Cambridgeshire, Essex, etc) with London being most densely populated. The North West contains the large Liverpool and Manchester conurbations. The South East of England forms a ring around London but does not contain any large cities and thus forms the third of the lowest population density regions.

The predicted upper limit to the effect of population density on disease transmission (Hu et al 2013) is seen in the only slightly higher volatility in London compared to the North West.

Figure 8: Relative volatility in year-to-year NHS staff sickness absence rates. Volatility in absence rates adjusted to equal number of total staff.
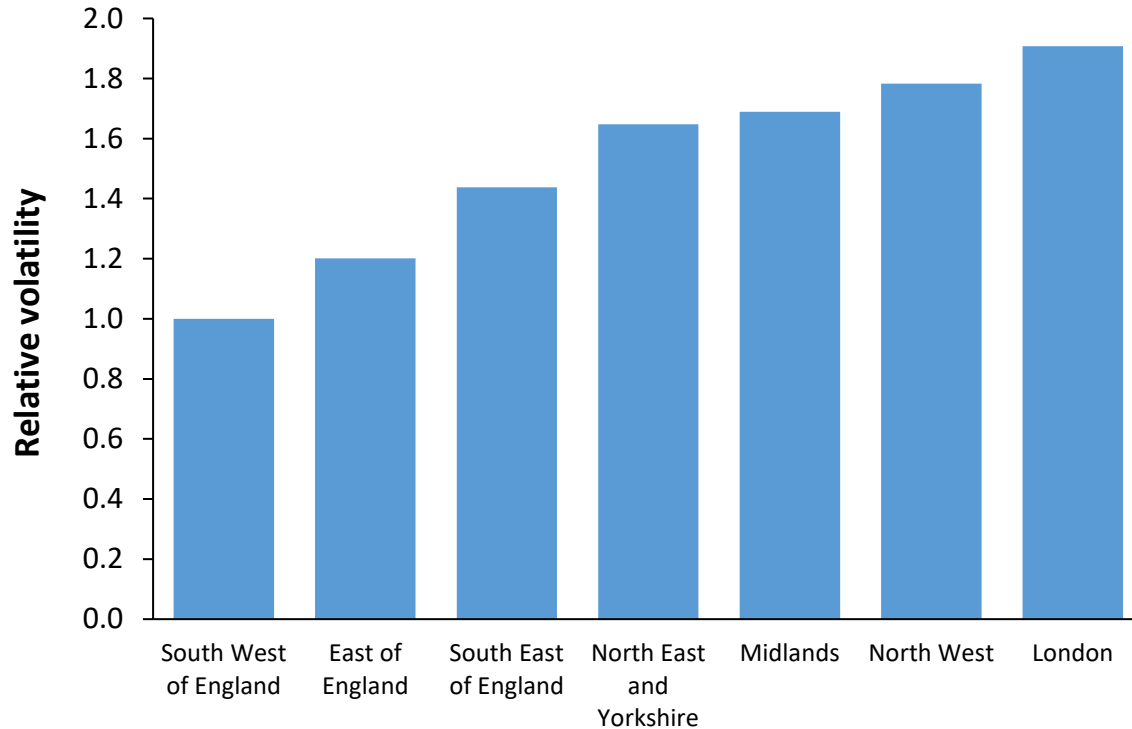
Discussion

It is often the 'experts' who are the last to accept the shift to a new paradigm (Greenwood 2019). Indeed as 'everybody knows' hospital LOS is a measure of efficiency/inefficiency and staff sickness absence rates are the responsibility of the employer. Among government agencies and politicians in the UK, there is a presupposition that periods of poor financial or operational performance are the direct result of poor management or the inability to manage demand.

This study has attempted to present such a new paradigm to explain why population density and associated pollution are important from an infectious/inflammatory perspective.

It goes without saying that while levels of pollution are influenced by population density they are also influenced by geography and industry. Studies are therefore required which link population density with directly measured levels of pollution. The exact role of population density is itself influenced by levels of household crowding and the health care behaviours of different social groups. Population mobility is also an important factor in disease transmission (Wang et al 2020).

When the effects of metrological variables are also included it is unsurprising that the volatility in health care admissions and costs remains highly location specific (Jones 2012b-f). Sickness absence represents a considerable cost to health care organizations and higher volatility in such costs makes the process of budgetary management even more difficult. Once again this is nothing to do with failure to manage staff sickness absence rates. See the Further Reading link for more studies on this topic.

Further research

Further studies are required regarding the volatility in deaths, admissions, length of stay, gender ratio, and sickness absence where both small-area population density and levels of pollutants are known along with socio-demographic factors such as poverty, social group composition, and age.

Health insurers need to re-analyse their data to see if these concepts apply more widely. Hospitals need to be aware that the volatility in capacity pressures is indeed location specific and conduct deeper analysis of their own past trends.

Conclusions

The volatility in deaths, the gender ratio of admissions and health care worker sickness absence supports the notion that outbreaks of a wide variety of infectious agents are the primary outcomes of the underlying relationships with weighted population density. Inflammation is the actual causative mechanism. These will then contribute to the location or place specific nature of financial and capacity risk, which is further modified by social group (which includes ethnicity) and other factors such as population mobility. This has nothing to do with 'incompetent' management or the supposed inability to manage demand. It is merely a reflection of reality.

While low population density may moderate the effect of volatility, the resulting smaller hospital size and the relationships between size, occupancy and turn-away (see Part 1 and the link to further reading) will more than counterbalance the population density effects. Small hospitals are always at a disadvantage.

Part 3 of this series will use influenza and COVID-19 as examples of complex interactions between pathogens. It will also discuss the possibility that outbreaks of a novel type or kind of infectious disease is confounding traditional analysis of trends in capacity and costs. It will also present the possibility that these outbreaks are responsible for the health insurance underwriting cycle.

Much of the emphasis of this series is that the absolute number of deaths is a measure of that which is otherwise not fully measurable. Hence, we can count back from death and document the number and cost of hospital admissions, bed days, outpatient attendances, emergency department visits, cost of drugs, etc. The cost of dying can be quantified. However, the unmeasurable part is how much morbidity is associated with the effect of the agents which precipitate final demise. Part 4 attempts to estimate the non-end-of-life related morbidity which these agents are also exacting upon wider human health.

Data Sources and methods

Data sources

Monthly deaths in U.S. states were obtained from the National Center for Health Statistics (2020). Inpatient admissions in England 1998/99 to 2019/20 were obtained from NHS Digital (2020a). NHS staff sickness rates were also from NHS Digital (2020b).

Monthly deaths in England and Wales were from the Office for National Statistics (2020a), for Scotland from National Records of Scotland (2020a), and for Northern Ireland were by request from the Northern Ireland Statistics and Research Agency.

Data relating to mid-2019 population and population density at Lower Super Output Area (LSOA) in England and Wales were from the Office for National Statistics (2020b). Raw population density in

Northern Ireland was from the Northern Ireland Statistics and Research Agency (2020), while that for Scotland was from National Records of Scotland (2020b).

Methods

Weighted population density (persons per square Km) for English and Welsh local authority areas were obtained by weighting the population density in each LSOA by the LSOA population, for each local authority area. Hence using the sum-product function (population, population density) divided by sum population. This was performed using Microsoft Excel. There is 2.59 square Km per square Mile.

Excess Winter Mortality (EWM) was calculated as a rolling percentage difference of eight months versus four months. Hence the percentage difference between average deaths September to December versus average deaths January to August. Move forward one month and recalculate. The maximum for the rolling EWM calculation usually occurs in the four months ending March, however, this calculation can peak between the four months ending February to the four months ending April. The maximum was chosen for each winter. The standard deviation (STDEV) of EWM was adjusted for local authority size by plotting the STDEV versus average deaths (2001 to 2020) and a power-law line of best fit calculated. STDEV was adjusted to the equivalent of 1,000 deaths per annum.

The year-to-year difference in total deaths was calculated by constructing a rolling 12-month total of deaths commencing the 12-months ending December 2001. This was compared to the 12-months ending December 2002 as the absolute value of the difference calculated as a standard deviation equivalent assuming Poisson statistics for whole numbers. Hence the difference divided by the square root of the average deaths in year n and n+1. Move forward one month and recalculate. This transformation is required to adjust for the effect of size. The standard deviation of the transformed differences was then calculated. Analysis of monthly sickness absence rates in NHS Regions was conducted in the same manner.

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Further Reading

Further studies relating to factors affecting financial and operational risk in healthcare can be found at http://www.hcaf.biz/2010/Publications_Full.pdf

References

Aghaeepour N, Ganio EA, Mcilwain D, Tsai AS, et al. An immune clock of human pregnancy. Sci Immunol. 2017 Sep 1;2(15):eaan2946. doi: 10.1126/sciimmunol.aan2946.

Agarwal D, Schmader K, Kossenkov A, et al. Immune response to influenza vaccination in the elderly is altered by chronic medication use. Immun Ageing 2018; 15: 19. https://doi.org/10.1186/s12979-018-0124-9Akheruzzaman M, Hegde V, Dhurandhar N. Twenty-five years of research about adipogenic adenoviruses: A systematic review. Obesity Reviews 2019; 20(4): 499-509. **doi:** 10.1111/obr.12808

Anisman H, Hayley S, Kusnecov A. The immune system and mental health. Elsevier Academic Press, 2019. https://doi.org/10.1016/C2016-0-01000-8

Aranow C. Vitamin D and the immune system. J Investig Med 2011; 59(6): 881-6. doi: 10.231/JIM.0b013e31821b8755.

Baggerly C, Cuomo R, French C, Garland C, Gorham E, Grant W, et al. Sunlight and vitamin D: necessary for public health. J Amer Coll Nutrit 2015; 34(4): 1-7.

Barreca A, Shimshack J. Absolute humidity, temperature, and influenza mortality: 30 years of county-level evidence from the United States. Am J Epidemiol 2012; 176 (Suppl 7): S114-122. doi: 10.1093/aje/kws259.

Batista M, Calvo-Fortes F, Silveira-Nunes G, et al. Inflammaging in endemic areas for infectious diseases. Frontiers in Immunology 2020; 11: 2879. doi: 10.3389/fimmu.2020.579972

Bauer M, Wetzker R. The cellular basis of organ failure in sepsis—signalling during damage and repair processes. Med Klin Intensivmed Notfmed 2020 · 115 (Suppl 1): S4–S9. https://doi.org/10.1007/s00063-020-00673-4

Bind M-A, Baccarelli A, Zantonella A, et al. Air pollution and markers of coagulation, inflammation, and endothelial function: Associations and epigene-environment interactions in an elderly cohort. Epidemiology 2012; 23(2): 332-340.

Boyd A, Orihuela C. Dysregulated inflammation as a risk factor for pneumonia in the elderly. *Aging Dis*. 2011;2(6):487-500.

Brundage J. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. The Lancet Infectious Diseases 2006; 6: 303-312.
doi: 10.1016/S1473-3099(06)70466-2

Buttigieg S, Abela L, Pace A. Variables affecting hospital length of stay: a scoping review. J Health Organ Manag 2018; 32(3): 463-493. doi: 10.1108/JHOM-10-2017-0275.

Canadian Women's Health Network. Chronic disease: What do sex and gender have to do with it? 2012. https://cwhn.ca/en/resources/primers/chronicdisease (accessed 2 November 2020)

Carozzi F, Provenzano S, Roth S. Urban Density and Covid-19. CEP Discussion Paper No 1711, ISSN 2042-2695, August 2020. Urban Density and COVID-19 (lse.ac.uk)

Channappanavar R, Perlman S. Age-related susceptibility to coronavirus infections: role of impaired and dysregulated host immunity. J Clin Invest 2020; 130(12): 6204-6213. https://doi.org/10.1172/JCI144115.

Chen M.-C, Wang C.-F, Lai B.-C, et al. Air pollution Is associated with poor cognitive function in Taiwanese adults. Int J Environ Res Public Health *2021;* 18: *316.*

Chen R, Yin P, Wang L, Liu C, Niu Y, Wang W. et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. BMJ 2018; 363: k4306. http://dx.doi.org/10.1136/bmj.k4306

Ciabattinia A, Nardini C, Santoroa F, et al. Vaccination in the elderly: The challenge of immune changes with aging. Seminars in Immunology 2018; 40: 83-94.
https://doi.org/10.1016/j.smim.2018.10.010

Ciurkiewicz, M, Herder, V, Beineke, A. Beneficial and detrimental effects of regulatory T cells in neurotropic virus infections. *Int. J. Mol. Sci.* 2020, *21*, 1705.

Cohen-Mansfield J, Skornick-Bouchbinder M, Brill S. Trajectories of end of life: A systematic review, *The Journals of Gerontology: Series B*, 2018; 73(4): 564–572. https://doi.org/10.1093/geronb/gbx093

Comunian S, Dongo D, Milani C, Palestini P. Air Pollution and Covid-19: The Role of Particulate Matter in the Spread and Increase of Covid-19's Morbidity and Mortality. Int J Environ Res Public Health. 2020; 17(12): 4487. doi: 10.3390/ijerph17124487

Condor Ferries. U.S. tourism and travel statistics 2020. https://www.condorferries.co.uk/us-tourism-travel-statistics (accessed 5 November 2020)

Cui Y, Zhang Z, Froines J, et al. Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. Environ Health. 2003; 2(1): 15. doi: 10.1186/1476-069X-2-15.

Dadvand P, Nieuwenhuijsen M, Agusti A, et al. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. Eur Resp J 2014; 44 (3): 603-613; doi: 10.1183/09031936.00168813

Decision Science News. Weighted population density, 2017. http://www.decisionsciencenews.com/2017/06/26/weighted-population-density/ (accessed 7 November 2020).

Dierig A, Heron LG, Lambert SB, et al. Epidemiology of respiratory viral infections in children enrolled in a study of influenza vaccine effectiveness. Influenza Other Respir Viruses. 2014 May;8(3):293-301. doi: 10.1111/irv.12229.

Domingo JL, Rovira J. Effects of air pollutants on the transmission and severity of respiratory viral infections. Environ Res. 2020;187: 109650. doi: 10.1016/j.envres.2020.109650.

Dopico X, Evangelou M, Ferreira R. *et al.* Widespread seasonal gene expression reveals annual differences in human immunity and physiology. *Nat Commun* 2015; **6,** 7000. https://doi.org/10.1038/ncomms8000

Durán A, González A, Delgado L, Mosquera J, Valero N. Serum level of C-reactive protein is not a parameter to determine the difference between viral and atypical bacterial infections. J Med Virol 2016; 88(2):351-355. doi: 10.1002/jmv.24341.

Ebihara S. Infectious disease in the aging. Lancet Infectious Diseases 2011;11(4): 271.

Ekamper P, van Poppel F, van Duin C, Garssen J. 150 Years of temperature-related excess mortality in the Netherlands. Demographic Research 2009; 21: 385-426.

Fernandez C, Manuel A. Obesity, respiratory disease and pulmonary infections. Annals of Research Hospitals 2017; 1(5): http://arh.amegroups.com/article/view/3827/4598

Finkel D, Sternang O, Jyihava J, et al. Functional aging index complements frailty in prediction of entry into care and mortality. J Gerontol A Biol Sci Med Sci 2018; 74(12):1980-1986. doi: 10.1093/gerona/glz155.

Fleming DM. A Winter's Tale: coming to terms with winter respiratory illnesses. London: Health Protection Agency; January 2005. https://www.avogel.co.uk/conference2015/Fleming-D-M-2005.1.pdf (accessed 29 October 2020)

Fleming D, Elliot A. Lessons from 40 years' surveillance of influenza in England and Wales. Epidemiol Infect. 2008; 136(7): 866–875.

Fulop T, Witkowski JM, Olivieri F, Larbi A. The integration of inflammaging in age-related diseases. Semin Immunol. 2018; 40:17-35. doi: 10.1016/j.smim.2018.09.003. Epub 2018 Oct 2. PMID: 30287177.

Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019 Dec;25(12):1822-1832. doi: 10.1038/s41591-019-0675-0.

Garland C, Cuomo R, Gorham E, Zeng K, Mohr S. Cloud cover-adjusted ultraviolet B irradiance and pancreatic cancer incidence in 172 countries. J Steroid Biochem Molec Biology 2016: 155(B): 257-263. doi:10.1016/j.jsbmb.2015.04.004

Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. The Lancet 2015; 386(9991): 369-375. Doi: 10.1016/S0140-6736(14)62114-0

Goldinger A, Shakhbazov K, Henders A, et al. Seasonal effects on gene expression. PLoS ONE 2015; 10(5): e0126995. https://doi.org/10.1371/journal.pone.0126995

Gramegna A, Sotgiu G, Di Pasqual, M. *et al.* Atypical pathogens in hospitalized patients with community-acquired pneumonia: a worldwide perspective. *BMC Infect Dis* 2018; **18,** 677. https://doi.org/10.1186/s12879-018-3565-z

Greenwood V. Do the deaths of top scientists make way for new growth? UNDARK, 11 June 2019. https://undark.org/2019/11/06/top-scientists-dying/

Hamilton G, O'Sullivan A, Huebner G, et al. Old and cold? Findings on the determinants of indoor temperatures in English dwellings during cold conditions. Energy and Buildings 2017; 141: 142-157. https://doi.org/10.1016/j.enbuild.2017.02.014

Hanlon P, Walsh D, Whyte B, et al. Hospital use by an aging cohort: an investigation into the association between biological, behavioral and social risk markers and subsequent hospital utilization. J Public Health Med 1998; 20(4): 467-76.

Hartwig S, Uhari M, Renko M, et al. Hospital bed occupancy for rotavirus and all cause acute gastroenteritis in two Finnish hospitals before and after the implementation of the national rotavirus vaccination program with RotaTeq®. BMC Health Serv Res 2014; 14: 632. doi:10.1186/s12913-014-0632-z

Healy J. Excess winter mortality in Europe: a cross country analysis identifying key risk factors. J Epidemiol & Community Health 2003; 57:784-789.

Herbinger K-H, Hanus I, Schunk M, et al. Elevated levels of C-reactive protein induced by imported infectious diseases: A controlled cross-sectional study of 11,079 diseases German travelers returning from the tropics and subtropics. Am. J. Trop. Med. Hyg 2016; 95(4): 938–944. doi:10.4269/ajtmh.16-0387

Hirata A, Kodera S, Gomez-Tames J, Rashed E. Influence of absolute humidity and population density on COVID-19 spread and decay durations: Multi-prefecture study in Japan. IJERPH 2020; 17(15): 5354. doi: 10.3390/ijerph17155354

Hové C, Trumble B, Anderson A, et al. Immune function during pregnancy varies between ecologically distinct populations, Evolution, Medicine, and Public Health. 2020, 2020,(1): 114–128, https://doi.org/10.1093/emph/eoaa022

Hu H, Nigmatulina K, Eckhoff P. The scaling of contact rates with population density for the infectious disease models. Mathematical Biosciences2013; 244(2): 125-134. https://doi.org/10.1016/j.mbs.2013.04.013

Jabr F. How does the flu actually kill people? Scientific American 2017; https://www.scientificamerican.com/article/how-does-the-flu-actually-kill-people/ (accessed 23 October 2020)

Johnson O. Population density and the spread of COVID-19. Parliamentary & Scientific Committee 29th June 2020. Population density and the spread of COVID-19 (scienceinparliament.org.uk)

Jones R. Trends in programme budget expenditure. Brit J Healthc Manage 2010a; 16(11): 518-526.

Jones R. Gender ratio and hospital admissions. Brit J Healthc Manage 2010b; 16(11): 541.

Jones R. Cycles in gender-related costs for long-term conditions. Brit J Healthc Manage 2011; 17(3): 124-125.

Jones R. Gender ratio and cycles in population health costs. Brit J Healthc Manage 2012a; 18(3): 164-165.

Jones R. Why is the 'real world' financial risk in commissioning so high? Brit J Healthc Manage 2012b; 18(4): 216-217.

Jones R. Volatile inpatient costs and implications to CCG financial stability. Brit J Healthc Manage 2012c; 18(5): 251-258.

Jones R. Cancer care and volatility in commissioning. Brit J Healthc Manage 2012d; 18(6): 315-324.

Jones R. End of life care and volatility in costs. Brit J Healthc Manage 2012e; 18(7): 374-381.

Jones R. Age and financial risk in healthcare costs. Brit J Healthc Manage 2012f; 18(7): 388-389.

Jones R. Year-to-year volatility in medical admissions. Brit J Healthc Manage 2012g; 18(8): 448-449.

Jones R. Financial risk in GP commissioning: lessons from Medicare. Brit J Healthc Manage 2012h; 18(12): 656-657.

Jones R. Financial risk and volatile elderly diagnoses. Brit J Healthc Manage 2013a; 19(2): 94-96.

Jones R. Financial risk and volatile childhood diagnoses. Brit J Healthc Manage 2013b; 19(3): 148-149.

Jones R. Analyzing excess winter mortality: 2012/13. Brit J Healthc Manage 2013c; 19(12): 601-605.

Jones R. An unexpected increase in adult appendicitis in England (2000/01 to 2012/13): Could cytomegalovirus (CMV) be a risk factor? BJMMR 2015; 5(5): 579-603. doi: 10.9734/BJMMR/2015/13302

Jones R, Sleet G, Pearce O, Wetherill M. Complex changes in blood biochemistry revealed by a composite score derived from Principal Component Analysis: Effects of age, patient acuity, end of life, day-of week, and potential insights into the issues surrounding the 'Weekend' effect in hospital mortality. BJMMR 2016; 18(5): 1-28. doi: 10.9734/BJMMR/2016/29355

Jones R. Outbreaks of a presumed infectious agent associated with changes in fertility, stillbirth, congenital abnormalities and the gender ratio at birth. BJMMR, 2017; 20(8): 1-36. doi: 10.9734/BJMMR/2017/32372

Jones R. Financial risk in health and social care budgets. Brit J Healthc Manage 2019; 25 (2): 79-84.

Jones R. The calendar year fallacy: The danger of reliance on calendar year data in actuarial calculations. Int J Health Plan Management 2019; 34(4): e1533-e1543. doi: 10.1002/hpm.2838

Jones R. Would the United States have had too few beds for universal emergency care in the event of a more widespread COVID-19 epidemic? IJERPH 2020a; *17: 5210.* https://doi.org/doi:10.3390/ijerph17145210

Jones R. How many extra deaths have really occurred in the UK due to the COVID-19 outbreak? XIII. Population density and risk of COVID-19 death. Healthcare Analysis & Forecasting, UK. 2020b. doi: 10.13140/RG.2.2.23027.35365

Jonker M, van Lenthe, Donkers B, et al. The impact of nursing homes on small-area life expectancy. Health & Place 2013; 19: 25-32. Doi: 10.1016/j.healthplace.2012.09.012

Kadi N, Khelfaoui M. Population density, a factor in the spread of COVID-19 in Algeria: statistic study. *Bull Natl Res Cent* 2020; 44, 138. https://doi.org/10.1186/s42269-020-00393-x

Kalbarczyk-Steclik M, Nicinska A. The last and the previous year of life in Europe: A comparative analysis of care received and daily living limitations. J Aging and Gerontol 2015; 3:1-7.

Karczewski J, Śledzińska E, Baturo A, Jończyk I, Maleszko A, et al. Obesity and inflammation. Eur Cytokine Netw. 2018;29(3):83-94. doi: 10.1684/ecn.2018.0415.

Klein S, Roberts C (eds). Sex and gender differences in infection and treatments for infectious diseases. Springer International Publishing, 2015. https://link.springer.com/book/10.1007%2F978-3-319-16438-0

Koehrsen W. The Poisson distribution and Poisson process explained. 20 January 2019. https://towardsdatascience.com/the-poisson-distribution-and-poisson-process-explained-4e2cb17d459 (accessed 5 November 2020)

Kumala I. Tackling the spread of pathogens in airports. International Airport Review 2017; issue 2 https://www.internationalairportreview.com/article/33571/tackling-spread-pathogens-airports/

Kuwabara A, Tsugawa N, Ao M, et al. Vitamin D deficiency as the risk of respiratory tract infections in the institutionalized elderly: A prospective 1-year cohort study. Clinical Nutrition ESPEN 2020; 40: 309-313. doi: 10.1016/j.clnesp.2020.08.012.

Lamsal L, Martin R, Rarrish D, Krotkov N. Scaling relationship for NO2 pollution and urban population size: A satellite perspective. Environ Sci Technol 2013; 47(14): 7855–7861. https://doi.org/10.1021/es400744g

Larsson K, Karenholt I, Thorslund M. Care utilization in the last years of life in relation to age and time to death: results from a Swedish unban population of the oldest old. Eur J Aging 2008; 5: 349-357. Doi: 10.1007/s10433-008-0099-z

Larsson K, Tornling G, Gavhed D, Müller-Suur C, Palmberg L. Inhalation of cold air increases the number of inflammatory cells in the lungs in healthy subjects. Eur Respir J. 1998 Oct;12(4):825-30. doi: 10.1183/09031936.98.

Lawlor D, Maxwell R, Wheeler B. Rurality, deprivation, and excess winter mortality: an ecological study. J Epidemiol & Community Health 2002; 56: 373-374.

Levi M, Keller T, van Gorp E, ten Cate H. Infection and inflammation and the coagulation system, *Cardiovascular Research* 2003; 60(1): 26–39. https://doi.org/10.1016/S0008-6363(02)00857-X

Long M, Martin E, Kreiss J. *et al.* Gender differences in HIV-1 diversity at time of infection. *Nat Med* 2000; **6,** 71–75. https://doi.org/10.1038/71563

Luan Y-y, Yao Y-m. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. Front Immunol 2018; 9: 1302. doi: 10.3389/fimmu.2018.01302

Luo J, Tang W, Sun Y, et al. Impact of frailty on 30-day and 1-year mortality in hospitalized elderly patients with community-acquired pneumonia: a prospective observational study. BMJ Open 2020; 10: e038370. doi: 10.1136/bmjopen-2020-038370

Mourtzoukou E, Falagas M. Exposure to cold and respiratory tract infections. Int J Tuberc Lung Dis 2007; 11(9): 938-43.

Meehan M, Penckofer S. The Role of Vitamin D in the aging adult. J Aging Gerontol. 2014 2(2):60-71.

Met Office. Hot spell August 1990. http://www.metoffice.gov.uk/climate/uk/interesting/aug1990/

Mundkur LA, Rao VS, Hebbagudi S, et al. Pathogen burden, cytomegalovirus infection and inflammatory markers in the risk of premature coronary artery disease in individuals of Indian origin. *Exp Clin Cardiol*. 2012;17(2):63-68.

National Institutes for Health. Understanding a common cold virus. 13 April 2009. https://www.nih.gov/news-events/nih-research-matters/understanding-common-cold-virus (accessed 1 November 2020).

National Records of Scotland. Monthly data on births and deaths registered in Scotland, Table 4: Council area, 2020a. https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/weekly-and-monthly-data-on-births-and-deaths/monthly-data-on-births-and-deaths-registered-in-scotland#:~:text=Monthly%20Data%20on%20Births%20and%20Deaths%20Registered%20in,in%20Scotland%20by%20month%20of%20registrat%20...%20 (accessed 3 November 2020)

National Records of Scotland. Population density, Table 9. 2020b. https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates/archive/mid-2005-population-estimates-scotland/list-of-tables#table9 (accessed 7 November 2020)

National Center for Health Statistics. VSRR - State and National Provisional Counts for Live Births, Deaths, and Infant Deaths, 2020. https://data.cdc.gov/NCHS/VSRR-State-and-National-Provisional-Counts-for-Liv/hmz2-vwda (accesed 5 November 2020)

National Institute of Care Excellence. Evidence review and economic analysis of excess winter deaths. 2009. https://www.nice.org.uk/guidance/NG6/documents/excess-winter-deaths-and-illnesses-concept-review2 (accessed 7 November 2020)

Northern Ireland Statistics and Research Agency. Mid-2019 Population estimates: Population densities, 2020. https://www.nisra.gov.uk/sites/nisra.gov.uk/files/publications/MYE19_POP_DENSITIES_0.xlsx (accessed 7 November 2020)

NHS Digital. Hospital admitted patient care activity, 2020a. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity (Accessed 3 November 2020)

NHS Digital. NHS sickness absence rates April 2020 to June 2020b, Provisional statistics. 22 October 2020. https://digital.nhs.uk/data-and-information/publications/statistical/nhs-sickness-absence-rates/june-2020 (accessed 4 November 2020)

Nicholl J. Case-mix adjustment in non-randomized observational evaluations: the constant risk fallacy. J Epidemiol Community Health 2007; 61(11): 1010-1013. doi:10.1136/jech.2007.061747

Noppert G, Aiello A, O'Rand A, et al. Race/Ethnic and educational disparities in the association between pathogen burden and a laboratory-based Cumulative Deficits Index. J. Racial and Ethnic Health Disparities 2020; 7, 99–108. https://doi.org/10.1007/s40615-019-00638-0

Office for National Statistics. Deaths registered monthly in England and Wales, 2020a. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/monthlyfiguresondeathsregisteredbyareaofusualresidence (accessed 3 November 2020)

Office for National Statistics. Lower layer Super Output Area population density, 2020b. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/lowersuperoutputareapopulationdensity (accessed 3 November 2020)

Ogbebor O, Odugbemi B, Maheswaran R, et al. Seasonal variation in mortality secondary to acute myocardial infarction in England and Wales: a secondary data analysis. BMJ Open 2018; 8: e019242. doi:10.1136/ bmjopen-2017-019242

O'Neill MS, Veves A, Sarnat JA, et al. Air pollution and inflammation in type 2 diabetes: a mechanism for susceptibility. *Occup Environ Med*. 2007;64(6):373-379. doi:10.1136/oem.2006.030023

O'Sullivan T, Waldetoft K, Brown S. Mapping infectious disease mortality onto the within-host dynamics of pathogen growth. 2020. medRxiv 2020.06.20.20134205; doi: https://doi.org/10.1101/2020.06.20.20134205

Pequeno P, Mendel B, Rosa C, et al. Air transportation, population density and temperature predict spread of COVID-19 in Brazil. PeerJ 2020; 8: e9322. Doi: 10.7717/peerj.9322

Public Health England. Notifiable diseases and causative organisms: how to report. Updated 26 October 2020. https://www.gov.uk/guidance/notifiable-diseases-and-causative-organisms-how-to-report#list-of-notifiable-diseases (accessed 1 November 2020).

Rabbitt P, Lunn M, Wong D. Death, dropout, and longitudinal measurements of cognitive change in old age. J Gerontol: Psychological Sciences 2008; 63B(5): P271-P278.

Rippee-Brooks M, Marcinczyk R, Lupfer C. What came first, the virus or the egg: Innate immunity during viral coinfections. Immunological Reviews 2020; 297(1): 194-206. https://doi.org/10.1111/imr.12911

Schlaberg R, Simmon K, Fisher M. A systematic approach for discovering novel, clinically relevant bacteria. *Emerg Infect Dis*. 2012; 18(3): 422-430. doi:10.3201/eid1803.111481

Seinost G, Golde WT, Berger BW, et al. Infection with multiple strains of Borrelia burgdorferi sensu stricto in patients with Lyme Disease. *Arch Dermatol.* 1999;135(11):1329–1333. doi:10.1001/archderm.135.11.1329

Sękowska A, Gospodarek-Komkowska E. New species of bacteria in human infections. Advancements of Microbiology – POSTĘPY MIKROBIOLOGII 2019; 58(1): 29–34. DOI: 10.21307/PM-2019.58.1.029

Setti L, Passarini F, De Gennaro G, et al. Potential role of particulate matter in the spreading of COVID-19 in Northern Italy: first observational study based on initial epidemic diffusion BMJ Open 2020; **1**0: e039338. doi: 10.1136/bmjopen-2020-039338

Sharma A, Ghatge M, Mundkur L, Vangala RK. Translational informatics approach for identifying the functional molecular communicators linking coronary artery disease, infection and inflammation. *Mol Med Rep*. 2016;13(5):3904-3912. doi:10.3892/mmr.2016.5013

Shi H, Tan SJ, Zhong H, et al. Winter temperature and UV are tightly linked to genetic changes in the p53 tumor suppressor pathway in Eastern Asia. *Am J Hum Genet*. 2009;84(4):534-541. doi:10.1016/j.ajhg.2009.03.009

Singer A, Meeker D, teno J, et al. Symptom trends in the last year of life from 1998 to 2010. Ann Intern Med 2015; 162: 175-183. Doi: 10.7326/M13-1609

Stenholm S, Kivimaki M, Jyiha M. Trajectories of self-rated health in the last 15 years of life by cause of death. Eur J Epidemiol 2016; 31(2): 177-185. Doi: 10.1007/s10654-015-0071-0

Tarwater P, Martin C. Effects of population density on the spread of disease. Complexity 2001; 6(6): 29-36. https://doi.org/10.1002/cplx.10003

Taylor S, Lopez P, Weckx L, Borja-Tabora C, et al. Respiratory viruses and influenza-like illness: Epidemiology and outcomes in children aged 6 months to 10 years in a multi-country population sample. Journal of Infection 2017; 74(1): 29-41. https://doi.org/10.1016/j.jinf.2016.09.003

Thai P, Candido C, Asumadu-Sakyia A, et al. Variation of indoor minimum mortality temperature in different cities: Evidence of local adaptations. Environ Pollution 2019; 246: 745-752. https://doi.org/10.1016/j.envpol.2018.12.061

Thomas R, Wang W, Su D. Contributions of age-related thymic involution to immunosenescence and inflammaging. *Immun Ageing* 2020; **17,** 2. https://doi.org/10.1186/s12979-020-0173-8

Thorn J, Turner E, Hounsome L, Walsh E, et al. Validating the use of Hospital Episode Statistics data and comparison of costing methodologies for economic evaluation: an end-of-life case study from the Cluster randomised triAl of PSA testing for Prostate cancer (CAP). BMJ Open. 2016; 6(4): e011063. doi: 10.1136/bmjopen-2016-011063.

Tucci V, Moukaddam N, Meadows J, et al. The Forgotten Plague: Psychiatric Manifestations of Ebola, Zika, and Emerging Infectious Diseases. J Glob Infect Dis. 2017 Oct-Dec;9(4):151-156. doi: 10.4103/jgid.jgid_66_17

Tung N, Cheng P-C, Chi T-C, et al. Particulate matter and SARS-CoV-2: A possible model of COVID-19 transmission. Science of The Total Environment 2021; 750: 141532. https://doi.org/10.1016/j.scitotenv.2020.141532.

Wang Q, Zhao Q, Wang G, Wang B, Zhang Y, Zhang J, Li N, Zhao Y, Qiao H, Li W, Liu X, Liu L, Wang F, Zhang Y, Guo Y. The association between ambient temperature and clinical visits for inflammation-related diseases in rural areas in China. Environ Pollut 2020; 261: 114128. doi: 10.1016/j.envpol.2020.114128.

Wang B, Liu J, Li Y, *et al.* Airborne particulate matter, population mobility and COVID-19: a multi-city study in China. *BMC Public Health* 2020; 20, 1585. https://doi.org/10.1186/s12889-020-09669-3

Wang L, Wei L, Ding R, Feng Y. Predisposition to Alzheimer's and age-related brain pathologies by PM2.5 exposure: Perspective on the roles of oxidative stress and TRPM2 channel. Front Physiol 2020; https://doi.org/10.3389/fphys.2020.00155

Wikipedia. List of U.S. states and territories by area, 2020a. https://simple.wikipedia.org/wiki/List_of_U.S._states_and_territories_by_area

Wikipedia. Geography of England, 2020b. https://en.wikipedia.org/wiki/Geography_of_England

Woolhouse ME, Gowtage-Sequeria S. Host range and emerging and reemerging pathogens. Emerg Infect Dis. 2005 Dec;11(12):1842-7. doi: 10.3201/eid1112.050997.

Woolhouse M, Scott F, Hudson Z, et al. Human viruses: discovery and emergence. Philos Trans R Soc Lond B Biol Sci 2012; 367(1604): 2864-2871. DOI: 10.1098/rstb.2011.0354

Wu, Nethery R, Sabath M, et al. Air pollution and COVID-19 mortality in the United States: Strengths and limitations of an ecological regression analysis. SCIENCE ADVANCE S04 NOV 2020: EABD4049.

Xie C, Li N, Wang H, et al. Inhibition of autophagy aggravates DNA damage response and gastric tumorigenesis via Rad51 ubiquitination in response to *H. pylori* infection. *Gut Microbes* 2020; 11(6): 1567-1589.

Zhang X, Rao H, Wu Y, *et al.* Comparison of spatiotemporal characteristics of the COVID-19 and SARS outbreaks in mainland China. *BMC Infect Dis* 2020; 20: 805. https://doi.org/10.1186/s12879-020-05537-y

Zuo T, Zhang F, Lui G, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 2020; 159(3): 944-955. https://doi.org/10.1053/j.gastro.2020.05.048 https://doi.org/10.1016/S1473-3099(11)70087-1

Appendix 1: The role of location or place in the expression of weighted population density

A logical extension of the role of weighted population density would be to rank every small area by population density and determine if the relationship with volatility still holds. As part of the supporting analysis behind this study deaths and population density for lower super output areas (LSOA) in England and Wales were ranked by population density.

Each LSOA contains around 1,500 persons (range 680 to 16,000) and have a size between 0.02 square Km (London) to 670 square Km in remote locations (ONS 2020b). Apart from lowest volatility for the most sparsely populated LSOA containing fewer than 100 people per square Km, i.e., national parks, forestry, remote areas and smaller islands (all with near absence of air pollution), a general relationship with population density could not be observed.

Clearly every small area is the end-product of the location or place where it is situated. Hence, small areas with equal population density will experience markedly different levels of pollution, will be exposed to markedly different weather patterns, and will contain widely different social groups and their associated health behaviours, economic circumstances, political views, and different levels of population mobility (Carozzi et al 2020, Wang et al 2020). The number of nursing home beds in each small area is a **major** confounding factor (Jonker et al 2013).

For this reason, the calculation of weighted population density at local authority level represents a suitable compromise. However, further smoothing was required to reveal the underlying relationship between weighted population density and volatility.

The end conclusion is that volatility will always be location or place specific because the volatility is a mix of weighted population density plus a variety of other factors and complex interactions between these parameters.

The pragmatic approach is therefore to measure the observed volatility for each hospital, health authority, commissioner, without necessarily needing to know exactly why one location or place is higher/lower than another. Part 4 of this series will therefore look at the size required to average out all the small area components to arrive at the minimum possible volatility.

The study of Carozzi et al (2020) failed to find a relationship with population density because they used the somewhat meaningless ratios of cases per 1,000 population and deaths per 1,000 population. Cases per 1,000 population needs to be age-weighted to account for the fact that maximum infection rate occurs at age 20 to 29. Deaths per 1,000 population is likewise not weighted. The best measure for deaths is an excess mortality calculation of either COVID-19 deaths per 100 deaths in the absence of Covid-19 (usually 2018 or 2019 depending on availability) or excess all-cause mortality, which accounts for unreported COVID-19 deaths.