Revisiting the point-source hypothesis of the coronary heart disease epidemic in light of the COVID-19 pandemic

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Abstract

The 20th century coronary heart disease pandemic remains a partial enigma. Here we focus on sex differences in mortality as an indicator of the disease during a time when classification of cause of death was uncertain. We suggest that cohorts born during a few decades around the turn of the century bore the brunt of the pandemic, and propose that the 1889-1895 Russian influenza epidemic may have contributed to this. That some evidence points to the introduction of a human seasonal coronavirus during the 1889-95 pandemic adds contemporary relevance to these speculations.

The rise and fall of coronary heart disease (CHD) in the UK, USA and other high income countries is often referred to as an epidemic or pandemic,[1] and remains – in part, at least – an enigma. The very rapid increase in CHD in the early 20th Century reflected the creation of specific categories of registerable causes of death and was seen to rise massively after Herrick[2] published his seminal 1919 paper in JAMA (Figure 1). Clearly what would later be referred to as CHD was occurring in the 19th Century, but at low levels and in different predominant forms to those seen during the 20th Century pandemic. Overall, heart disease showed a marked epidemic pattern, with rates in the US increasing from the start of the century – when data first became available – to the mid-century, after which an accelerating decline commenced (Figure 2).

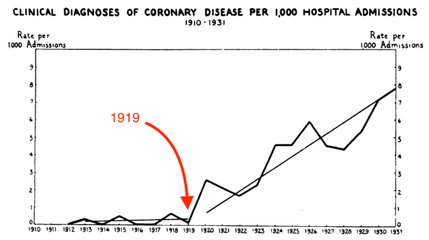


Figure 1: from Levy et al. 1933[3] with arrow indicating year of publication of Herrick's seminal paper, indicating the increased registration of deaths as CHD occurring after that publication, which could not plausibly represent a real trend in disease, as other authorities noted at the time.[4]

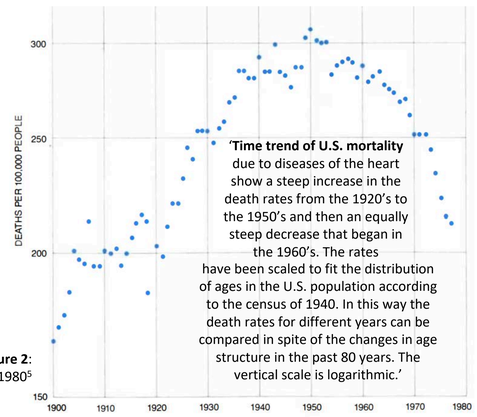


Figure 2: Stallones, 1980[5]

'Heart disease' is a broad category, however, and in the early 20th Century mortality from rheumatic and other valvular and infectious heart diseases was declining. Balancing this was the reduction in use of categories such as 'senility' which will have contained heart disease deaths. The 'myocardial disease' category would have contained several non-CHD classes which were declining, whilst also containing CHD deaths, as careful autopsy and death certification studies showed[4]. We have created a highly conservative combination of myocardial disease and CHD, but even this shows a clear increase (Figure 3). Most strikingly, CHD showed a large male to female excess.

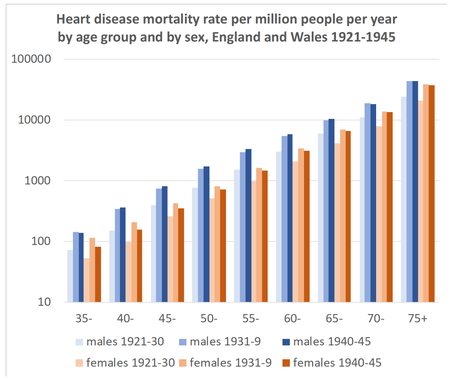


Figure 3: Drawn using data from Ryle and Russel, 1949[6]

The substantial emerging sex difference for CHD was large enough to be seen in trends for all-cause mortality – which could not be influenced by cause of death classification. As expected this was seen particularly in the mid-life ages (Figure 4).[7] We suggest that the increase in CHD occurred from the turn of the century or before, with classificatory changes leading to the impression of its implausibly rapid emergence.

In the first textbook of non-communicable disease epidemiology, '*The Uses of Epidemiology*', published in 1957,[8] Jerry Morris demonstrated that the substantial widening in the mortality sex difference was entirely generated by CHD and the quantitatively much less important contribution of lung cancer (Figure 5).

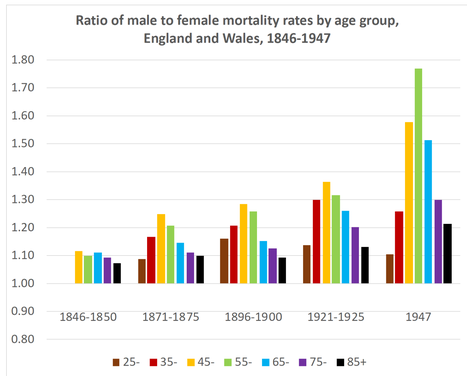


Figure 4: Drawn using data from Logan, 1950[7]

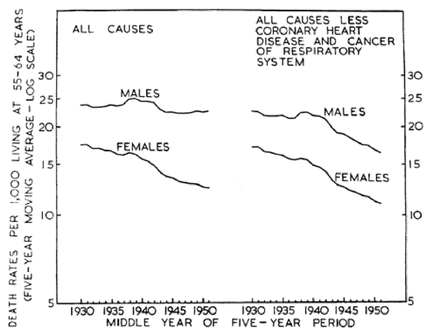


Figure 5: Morris, '*The Uses of Epidemiology*', 1957[8]

The sex difference in all-cause mortality amongst the middle-aged and older dramatically increased for the birth cohorts born after around 1880.[9]

In Figure 6 we present these sex differences from combined data of 5 countries that suffered few casualties in World War One and earlier wars (including civil wars).

Jerry Morris (1910-2009)

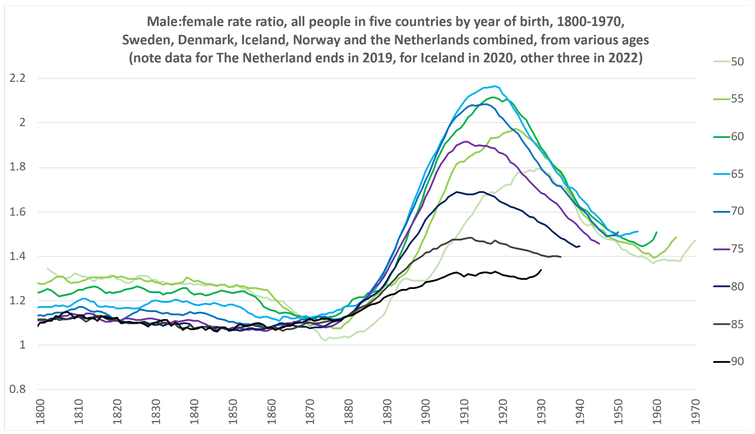
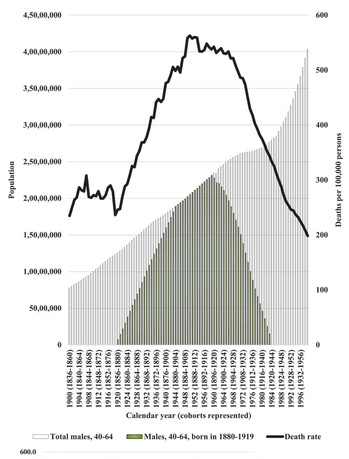


Figure 6: Drawn Using Data from the Human Mortality Database, 2023[10]

Male population ages 40–64, those born in 1880–1919; male age-standardized heart disease death rate— United States: 1900–99



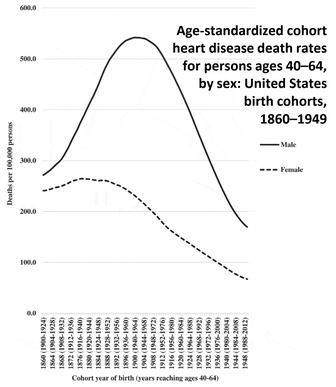


Figure 7: Blanchard, et al. 2020 (combining two figures)[12]

The dramatic increase in the sex ratios in mortality and the successively later peaks for mortality at younger ages is clear. The cohorts born around the end of the 19th century had peak heart disease mortality (Figures 7 & 8). These data are for total heart disease, of which the proportion that is CHD will be considerably higher in men than women. The CHD epidemic only clearly exceeded the countervailing reductions in other forms of heart disease in men, as has been previously discussed at length.[11]

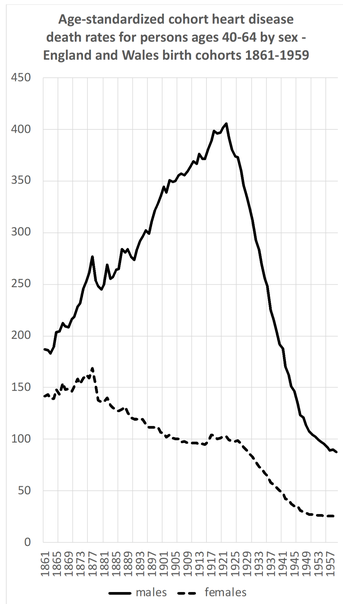


Figure 8: Drawn using data from ONS 2011[13]

Trends in associated factors

A key contribution by Morris in 1951 was from an extensive autopsy study dating back to the beginning of the century which showed that the degree of atherosclerosis decreased over a 40-year period, whereas presence of thrombus increased.[14] Blood pressure in young adults decreased in the UK from mid-century[15], and decomposition of stroke mortality shows a decrease across the century for hemorrhagic stroke – which is highly dependent on blood pressure – whereas ischaemic stroke mimicked CHD trends (Figure 9).[16] Dietary data fail to match the CHD rise[1] Whilst smoking was steadily increasing – especially in males – at the most rapid period of rising CHD mortality in the US a third of male cases and virtually all of the female cases were non-smokers[4]. These were closely similar to the prevailing smoking rates in the population at large. A permissive environment was certainly essential for the rise of CHD, but alone was insufficient to account for it[1].

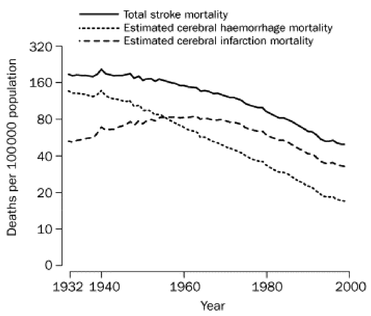


Figure 9: Lawlor et al. 2002[16]

What happened at the end of the 19th Century?

The 1889-95 'Russian influenza' pandemic (henceforth RIP) was the major international public health issue at the end of the 19th Century. Whilst generally considered a 'mild epidemic' its UK mortality rates by age for the highest mortality year was greater than that during any year of the COVID-19 pandemic (as were rates in the 1951 'flu season, which was not considered an epidemic, let alone a pandemic). What distracted attention from the not inconsiderable mortality during the RIP was that it occurred at a time when there was a much younger age distribution of the general population. The most dramatic aspect of RIP in the UK, US, parts of Australia and other places was that it represented a transition from a long period of low influenza mortality to a situation of continued high influenza that didn't revert to the low level it had been at for a century.[17] Christopher Andrewes – who identified the influenza virus in 1933 – repeatedly updated an iconic graph[18] showing this. We have updated[19] his final version of this in Figure 11.

Andrewes thought two diseases were introduced around 1889: influenza and some second infectious respiratory agent. He reproduced a supposed chart of influenza mortality, but added

> "a line joining the 'troughs'. Such a line indicates deaths from 'influenza' in the years when no influenza virus is recovered. Something has apparently been declining just as remarkably as the influenza which produces sharp outbreaks."[17]

He thought the second disease

> "could be a 'basic influenza' not recognizable by laboratory tests, or some other disease which became important when influenza arrived in 1890 and is now declining *pari passu* with it".[17]

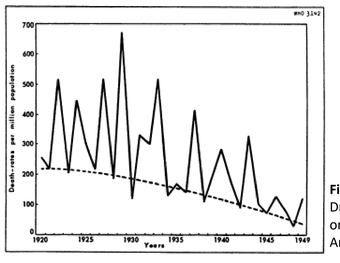


Figure 10: Drawn originally by Andrewes[17]

Christopher Andrewes (1896-1988)

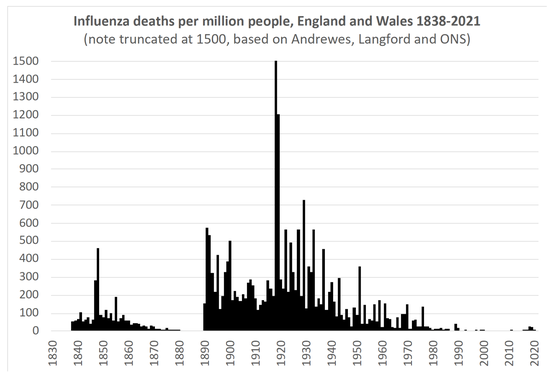


Figure 11: Drawn originally by Andrewes[18] and extended back by Langford[19] and forward by ONS[13].

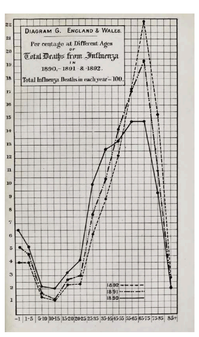


Figure 12: Parsons, 1894[20]

Two early signals (not appealed to by Andrewes) support his interpretation:

(1) The age distribution of mortality was different for the first and subsequent two waves of RIP (Figure 12).[20]

(2) Mortality by area for the first wave of RIP did not predict the mortality in the 2nd or 3rd waves, whereas mortality in the 2nd wave was inversely related to mortality in the 3rd wave (Figure 13).

The age distribution in the subsequent waves of the RIP increased extremely steeply with age, reminiscent of COVID-19 in 2020. The lack of protection in the 2nd 1890 wave of the RIP suggests no immunity to it was induced by the 1st wave, whereas the 2nd wave induced immunity to the 3rd wave

A paper using phylogenetic data from 2005 suggested that the seasonal coronavirus HCoV OC43 was introduced from its bovine source into humans around 1890[21] and considerable new data support this (low precision) dating[22]. Data from many countries have shown that later waves of what was assumed to be RIP produced an extreme age curve in mortality – with little increase in infant or pre-old age mortality[23] – here we show this was the case in London too after January 1890 (Figure 14), and so ***we suggest that subsequent waves of RIP could have been Andrewes' 'second disease', a seasonal HCoV*** (Figure 15).

That the RIP produced long term consequences on health has been widely accepted with respect to the unexplained peak age of excess all-cause mortality during the 1918 influenza pandemic mapping to those born around 1889[24], and also being greater for males than females (Figure 16).

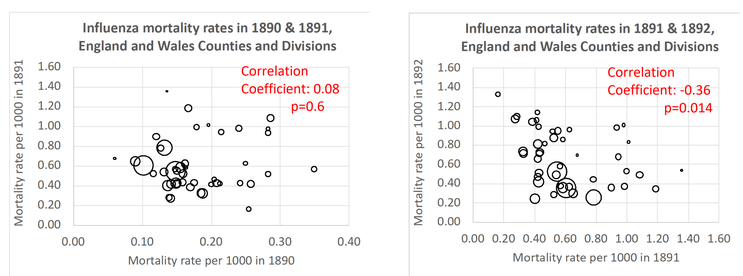


Figure 13: Drawn with data from Parsons, 1894[20]. (note the area of the circles is drawn proportionate to population in 1891).

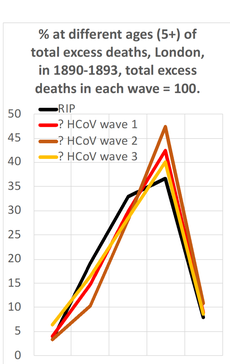


Figure 14: Drawn using official data[25]

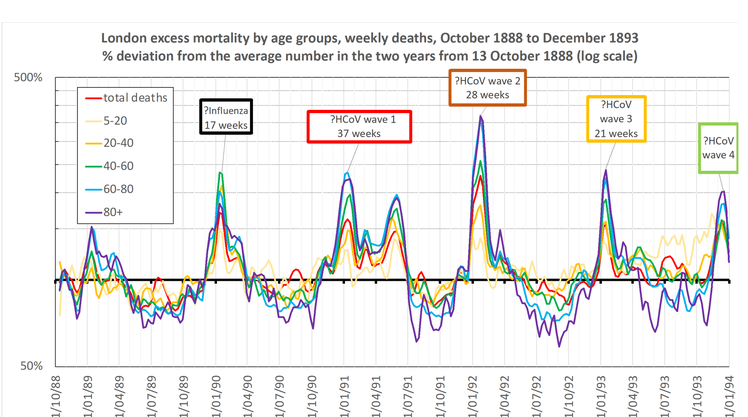


Figure 15: Drawn using official data[25] (note each wave begins and ends when total deaths are in excess, wave 4 incomplete).

How could HCoV infection have influenced the CHD epidemic?

We propose a speculative hypothesis that, against a permissive background (established by an increase in smoking combined with other contributory - but not sufficient - causes related to economic development), repetitive HCoV43 infection in an immunologically naïve population leads to increased CHD mortality. We know that infection and inflammation alone do not generate CHD in populations at low risk of CHD.[26] Equally, we know that interleukin 6 receptor (IL6-R) blockade reduces the risk of CHD in high-risk populations[27] and improves survival in COVID-19 infection.[28] The remarkably consistent shape and timing of the CHD epidemic in countries that experienced this outside of particular circumstances (e.g. the collapse of state capitalism in central and eastern Europe), despite very different trajectories for other risk indicators, provides indirect support of some external and near-universal factor contributing.[29]

Median excess mortality by age and sex for the 1918–20 pandemic, based on data from 13 countries with available complete age-specific mortality data

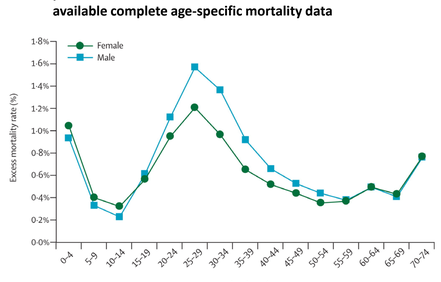


Figure 16: Murray et al., 2006[24]

Hazard ratios (log scale) for first arterial event after COVID-19 by time since diagnosis, overall and stratified by whether hospitalized with COVID-19

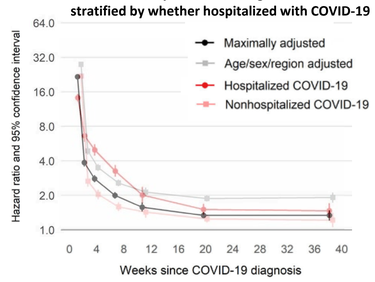


Figure 17: Knight et al., 2022 (combining two figures).[30]

In the current pandemic, continued elevated risk for overall arterial events (including CHD and ischaemic stroke) has been reported at 36 weeks post infection (Figure 17[30]) and this has persisted beyond this time. Whilst underlying risk could generate this finding, it is possible that repeat infection in an early 20th century population among which artificial vaccination was obviously not available led to a long-lasting relative elevation in risk. Further work on this highly speculative hypothesis will primarily depend upon identifying historical human and bovine samples allowing precise identification of when HCoV OC43 was introduced into human populations. Longer follow up individuals infected with SARS-CoV-2 when they were immunologically naïve, with a comprehensive set of sensitivity analyses, will allow better characterisation of possible the long-term cardiovascular effects of a novel HCoV entering human populations.

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