Commentary: The art and science of epidemiology: governed by the seasons?

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Epidemiology is the study of ‘the distribution and determinants of health-related events in specified populations, and the application of this study to the control of health problems’.1 Observational epidemiology is bedevilled by problems of uncertainty, bias, and confounding in a world that demands certainty and clear guidance from health scientists.2 The discrepant findings between observational studies and randomized controlled trials of the associations between hormone replacement therapy and coronary heart disease (CHD), and the media and health professional responses to these discrepancies, are a particular example. Two studies3,4 published in this issue of the International Journal of Epidemiology (IJE) are, I think, important since they demonstrate examples of good epidemiological science and the art required in appropriately using epidemiological findings to affect public health policy.

In 1999 Moore and colleagues undertook a study, that was published in the IJE, which showed that individuals who were born during the ‘hungry season’ in rural Gambia and who survived to at least 15 years of age had a greatly increased risk of mortality (primarily due to infectious causes) in young adulthood.3 Mortality under the age of 15 years was not affected by season of birth, and when all age groups were combined there was no overall difference in mortality by season of birth.3,5 They explored a number of possible explanations for the association between season of birth and mortality beyond the age of 15 years and excluded ‘chance’ on the basis of the strong effects and small P-values. Explanations relating to maternal or infant infectious or toxin exposures seemed unlikely. There was, however, a link between decreasing maternal weight in the last trimester of pregnancy, lower birthweight infants, and the increased risk of mortality from infectious diseases in young adulthood, all of which were related to the ‘hungry season’. The authors hypothesized that maternal, and hence fetal under-nutrition during critical periods of development, programmed abnormalities in immune function resulting in greater risk to infectious diseases in later life.5 Those findings and the suggested hypothesis were very much in line with the fetal origins of adult disease hypothesis which, until that time, had largely investigated the fetal origins of chronic degenerative adult diseases such as diabetes and cardiovascular disease in the developed world.7 Although a chance finding seemed unlikely, and the suggested explanation for the association was both plausible and backed-up by data demonstrating the associated changes in maternal weight and birthweight, the authors recognized the importance of replicating their findings. Moore and colleagues searched for other suitable datasets and in today’s IJE repeat their analyses in a rural population from Bangladesh.3 At the same time Simondon and colleagues have undertaken similar analyses in a rural population from Senegal.4 Neither study confirms the previous findings, but the fact that Moore et al. in particular recognize the importance of publishing their null findings is an example of good science.

Moore and colleagues state (and demonstrate) that:

The Demographic Surveillance System from the rural area of Matlab in Bangladesh met the necessary criteria of meticulously recorded births and deaths within an area of high nutritional seasonality.3

They re-present some of the results from the earlier Gambian study and also pool data from both studies to test for statistical heterogeneity in their findings. These analyses show that whilst those born around the time of the hungry season (compared with those born during the harvest season) in The Gambia have a marked increased risk of mortality in young adulthood (≥15 years), those born around the time of the hungry season in Bangladesh have no such increased risk. Season of birth in Bangladesh was not associated with mortality in later life. The authors suggest that since overall mortality in the 15 plus age group is greater in The Gambia than in Bangladesh (2% versus 0.1%), underlying differences in immune functioning (resulting from fetal programming) may not be apparent in populations with relatively low overall mortality. Clearly, an important consideration here is the proportion of deaths in both populations that are related to infectious diseases. For the Gambian data the authors have shown that infectious diseases do indeed account for the majority of deaths,5 but similar data are not presented for Bangladesh. Even with a lower overall mortality rate, if the majority of deaths in the 15 year plus age group in rural Bangladesh are due to infectious causes then one would expect some seasonal effect if Moore and colleagues earlier hypothesis concerning programming of immune functioning was correct.

More intriguing are the findings of Simondon and colleagues from surveillance data routinely collected from a rural area of Senegal.4 The geographical proximity of Senegal and The Gambia make these two data sets an appropriate comparison and one would have expected the results from Senegal to be

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similar to those from The Gambia. The overall mortality for those aged ≥14.5 years in this study was similar to that for The Gambia at 3%. Therefore if differences in mortality rates explained the inconsistent results between those from The Gambia and Bangladesh one would expect the results from Senegal to be similar to those of The Gambia. Simondon and colleagues report their findings as null:

This study found no increased risk of death among young adults born during the hungry season in a rural West African area despite large seasonal variations in women’s nutritional status.

Indeed their results showed a greater decrease in maternal weight during the hungry season in Senegal than that reported in the earlier study from The Gambia.

Both Moore and colleagues, and Simondon and colleagues, suggest that the discrepancies in their findings may be explained by a cohort effect. The suggestion here is that among older birth cohorts from West Africa season of birth did have an important effect on mortality in young adulthood but among younger cohorts it does not. The Gambian data was confined to individuals born during the 1950s and 1960s whilst that from Senegal (for those dying age ≥14.5 years) was confined to individuals born between 1978 and 1984. Since there was a marked seasonal effect on maternal and birthweight in the Senegalese study (as well as the Gambian study) this cohort effect could not be due to fetal under-nutrition and associated programming of immune function, as originally suggested. Moore and colleagues have changed their earlier hypothesis and now suggest that the consumption of bush foods to ward off famine in earlier cohorts or the use of old forms of insecticide on stored crops, rather than maternal and fetal under-nutrition, might have programmed changes in immune function. This hypothesis itself requires further investigation, which the authors propose to undertake. An equally plausible conclusion from these three studies would be that the heterogeneous results represent random variation around a null association between season of birth and mortality in young adulthood.

In the light of these findings do these studies help us in anyway with the ‘control of health problems’? At first sight perhaps not. However, though the main results of these studies are contradictory there are some remarkable consistencies. Seasonal factors have profound effects in all three populations (Gambian, Senegalese, Bangladeshi) on fertility, maternal weight, birthweight, and infant mortality, highlighting the dependency in these populations on the seasonable availability of food for overall health and vitality. These adult weights, birthweights, and infant mortality rates are also a stark reminder of the marked differences in health experiences between the developed and developing world. Such differences are not inevitable. In their description of mortality and morbidity in Senegal Simondon and colleagues point out how ‘childhood morbidity and mortality from vaccine-preventable diseases have decreased sharply since the onset of immunisation programs in the 1980s...’9 Although data showing the desperate health statistics of developing compared with developed countries are not new, they should serve as a reminder of the public health community’s responsibilities towards reducing global inequalities. Despite the reliance on seasonal food harvests in these rural communities, rapid urbanization in developed countries is also associated with adverse health outcomes. With respect to the fetal origins of chronic adult diseases there is increasing evidence to suggest that the greatest risks are likely to be seen in developing countries where the effects of extreme poverty in early life and in earlier generations are increasingly becoming combined with adverse Western diets and lifestyles in adulthood.8 Epidemiologists and public health practitioners need to continue to work together to determine the best ways of improving health outcomes in the developed world.

A number of historical population studies from developing countries have also found that life expectancy, all-cause mortality, and cardiovascular disease mortality is patterned by season of birth.9–14 As with the studies discussed above several reasons have been postulated for these associations. One suggestion is that cold exposure during intrauterine development and early infancy may have a direct effect on physiological development leading to increased obesity, insulin resistance, and thence type 2 diabetes and cardiovascular disease.9,13–17 Few human studies have had appropriate temperature data to directly test this hypothesis, but in a study of British middle-aged adults, cold exposure around the time of birth was associated with increased obesity in men, with a weaker and non-significant association in women.17 We have recently shown that cold ambient temperature around the time of birth is associated with insulin resistance and prevalent CHD in British women aged 60–79 years.18 That study was cross-sectional and may have been influenced by survivor bias. Further, it was a one-off study and we should learn from the example set by Moore and colleagues in this issue of the IJE about the importance of repeating similar analyses in other populations.

If cold exposure around the time of birth is associated with increased CHD risk then what are the public health implications in a modern world, where it is relatively technically easy to keep a person warm? Failure to keep warm during cold seasons in developed countries tends to be related to housing quality and poverty. Waiting at the bus stop in the cold and not being able to adequately heat the home are outcomes of social and economic position. Current housing quality in Britain tends to be worse in the North where the climate is colder.19 As with the marked seasonal variations in adult weight, birthweight, and infant mortality in rural developing countries a detrimental health effect of cold exposure in early life in a developed country illustrates the potential for inequality in socioeconomic characteristics (global or local) to interact with natural inequalities in the physical environment (drought and floods affecting crop production and geographical variations in extreme cold) to generate and exacerbate health inequalities.19

Shakespeare’s writings are full of examples of his belief in the effects of season of birth on an individual’s future fate (based on astrological theories). In Romeo and Juliet the adverse outcomes are predicted from the fact that the lovers are ‘star-crossed’. However, there are also examples that challenge this pre-ordained fate based on birth season:

This is the excellent foppery of the world, that, when we are sick in fortune,—often the surfeit of our own behavior,—we make guilty of our disasters the sun, the moon, and the stars: as if we were villains by necessity; fools by heavenly
compulsion; knaves, thieves, and treachers, by spherical predominance; drunkards, liars, and adulterers, by an enforced obedience of planetary influence; and all that we are evil in, by a divine thrusting on: an admirable evasion of whom master man, to lay his goatish disposition to the charge of a star! My father compounded with my mother under the dragon’s tail; and my nativity was under Ursa major; so that it follows, I am rough and lecherous. Tut, I should have been that I am, had the maidenliest star in the firmament twinkled on my bastardizing.

Edmund, Illegitimate son of Gloucester. From King Lear Act 1 Scene 2.

As public health practitioners we cannot dictate the seasons during which individuals are born. However, we can use our findings to identify policy interventions aimed at reducing nature’s global and local inequalities.

References