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The origins of the developmental origins theory

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Current orthodoxy states that coronary heart disease results from the unhealthy lifestyles of westernized adults together with a contribution from genetic inheritance. This does not provide a secure basis for prevention of the disease. Geographical studies gave the first clue that the disease originates during intra-uterine development. Variations in mortality from the disease across England and Wales were shown to correlate closely with past differences in death rates among newborn babies. In the past most deaths among newborns were attributed to low birthweight. This led to the hypothesis that undernutrition *in utero* permanently changes the body's structure, function and metabolism in ways that lead to coronary heart disease in later life. The association between low birthweight and coronary heart disease has been confirmed in longitudinal studies of men and women around the world. The developmental model of the origins of the disease offers a new way forward.

Keywords: birthweight, coronary heart disease, geographical studies.

Current orthodoxy states that coronary heart disease results from the unhealthy lifestyles of westernized adults together with a contribution from genetic inheritance. Such a view, however, leaves its changing incidence and geography largely unexplained, and offers little insight into why one person develops the disease while another does not. The effectiveness of preventative measures based on this view of the disease has been questioned [1].

In many Western countries the steep rise of coronary heart disease has been followed by a fall [2]; in the USA this has been of the order of one quarter over 20 years. No parallel changes in adult lifestyle seem to explain it. In Britain there were large changes in lifestyle during the Second World War, especially in diet. Death rates from coronary heart disease in middle-aged men and women, however, continued to rise throughout the war and the period of postwar rationing [3].

The geography of heart disease in Britain is paradoxical. Rates are twice as high in the poorer areas of the country, and in lower income groups [4]. The steep rise of the disease in Britain and other Western countries was associated with rising prosperity [5, 6]. So why should its rates be lowest in the most prosperous places, such as London and the home counties, and in the highest income groups? [7, 8] Biochemical and physiological measurements in adult life, including serum cholesterol and blood pressure, have been shown to be linked to coronary heart disease [9]. Yet even when combined with these biological risk factors, adult lifestyle has limited ability to predict coronary heart disease [10]. Rose pointed out that, for a man falling into the lowest risk groups for cigarette smoking, serum cholesterol concentrations, blood pressure and preexisting symptoms of coronary heart disease, the most common cause of death is coronary heart disease [11].

It is, perhaps, surprising that it was geographical studies that gave the early clue that answers to these paradoxes may come from events *in utero*. Nevertheless, the first indication that coronary heart disease might be linked to impaired fetal growth came from the demonstration that differences in rates of death from

coronary heart disease in different parts of England and Wales paralleled previous differences in death rates among newborn babies [12]. In these early studies the death certificates for all people who had died in England and Wales during 1968–1978 were used to calculate coronary heart disease rates for men and women in each of the 1366 local authority areas [13]. The concentration of low mortality from coronary heart disease in the south and east contrasted with the high mortality in the northern industrial towns, and the poorer rural areas in the north and west of the country.

Of the 23 common causes of adult death other than coronary heart disease, only chronic bronchitis, stomach cancer and chronic rheumatic heart disease had a similar close geographical relationship with past infant mortality. Such a relationship with infant mortality would be expected for these diseases, because they are linked to poor social conditions, and their rates, like those of infant mortality declined, during the last century. It was, however, paradoxical that coronary heart disease was related to infant mortality because the rates increased during this century.

One possible explanation of this relationship was that the poor social conditions which caused infant deaths in the past are in some way linked to adult lifestyles which cause death from coronary heart disease. The nature of such a link was not, however, apparent. Differences in cigarette smoking did not appear to follow those of past infant mortality because the distribution of deaths from lung cancer was strikingly different from that of past infant mortality. Therefore it could not be argued that the social conditions giving rise to infant death led to higher cigarette smoking in later life and hence to raised heart disease rates. Similarly, differences in dietary fat consumption did not have the same geographical distribution as past infant mortality [14]. The close geographical similarity between past infant mortality and current mortality from coronary heart disease was most readily reconciled with their opposing time trends through the hypothesis that adverse environmental influences *in utero* and during infancy, associated with poor living standards, directly increased susceptibility to the disease.

Findings from other studies supported the general hypothesis that coronary heart disease is linked with adverse influences in early life. Forsdahl [15] reported that arteriosclerotic heart disease correlated with past infant mortality in the 20 counties of Norway, and he was the first to suggest that a poor standard of living in childhood and adolescence was a risk factor in heart disease. Another study compared east and west Finland and came to similar conclusions: that poor living conditions in childhood, with bad housing and recurrent exposure to infection, increased the later risk of coronary heart disease [16]. In 17 states of the USA, mortality from coronary heart disease was shown to be related to infant mortality resulting from diarrhoeal disease, which again suggested that the disease is associated with poor living conditions in childhood [17].

Other observations which suggested that influences in childhood were linked to coronary heart disease include those made by Rose [18]. He reported that siblings of patients with coronary heart disease had stillbirth and infant mortality rates that were twice as high as those of controls. He concluded that 'ischaemic heart disease tends to occur in individuals who come from a constitutionally weaker stock', a conclusion foreshadowing what is known today. The study of London civil servants by Marmot *et al.*[19] showed that death rates were higher in those who were shorter in stature, and who may therefore have had a worse environment in early life. Among long-term employees of the Bell System Company in the USA, men whose parents had been in 'white collar' occupations had a lower incidence of coronary heart disease than those from blue collar families [20].

The size of the geographical study in England and Wales, based on almost one million deaths from coronary heart disease, together with the remarkably complete and detailed infant mortality records, made it possible to examine whether coronary heart disease was associated with specific causes of infant death and hence with particular aspects of the early environment. Infant deaths were divided into neonatal (deaths in the first month after birth) and postneonatal (deaths from 1 month to 1 year). They were also divided into

five causes, using a classification devised 50 years ago for an extensive analysis of the social cause of infant mortality [21]. congenital, bronchitis and pneumonia, infectious diseases, diarrhoea and 'other'.

The distributions of neonatal and postneonatal mortality throughout England and Wales were broadly similar. Nevertheless there were areas where the rate of one was high while the other was low. The 15 boroughs of London were important in this respect. London had low neonatal but high postneonatal mortality. The 212 local authority groups in the country were ordered according to the neonatal mortality rates during 1911–1925 and divided into five groups according to the level of mortality [22]. Neonatal mortality rose from 30 per 1000 births in group 1 to 44 in group 5. Five groups with increasing postneonatal mortality were derived in the same way, mortality rising from 32 per 1000 in group 1 to 73 in group 5. In this way the relationship of neonatal and postneonatal mortality to adult mortality could be examined within a grid of 25 cells (Table 1).

Table 1 compares death rates from stroke, coronary heart disease and chronic bronchitis. Within any of the five bands of postneonatal mortality, standardized mortality ratios for stroke increased sharply with increasing neonatal mortality. There was no independent trend in stroke mortality with postneonatal mortality. Mortality from coronary heart disease had similar but separate trends with neonatal and postneonatal mortality. Mortality from chronic bronchitis rose steeply with increasing postneonatal mortality, but had no independent trend with neonatal mortality.

Seventy years ago, most neonatal deaths occurred within a week of birth and were commonly associated with low birthweight. They therefore depended on adverse intrauterine rather than postnatal influences [23]. Of such deaths, 80% were certified to be the result of 'congenital' causes, which also correlated geographically with stroke and coronary heart disease. The figure shows the close geographical association between coronary heart disease and neonatal mortality in England and Wales. This link between neonatal mortality and both coronary heart disease and stroke suggested that early influences predisposing to cardiovascular disease act during prenatal life. Postneonatal deaths were the result of respiratory infection, diarrhoea and other infections, reflecting inadequate housing, overcrowding and other adverse influences in the environment after birth. The link between postneonatal mortality and coronary heart disease and chronic bronchitis pointed to influences acting during early postnatal life.

Table 1 Standardized mortality ratios for stroke, coronary heart disease and chronic bronchitis in the 212 local authority areas of England and Wales grouped by neonatal and postneonatal mortality (1911–25)

	Postneonatal mortality				
Neonatal mortality	1 (lowest)	2	3	4	5 (highest)
Stroke					
1 (lowest)	85	81	79	78	79
2	86	90	98	74	76
3	102	100	104	104	104
4	–	108	110	115	117
5 (highest)	124	–	121	123	117
Coronary heart disease					
1 (lowest)	84	89	91	88	98
2	85	93	95	88	91
3	86	94	99	106	113
4	–	98	109	111	115
5 (highest)	83	–	114	119	116
Chronic bronchitis					
1 (lowest)	67	78	106	115	161
2	64	84	85	104	126
3	69	65	89	88	151
4	–	91	99	120	142
5 (highest)	41	–	108	123	144

These geographical studies led to the hypothesis that undernutrition *in utero* and during infancy permanently changes the body's structure, physiology and metabolism and leads to coronary heart disease and stroke in adult life. The principle that the nutritional, hormonal and metabolic environment afforded by the mother may permanently programme the structure and physiology of her offspring was established long ago [24]. It is a manifestation of the general phenomenon

of developmental plasticity. Like other living creatures in their early life human beings are 'plastic' and able to adapt to their environment. The development of the sweat glands provides a simple example of this. All humans have similar numbers of sweat glands at birth but none of them function. In the first three years after birth a proportion of the glands become functional, depending on the temperature to which the child is exposed. The hotter the conditions, the greater the number of sweat glands that are programmed to function. After three years the process is complete and the number of sweat glands is fixed. Thereafter, the child who has experienced hot conditions will be better equipped to adapt to similar conditions in later life, because people with more functioning sweat glands cool down faster.

This brief description encapsulates the essence of developmental plasticity: a critical period when a system is plastic and sensitive to the environment, followed by loss of plasticity and a fixed functional capacity. For most organs and systems the critical period occurs *in utero*. There are good reasons why it may be advantageous in evolutionary terms for the body to remain plastic during development. It enables the production of phenotypes that are better matched to their environment than would be possible if the same phenotype was produced in all environments. Developmental plasticity is defined as the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development [25].

To explore the developmental origins of cardiovascular disease required studies of a kind that had not hitherto been carried out. It was necessary to identify groups of men and women now in middle or late life whose size at birth had been recorded at the time. Their birthweight could thereby be related to the later occurrence of coronary heart disease. In Hertfordshire, UK, from 1911 onwards, when women had their babies they were attended by a midwife, who recorded the birthweight. A health visitor went to the baby's home at intervals throughout infancy, and the weight at 1 year was recorded. Table 2 shows the findings in 10 636 men born between 1911 and 1930 [26]. Hazard ratios for coronary heart disease fell with increasing birthweight. There were similar and stronger trends with weight at 1 year. A subsequent study confirmed a similar trend of decreased hazard ratios for coronary heart disease with increasing birthweight among women born during this time but no trend with weight at 1 year [27].

Table 2 Hazard ratios (95% confidence intervals) for death from coronary heart disease (CHD) according to weight at birth and at age 1 year in 10 636 men in Hertfordshire

	Death from CHD	
Weight (lb)	Before 65 years	All ages
At birth		
≤5.5	1.50 (0.98–2.31)	1.37 (1.00–1.86)
−6.5	1.27 (0.89–1.83)	1.29 (1.01–1.66)
−7.5	1.17 (0.84–1.63)	1.14 (0.91–1.44)
−8.5	1.07 (0.77–1.49)	1.12 (0.89–1.40)
−9.5	0.96 (0.66–1.39)	0.97 (0.75–1.25)
>9.5	1.00	1.00
P for trend	0.001	0.005
Age 1 year		
≤18	2.22 (1.33–3.73)	1.89 (1.34–2.66)
−20	1.80 (1.11–2.93)	1.58 (1.15–2.16)
−22	1.96 (1.23–3.12)	1.66 (1.23–2.25)
−24	1.52 (0.95–2.45)	1.36 (1.00–1.85)
−26	1.36 (0.82–2.26)	1.29 (0.93–1.78)
≥27	1.00	1.00
P for trend	<0.001	<0.001

The association between low birthweight and coronary heart disease has now been replicated among men and women in Europe, North America and India [28–33]. These associations are independent of the duration of gestation and must therefore be the result of slow fetal growth. Studies of the Helsinki birth cohort have confirmed that coronary heart disease is also associated with slow early postnatal growth [34]. Studies in Europe and the US have shown that low birthweight is associated with an increased risk of stroke in adult life [35–40]. Recent findings in the Helsinki birth cohort are consistent with the thesis

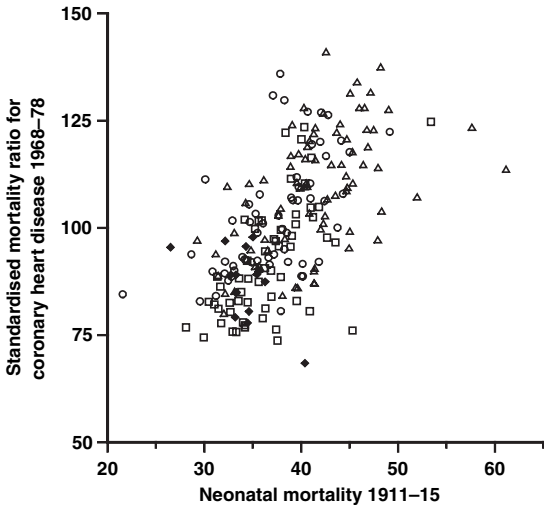

Fig. 1 Standardized mortality ratios for coronary heart disease in England and Wales during 1968–79 and neonatal mortality during 1921–25 (♦ London boroughs; △ county boroughs; ○ urban districts; □ rural districts)

that hemorrhagic stroke, formerly the commonest form of stroke, originates in the prenatal environment and is not influenced by the environment into which the baby is born [41]. In contrast coronary heart disease and thrombotic stroke originate in both the prenatal and early postnatal environments [41, 42].

The deductions from the early ecological studies have therefore been confirmed in studies of individuals. The orthodox view that cardiovascular disease results from adult lifestyles and genetic inheritance has not provided a secure basis for prevention of these disorders. The developmental model of the origins of chronic disease now offers a new way forward.

Conflict of interest

No conflict of interest was declared.

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