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29th C. Elaine Field Lecture

Fetal Programming or Adult Lifestyle Lessons from the Newcastle 1000 Families Study

AW ***CRAFT***

Abstract It is a privilege and a real pleasure for me to present this 29th Elaine Field Memorial Lecture. Professor Field established the Department of Paediatrics in Hong Kong in 1961 and led it until her retirement in 1976. Then followed a long and well deserved retirement until her recent death in England in 2002. It is perhaps apt that my lecture this year has real connections with her, the work that she did and the Department that she founded and which has continued to thrive for the last quarter of a century since she left. Elaine Field spent many of her early years in the North East of England going to school in Sunderland which is barely 12 miles from my own home town of Newcastle upon Tyne. The second and direct connection between my lecture and Elaine Field is her very important academic study published as a book in 1973 "Growing up in Hong Kong".[1] The subject of my paper relates to an earlier study, about growing up in Newcastle upon Tyne. This was led by Dr. F. J. W. Miller and his visit to Hong Kong is recorded in Field's book. Prof. C. Y. Yeung remembers this visit and the long discussions which took place between Field and Miller about how to set up the Hong Kong study. Both studies received their initial financial support from the Nuffield Foundation. Were the findings of these 2 studies on opposite sides of the world the same? We will see!!

Key words Cohort study; Fetal programming

Introduction

In recent years the concept that much serious adult disease is a result of intrauterine programming has gained considerable support. Professor David Barker and his colleagues from Southampton, in a series of elegant retrospective studies, have developed these ideas into what is now known as the Barker Hypothesis.[2] The majority of his work has been opportunistic in that he has identified data sets, many from the 1920's and 1930's which were collected by obsessional individuals who would never have thought that the birth data that they were noting would ever be used in this way. Clearly one of the best ways to test this hypothesis would be a prospective Cohort study which collected all of the appropriate pre-conceptional, and fetal data and then followed the subjects through until late life. Such studies are now underway e.g. the ALSPAC Study[3] but these subjects are still only just entering their teens and we cannot afford to wait another 50 years or more for answers.

Cohort studies are of course not new but prior to the Second World War they were virtually unheard of. In Newcastle upon Tyne, in the North of England, Sir James Spence had the vision in 1947 to establish one of the first ever longitudinal cohorts which became known as the Newcastle 1000 Families Study. The subjects are now well into their 6th decade of life and the wealth of data which has been collected on them since birth, along with a detailed follow up at the age of 50, enables us to ask the question - what are the relevant influences of fetal and infant life, childhood and adulthood on disease in later life?

Department of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, United Kingdom

AW **CRAFT** *MD, PRCPCH*

Correspondence to: Prof AW **CRAFT**

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Background to the Study

The initial thoughts which led to this study arose through observations made by James Spence, one of the first ever full time paediatricians in the United Kingdom and from 1942, the first holder of a University Chair of Child Health in England. Prior to the Second World War Newcastle was a heavily industrialised city famous for coal mining, steel manufacturing and ship building. However, in spite of almost 150 years of heavy engineering heritage there had been little investment in the infrastructure of the city, unemployment was high and housing poor. In those pre-war days the City Council was responsible for the health of its citizens and it became very concerned about the death rate in infancy which was one of the highest in the country. In 1939 the infant mortality rate was 62 per 1000 live births. It is difficult, living in the 21st century, to really conceive what this meant. The United Kingdom currently has an infant mortality rate of only 5.5 per 1000 and Hong Kong 5.8. China is 27. An infant mortality rate of 62 in the present day is seen in Kenya and Cameroon. The City Council was so concerned that they asked Spence to undertake a review of all deaths of babies and also an investigation into the health and nutrition of the children between 1-5 years in the City of Newcastle upon Tyne.[4] In 1939 there were 272 deaths in babies up to 1 year of age and 102 of these were due to infection. Some of the major findings from that study are shown in Table 1.

A separate investigation was done into the amount of money spent on food and the majority of families were spending well under the national recommended levels at that time. Spence concluded that the excess infant mortality was due to death from acute infection.

As World War II ensued little further could be done to investigate the problems. There was no research done during this time and little could be done to improve the social fabric of the City. There was no investment in housing and many of the children were evacuated from the big cities. However, there were some benefits of war in that there was full employment, most families had a good income and because of this they had a reasonable diet. Food was rationed but this meant that no one went without food and similarly nobody had too much.

The Start of the Thousand Families Study

The end of the war came in 1945 and the young doctors began to return to take up their former careers. One of these was Fred Miller and in 1946 Spence is reported to have said to him at a weekly departmental meeting "Well Freddie what are we going to do about all these infections"? Thus was born the Newcastle 1000 Families Study. The initial aim of the study was to confirm the pre-war findings that infection was the major cause of infant mortality but it also intended to look at infant morbidity and in particular to try and identify factors which pre-disposed to infection. Finally it wished to place the health of infants within the context of the family. In May and June 1947 there were 1142 babies born within the boundaries of the City of Newcastle upon Tyne. Virtually all of these were recruited into the study which was expected to last for one year. Only 4 families refused to participate. A red spot was put on the child's general practitioner medical record so that the doctor would know that the child was a member of this 1000 Families study and that the study team could be notified when the child was unwell. These children, therefore, became known as the Red Spot Babies. Even today they call themselves "red spots".

First year data collection included an antenatal chart, a midwife's report of the babies first 14 days, the doctors report of any illnesses, along with in-patient and out-patient hospital records. The most important source of data collection was the health visitor. Health visitors are public health nurses who have a statutory responsibility to visit children at home during their early years of life. A special housing survey was also undertaken. The main analysis, therefore, looked at the number of infections for each child and related this to the housing condition, parenting skills,

Table 1 Summary of findings of 1-5 years old in Newcastle in 1939

45 %	had parents who were unemployed
22%	lived in houses with more than 2.5 people per room
73%	spent less than the minimum on food
46%	were underweight
18%	had anaemia
43%	had gross tooth decay

Table 2 Housing conditions

152 (15%) of houses were 'unfit'
322 (33%) of households were overcrowded
(i.e. >2 people in 1 room; >3 in 2 rooms; >5 in 3 rooms etc.)
228 (23%) shared a toilet with another family
413 (43%) had no bath

income and family support. To give some idea of the circumstances in which children were living the major findings of the housing survey are shown in Table 2.

967 of the original cohort were followed to the end of the first year and between them they had 1625 episodes of illness, 799 of these being respiratory tract infections. The results were all documented in a book by Spence and his colleagues, "A Thousand Families in Newcastle upon Tyne".[5] It concluded that infections were related to social factors but the single most important factor, was "maternal capacity". Mothers were categorised by the Health Visitor into "satisfactory", defined as "where the mother's capacity in her home and family is sufficient to safeguard the health of her infant i.e. she can cope". The "unsatisfactory" mothers were those at the lowest end of the scale, those with problem families, indifferent mothers i.e. the "non-copers". An example of a health visitor's literary skill is shown in the following extract from the records.

> *"A family consists of the parents and 8 children, the eldest of whom is 11 years. They live in an upstairs flat of 2 rooms in a dismal house in a deteriorating neighbourhood. The living-room, furnished with a table, a dresser, a double bed, and infant's cot, and containing a kitchen range and a gas stove, is almost always dirty and untidy. The father, a Corporation scavenger, earns £5 a week. The mother, a cheerful, talkative, unintelligent woman, is always full of fine intentions and specious explanations, but her fitful inroads on the domestic confusion are quite ineffectual. The children, with their dirty makeshift clothes and running noses, swarm over the battered furniture like a tribe of monkeys. Two further infants have been born since the beginning of this survey and only the fullest use of cots and prams with 'topping and tailing' in the three beds, can provide sleeping space for everybody. Yet in spite of parental fecklessness and a wretched house, there is a streak of cheerfulness and rough justice which has kept the family in being."*

This important finding that parenting skills were a very important determinant of a child's health was revolutionary in its day. However, it must be recognised that they had limited tools available for statistical analysis and could not undertake the multivariate analyses available today.

The study was so successful that it was decided to continue until the children went to school. The pre-school years are chronicled in "Growing Up in Newcastle upon Tyne".[6] Clearly the study could not stop there and it continued in considerable detail with regular home and school visits up to the age of 15 years and once again the results were all reported as "The School Years".[7] The analyses continued to show strong socio-economic gradients in health, growth and school achievement. An example of the findings is shown in Figure 1 where height and social class are clearly related. Having clearly documented the children's lives up to the end of their school years no further comprehensive study was planned. However, a limited follow up of 272 of the original cohort was undertaken by a child psychiatrist, Professor Israel Kolvin, and he particularly looked at the children's behaviour and criminality. Once again there were clear socio-economic gradients associated with adverse mental health and what is more, there seemed to be continuities of these findings between generations. The results of this study were documented in a further book, the 4th in the series, "Continuities of Deprivation".[8] The major conclusions of this study were:-

- We have seen that many children seem destined to experience a disproportionate burden of adversity-due in part to the nature, attitudes and behaviour of parents and grandparents.
- Protective factors are to be found in the nature of the child and in parents and in aspects of family life.
- An equable temperament, scholastic ability, social competence, parents who plan and provide good emotional care and close emotional supervision are all important.
- These positive characteristics bring about their effects through chain reactions, often in social contexts over the course of time.

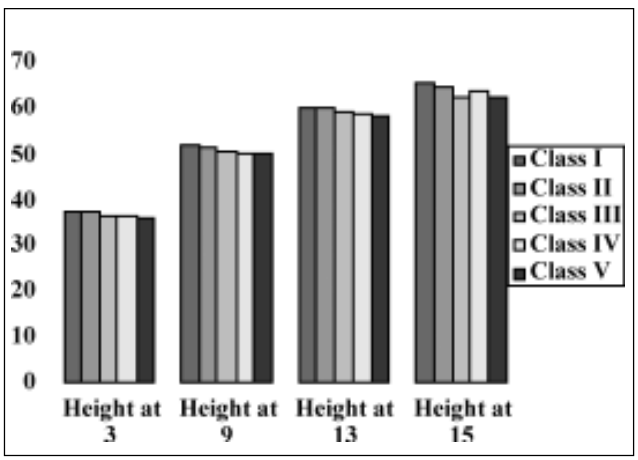

Figure 1 Height and social class in the 1000 families children.

The early and middle adult years are generally of little interest to epidemiologists studying adult disease as this tends to be the healthiest period of life and one has to wait till the later years before a significant number of illnesses/ diseases develop. The study, therefore, went into abeyance and all of the data was stored in the Newcastle City Archive.

Follow-up Age 50 Years

Planning for a further follow-up of the 1000 Families Study began in the early 1990's at a time when the Barker Hypothesis was gaining considerable credence. In a series of elegant analyses Barker and his team had demonstrated statistical associations between the anthropometry of newborn babies and subsequent mortality and morbidity. These statistical associations led to the concept of "fetal and infant origins of adult disease". The hypothesis being –

Under nutrition in utero programmes fetal metabolism to produce a "thrifty" phenotype.

Thus babies who are small at birth become adults with increased susceptibility to: hypertension; cardio-vascular disease; central obesity; glucose intolerance.

It was recognised that the 1000 Families cohort might allow us to ask the question: "What are the relevant contributions to adult health of fetal/infant vs childhood vs adult experience?"

The first thing to do was to see how many of the study members could be traced. Nine hundred and sixty-seven had been followed to the end of the first year and records from the Office for National Statistics told us that 46 had subsequently died. Eight hundred thirty-two were traced to a private address, either through personal contact, press releases or through the National Health Service Central Register. Five were in Canada, 2 in the USA, 2 in Australia and 5 in Asia. One of the first tasks for the new study group was to catalogue and computerise all of the important data which had been stored. This allowed further analysis to be undertaken on the original data. As already indicated the original research team had considered maternal capacity rather than poverty or social disadvantage to be the single most important factor in determining the health of children. A further analysis of this data was, therefore, undertaken to see whether the use of multivariate techniques could give us some indication of what actually was being measured by "maternal capacity". The main findings of the original and new analyses are shown in Table 3.

It is clear that social class and overcrowding were much more important than maternal capacity which seemed to disappear from the analysis when other factors were taken into consideration. We came to a new conclusion. Even the most satisfactory mother could do little to mitigate the insidious effects of grinding poverty on the health of her children. Details of this analysis are in the paper by Parker et al.[9]

The new study was in two parts. First of all there was a postal questionnaire which was sent to 832 of those whom we had identified and was returned by 574 (69%). This included standard, well validated questionnaires on health and lifestyle, including nutrition, as well as a psychiatric screening tool. Those who responded were then asked to participate in a health check which involved them coming to hospital for a series of investigations. These included anthropometry, blood pressure, lung function, glucose tolerance, bone mineral density, carotid artery intima media thickness by ultrasound and blood for serum, lipids and clotting factors. Four hundred and twelve of the cohort participated in this which is 49% of those who had been traced.

Further details of the methods that were used for follow up are given in the paper by Lamont et al.[10]

Pathways to disease are complex and in order to consider factors operating at different stages of life we decided that a conceptual framework analysis approach would be appropriate. Figure 2 gives an example of such a framework and how one might consider factors operating at different levels. This approach has now been used to assess the relative contributions of the 3 phases of life i.e. fetal/infant, childhood and adult life style for the subsequent development of both cardiovascular disease and for central metabolic syndrome.

Cardiovascular Disease

Even by the age of 50 very few of the cohort had actually had a cardiac "event". However, it is now clear that the measurement of carotid artery intima thickness is a good

Table 3 The Thousand Families Study – results: reanalysis using mulitvariate model – respiratory tract infections in infancy

	Original analysis	**New analysis**
	Increase in risk	
Social class	16%	13%
Overcrowding	37%	29%
Maternal capacity	36%	No effect

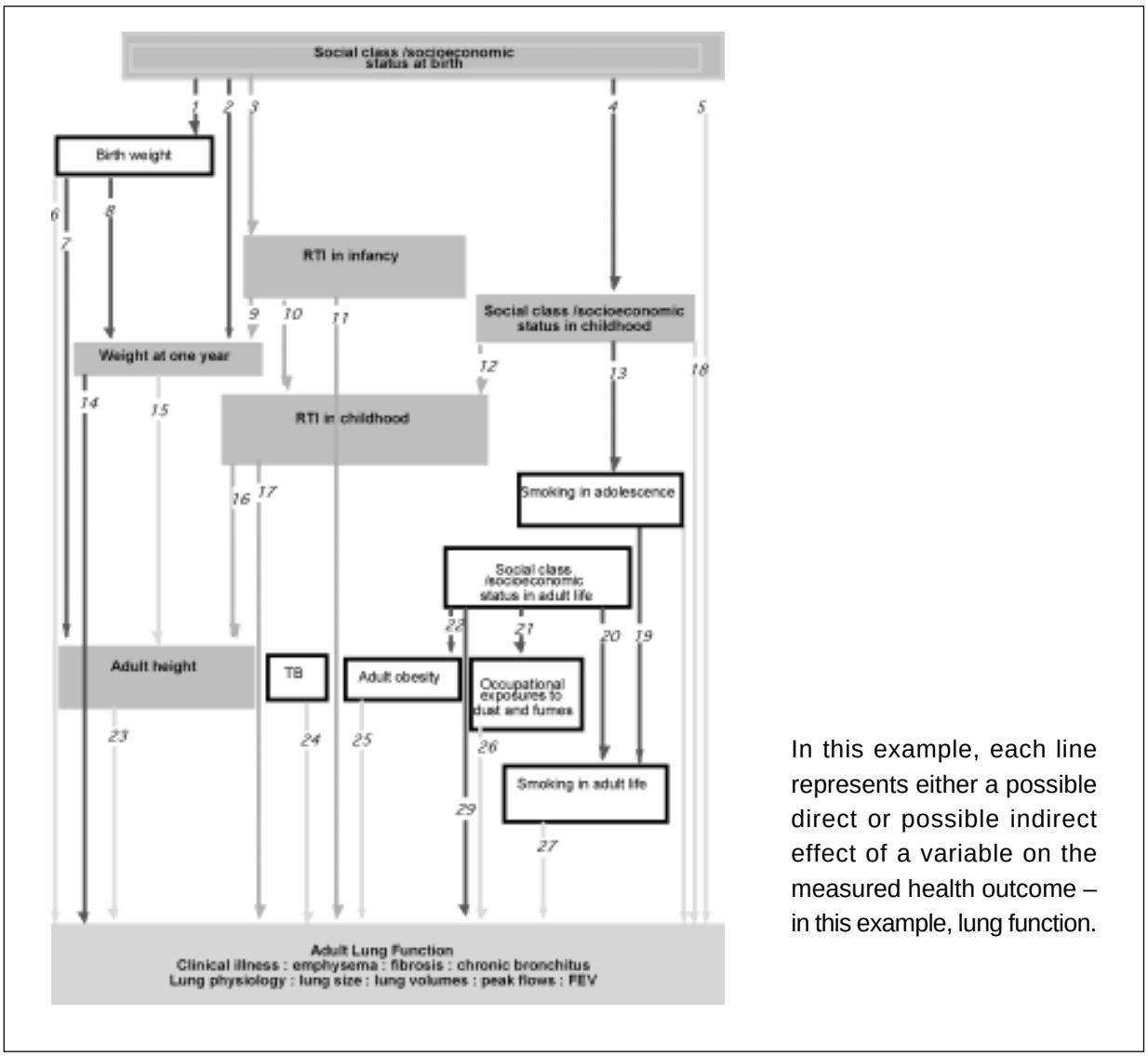

Figure 2 Pathways to disease are complex.

surrogate measure predictive of future cardiac events. Measurement of the patients carotid artery intima media thickness by Bmode ultrasound, 7 mHz, at 3 predetermined sites on both carotids was undertaken. The relative influences of different periods of life can be seen in Tables 4, 5 and 6 and a summary of the percentage of variance explained in Table 7. Finally these results are shown graphically in Figure 3 where it can be seen that factors operating around birth and during childhood are not so important as adult lifestyle in explaining the variance in carotid artery intima thickness. Further details of this analysis are given in the paper by Lamont et al.[10]

Central Metabolic Syndrome

This is defined as hyper-insulinaemia, dyslipidaemia and obesity and the important components are body mass index, weight: hip ratio, systolic and dyastolic blood pressure, serum HDL, cholesterol and triglycerides and fasting 2 hours insulin and plasma glucose. Once again these were analysed through a conceptual framework analysis and the major results are given in Tables 8, 9, 10 and 11. The proportion of variance explained by each of the life periods is summarised in Figure 4. A more detailed analysis is in the paper by Parker et al[11] Once again it can be seen that adult lifestyle is the most important influence.

Table 4 Results: carotid artery intima thickness – prenatal/infant influences

	Men	**Women**
	N=141	**N=182**
	Standardised regression co-oefficient	
Family history of angina, heart disease, stroke	-0.09 (95%CI -0.25-0.07)	-0.04 (95%CI -0.19-0.10)
Social class at birth	-0.05 (95%CI -0.21-0.11)	-0.16 (95%CI -0.30-(-0.02))*
Poor housing at birth	0.10 (95%CI -0.06-0.26)	0.08 (95%CI -0.07-0.22)
Birthweight (adjusted for gestational age)	-0.17 (95%CI -0.33-(-0.02))*	-0.04 (95%CI -0.18-0.10)

* significant

Table 5 Results: carotid artery intima media thickness – childhood influences

	Men	**Women**
	N= 141	**N=182**
	Standardised regression co-oefficient	
Social class in childhood	0.02 (95%CI-0.14-0.18)	-0.09 (95%CI -0.24-0.05)
Poor housing in childhood	-0.06 (95%CI -0.22-0.10)	0.02 (95%CI -0.12-0.17)
Adverse life events in childhood	0.06 (95%CI -0.10-0.22)	0.09 (95%CI -0.06-0.23)
Infections in childhood	-0.01 (95%CI -0.17-0.15)	-0.08 (95%CI -0.22-0.07)
Catch-up growth in childhood (adjusted for both adult height and birth weight)	0.12 (95%CI -0.04-0.28)	0.04 (95%CI -0.11-0.18)

Table 6 Results: carotid artery intima media thickness – adult influences

Adult socioeconomic position and lifestyle	**Men**	**Women**
	N= 141	**N=182**
	Standardised regression co-oefficient	
Adult social class	-0.04 (95%CI-0.12-0.12)	-0.10 (95%CI -0.24-0.05)
Ever cigarette smoker	0.06 (95%CI -0.10-0.22)	-0.20 (95%CI 0.06-0.34)*
Exercise level	-0.20 (95%CI -0.35-(-0.04))*	-0.17 (95%CI -0.31-(-0.03)*
Alcohol intake	-0.01 (95%CI -0.17-0.15)	0.06 (95%CI -0.08-0.20)
% total energy from fat	0.10 (95%CI -0.06-0.26)	0.04 (95%CI -0.10-0.18)

* significant

Table 7 Results: carotid artery intima media thickness – summary

	Men	**Women**
	N= 141	**N=182**
	Percentage of variance explained	
Family history of cardiovasular disease	0.8 (95%CI 0-5.9)	0.5 (95%CI 0-5.9)
Socioeconomic position at birth and birthweight	2.2 (95%CI 0.1-6.4)	2.0 (95%CI 0.1-5.5)
Socioeconomic position, adverse life events, illnesses and growth pattern in childhood	3.2 (95%CI 0.3-6.8)	2.2 (95%CI 0.2-5.0)
Total early life (including indirect effects)	9.15 (95%CI 2.4-12.3)	4.7 (95%CI 2.1-6.7)
Adult socioeconomic position and lifestyle (including indirect effects)	3.42 (95%CI 0.5-6.2)	7.56 (95%CI 2.1-13.0)

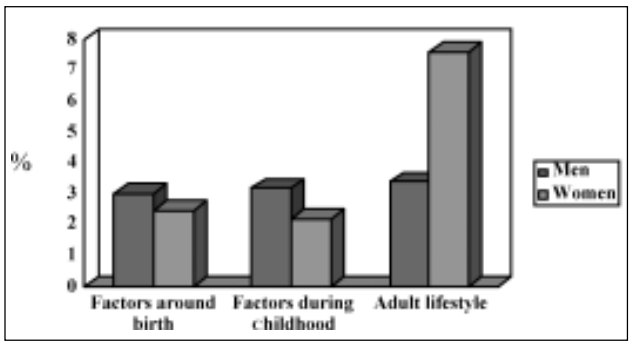

Figure 3 Central metabolic syndrome: proportion of variance explained.

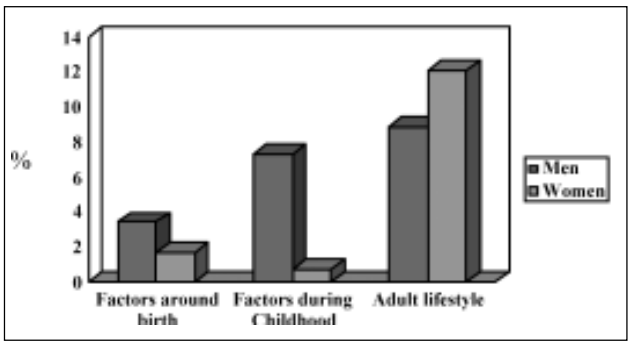

Figure 4 Carotid artery intimal thickness: proportion of variance explained.

Table 8 Results: central metabolic syndrome – prenatal/infant influences

	Men N = 141	**Women N = 182**
	Standardised regression co-oefficient	
Family history of diabetes, high BP, or overweight	-0.03 (95%CI -0.20-0.13)	-0.06 (95%CI -0.21-0.09)
Social class at birth	-0.09 (95%CI -0.26-0.08)	-0.15 (95%CI -0.29-0.00)*
Poor housing at birth	-0.04 (95%CI -0.21-0.12)	0.14 (95%CI -0.01-0.29)*
Birthweight (adjusted for gestational age)	-0.13 (95%CI -0.29-0.04)	0.01 (95%CI -0.13-0.16)

* significant

Table 9 Results: central metabolic syndrome – childhood influences

	Men N= 141	**Women N=182**
	Standardised regression co-oefficient	
Social class in childhood	0.01 (95%CI -0.16-0.17)	-0.09 (95%CI -0.24-0.05)
Poor housing in childhood	-0.02 (95%CI -0.18-0.15)	0.06 (95%CI -0.09-0.20)
Adverse life events in childhood	0.14 (95%CI -0.03-0.30)	0.14 (95%CI -0.01-0.28)
Infections in childhood	-0.01 (95%CI -0.17-0.16)	-0.03 (95%CI -0.18-0.12)
Catch-up growth (adjusted for both adult height and birth weight)	0.17 (95%CI 0.00-0.33)	0.01 (95%CI -0.13-0.16)

Table 10 Results: central metabolic syndrome – adult influences

	Men N = 141	**Women N = 182**
	Standardised regression co-oefficient	
Adult social class	-0.11 (95%CI -0.28-0.06)	-0.10 (95%CI -0.24-0.05)
Exercise level	-0.25 (95%CI -0.41-(-0.09))*	0.16 (95%CI -0.31-(-0.02))*
Ever smoked	0.12 (95%CI -0.05-0.29)	0.09 (95%CI -0.06-0.24)
Low to moderate alcohol consumption	0.08 (95%CI -0.09-0.25)	-0.01 (95%CI -0.16-0.13)
% energy from fat	0.03 (95%CI -0.14-0.19)	0.07 (95%CI -0.08-0.22)

* significant

Table 11 Results: central metabolic syndrome – summary

	Men N= 141	**Women N=182**
	Percentage of variance explained	
Family history	0.05 (95%CI 0-0.45)	0.03 (95%CI 0-0.35)
Socioeconomic position at birth and birthweight	3.35 (95%CI 0.20-9.8)	1.68 (95%CI 0.04-4.65)
Total early life	10.4 (95%CI 4.1-14.2)	4.9 (95%CI 1.7-6.1)
Adult socioeconomic position and lifestyle	8.9 (95%CI 2.1-12.1)	12.1 (95%CI 3.8-17.8)

Childhood Obesity

The Newcastle 1000 Families has also allowed us to look at the implications of childhood obesity for adult health. The worldwide epidemic of obesity is now considered to be one of the major public health issues of the day and great efforts are being put into identifying factors which might be preventable. A summary of the findings, which are reported in detail by Wright et al[12] were that there was no excess health risk from childhood obesity as a whole. Childhood BMI seems to be linked to adult BMI but not to the percentage of body fat. It was only obese 13 years old who had a significant increased risk of adult obesity and indeed the highest adult risk of disease was for those who were thin as children and then obese as adults.

Conclusion

From the 1000 Families Cohort study it would appear that there is only a small influence of foetal and infant factors in adult disease but by far and away the most important factors are those of adult lifestyle. Why then do we seem to be getting a different answer to Barker? The simple answer is that we are seeing a "Barker" effect but that it is small when compared to adult lifestyle. Secondly it could be that the Barker hypothesis is wrong! A recent paper in the Lancet was entitled "Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure?" The authors analysed 55 separate studies which had reported regression co-efficients for birthweight and adult systolic blood pressure. Their interpretation of the data was as follows. "Claims for a strong inverse association between birthweight and subsequent blood pressure may chiefly reflect the impact of random error, selective emphasis of particular results, and inappropriate adjustment for current weight and for confounding factors. These findings suggest that birthweight is of little relevance to blood pressure levels in later life".[13] The Newcastle 1000 Families experience would appear to confirm these findings.

Finally it must be remembered that the Thousand Families cohort was different to most of those studied by Barker. They are one of the few cohorts whose mothers were all reasonably well nourished. In pre-second world war days and indeed now there is considerable variation in nutritional status of mothers. Most are well nourished but a significant minority are seriously undernourished. The mothers of the Red Spots had just been through a war where food rationing had ensured adequate nutrition for all.

Finally we return to Elaine Field's study of growing up in Hong Kong. One hundred and twenty-two of the original cohort were traced at the age of 30 years. The aim was to relate adult blood pressure to fetal and infant growth. Having adjusted for confounding factors they found that birth length, ponderal index at birth and postnatal change in ponderal index between 6-18 months i.e. catch up growth, were all inversely associated with adult blood pressure.[14]

I am sure Elaine Field would have appreciated that both the Newcastle Thousand Families and her own Hong Kong study were still playing an important part in medical history so long after their inception.

References

1. Field CE, Baber FM. Growing up in Hong Kong. Hong Kong, University Press, 1973.
2. Barker DJP. Mothers, babies and health in later life (2nd ed). London: Churchill Livingstone, 1998
3. Golding J, Pembrey M, Jones R. ALSPAC – the Avon Longitudinal Study of Parents and Children. I. Study methodology Paediatr Perinat Epidemiol 2001;15:74-87.
4. Spence JC, Miller FJW. Report of an Investigation into the Causes of Infant Mortality in Newcastle upon Tyne, 1939. Christie, Malcolm: Newcastle upon Tyne, 1941.
5. Spence J, Walton WS, Miller FJW, Court SDM. A Thousand Families in Newcastle upon Tyne. Oxford University Press: London, 1954.
6. Miller FJW, Court SDM, Walton WS, Knox EG, Growing up in Newcastle upon Tyne. London: Oxford University Press, 1960
7. Miller FJW, Court SDM, Knox EG, Brandon S. The School Years in Newcastle upon Tyne 1952-62. London: Oxford University Press, 1974.
8. Kolvin I, et al. Continuities of Deprivation: The Newcastle Thousand Families Study. Gower, Aldershot, 1990.
9. Parker L, Lamont DW, Wright CM, Cohen MA, Alberti KG, Craft AW. Mothering skills and health in infancy: the Thousand Families study revisited. Lancet 1999;353:1151-2.
10. Lamont D, Parker L, White M, et al. Risk of cardiovascular disease measured by carotid intima-media thickness at age 49-51: lifecourse study. BMJ 2000;320:273-7.
11. Parker L, Lamont DW, Unwin N, et al. A lifecourse study of risk for hyperinsulinaemia, dyslipidaemia and obesity (the central metabolic syndrome) at age 49-51. Diabet Med 2003;20:406-15.
12. Wright CM, Parker L, Lamont D, Craft AW. Implications of childhood obesity for adult health: findings from the thousand families cohort study. BMJ 2001;323:1280-4.
13. Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? Lancet 2002;360:659-65.
14. Cheung YB, Low L, Osmond C, Barker D, Karlberg J. Fetal growth and early postnatal growth are related to blood pressure in adults. Hypertension 2000;36:795-800.