LONGEVITY DETERMINED BY PATERNAL ANCESTORS' NUTRITION DURING THEIR SLOW GROWTH PERIOD

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Received 22-XI-1999

ABSTRACT

Social circumstances often impinge on later generations in a socio-economic manner, giving children an uneven start in life. Overfeeding and overeating might not be an exception. The pathways might be complex but one direct mechanism could be genomic imprinting and loss of imprinting. An intergenerational "feedforward" control loop has been proposed, that links grandparental nutrition with the grandchild's growth. The mechanism has been speculated to be a specific response, e.g. to their nutritional state, directly modifying the setting of the gametic imprint on one or more genes. This study raises the question: Can overnutrition during a child's slow growth period trigger such direct mechanisms and partly determine mortality?

Data were collected by following-up a cohort born in 1905 in Överkalix parish, northernmost Sweden. The probands were characterised by their parents' or grandparents' access to food during their own slow growth period. Availability of food in the area was defined by referring to historical data on harvests and food prices, records of local community meetings and general historical facts.

If there was a surfeit of food in the environment when the paternal grandfather was a 9-12 year old boy a shortening of the proband survival could be demonstrated. The influence of parents', maternal grandparents' and paternal grandmothers' access to food during their slow growth period was discounted in a multivariable analysis. The results are indicative of very early programming mechanisms in human adaptation to the social environment.

Keywords: Genomic imprinting, childhood nutrition, off-spring.

1. INTRODUCTION

Overfeeding of children and adolescents may program their own lipid and other metabolic systems for life (McGill, 1998). A mother's own nutrition during her childhood can influence her child's disease risk as an adult as to cardiovascular disease, diabetes mellitus type II and hypertension (Martyn *et al.*, 1996) and the effects probably cover a wider range of disease determinants (Signorelli and Trichopoulos, 1998). The nutrition of the grandmother during pregnancy influences the mother's nutrition during her fetal life and influences the grandchild's birth weight

Acta Biotheoretica **49**: 53–59, 2001.

(Lumey and Stein, 1997). One mechanism could be epigenetic. Whether imprints are initiated or erased is essential for normal development and ultimately for the long-range prevention of disease (Picton *et al.*, 1998; Kato *et al*,. 1999). An intergenerational ”feedforward” control loop has been proposed, that links grandparental nutrition with the grandchild’s growth. The mechanism could be a specific response, e.g. to their nutritional state, directly modifying the setting of the gametic imprint on one or more genes (Pembrey, 1996).

The growth of the child is slowest in the period before the prepubertal peak in growth velocity. Overeating during this period might initiate or erase imprints of the gamete under its development and have impact on the offspring.

The purpose of this paper is to consider the possible intergenerational effects on survival from overnutrition during the slow growth period of childhood.

We found that a grandchild’s survival was curtailed when the paternal grandfather had experienced a surfeit of food during the slow growth period and prolonged if the food availability was poor.

2. MATERIALS AND METHODS

The cohort used for the analysis consisted of 94 probands from a random sample of 99 individuals, drawn at random from the 199 children born in the parish of Överkalix, northern Sweden, in 1905. During the 19th century the area was an isolated and impoverished remote community. The 99 individuals in the sample were identified in the parish registers of the Swedish and Finnish communities and most of them could be traced up to their death. Two were still alive, three had left the country at 22-23 years of age and could not be traced. Their parents and grandparents were traced back to their birth. Birth dates, the dates May 1st and November 1st and historical data on harvests were used to assess ancestors’ access to food during the slow growth period (SGP) of their childhood. Birth years only, were retrieved for 13 of the grandparents. Sensitivity analyses have been performed where they were excluded and included, and denoted as living through years of a surfeit of food or a poor availability. All but one of the significant results were unchanged.

The availability of food in the area during any one year was classified on the basis of regional harvest statistics (Communications from the County Governor in Västerbotten to His Majesty the King, unprinted), grain prices (Jörberg, 1972), the estimates of a 19th century statistician (Hellstenius, 1871), and general historical facts. Food availability was classified as poor, moderate, or good. The harvesting was largely completed in September, followed by slaughtering later in the fall. We used May 1st the subsequent year as the worst time following a crop failure. The best time following a good harvest was represented by November 1st while intermediate availability was represented by July 1st. An ancestor’s age on those dates was used to determine the availability of food during his or her SGP.

The SGP was determined visually out of the growth velocity during childhood measured in centimeters height increase per year. The ages at which the ancestors lived through their SGP were set at 8-10 years for girls and 9-12 years for boys. The period had to be estimated from a modern cohort and turned out to be shorter for girls than for boys (Prader *et al*., 1989). Furthermore the secular decrease in age at puberty had to be taken into account (Tanner, 1981).

The delay of parents’ and grandparents’ puberty compared to the modern cohort was set to one year. The proband’s age at death was used as the respondent variable in a model. Causes of death were however recorded. Explanatory variables were each of the six ancestors', parents' and grandparents', access to a relative abundance of food some time during the SGP, exposure to food shortage some time during the same period and moderate availability throughout the whole SGP.

Statistical analysis

A linear multiple regression analysis was performed with age at death as the respondent variable and experience of either some year of famine, or some year of good harvest or only intermediate years during ancestors' SGP as explanatory or independent indicator variables. They were introduced in a logical sequence. The variables for the mother were introduced first and then the other variables added in this order: father, maternal grandmother, maternal grandfather, paternal grandmother and paternal grandfather. The program used was PROC REG in SAS.

3. RESULTS

The availability of food

The crops were often meagre during the 19th century in the area studied. We classified the harvests of 1800, 1812, 1821 and 1829 as total crop failures. In the period 1831-36, all years but 1834 suffered a total crop failure and as 1834 was affected by lack of seed-corn we classified it as a total crop failure as well. This was also true of 1809 because of hostilities when the soldiery requisitioned much of the local food stocks and interfered with bringing in the harvest. In 1851 and 1856 there was again total crop failure and the harvests in 1867, 1877, 1881, 1888 and 1889 were very poor.

A surfeit of food was available after the harvest in 1799, 1801, 1813-15, 1822, 1825-26, 1828, 1841, 1844, 1846, 1853, 1860-61, 1863, 1870, 1876, 1879 and 1880. All the other years had moderate harvests, neither very poor nor abundant.

Slow growth velocity and availability of food

There was a deleterious effect on the survival of the proband if the paternal grandfather was 'overfed', i.e. experienced at least one November 1st after a good harvest when he was 9-12 years old. A model including the other five ancestors' nutrition during the SGP accounted for 12% of the variance. Conversely probands benefited regarding survival from the paternal grandfathers' experiencing at least one May 1st after a poor harvest during the SGP when they were 9-12-year-old boys. This model accounted for 12% of the variance as well. The difference in survival was 32 years between the grandchildren, whose paternal grandfathers had these two extremes of experiences during their SGP. If the paternal grandfathers experienced only moderate availability during this period of their childhood, no effect could be detected on the proband's survival (Table 1).

Other periods studied

The ages 0-2 years for girls and boys, 3-7 years for girls, 3-8 years for boys, 11-15 years for girls, and 13-16 years for boys have been checked as to the influence of availability of food on the offsprings' mortality but the effect of nutrition demonstrated during the SGP could not be reproduced (data not shown).

Table 1. Probands' average longevity in years related to their ancestors' access to food during their own slow growth period (SGP) prior to the prepubertal peak.

Variable	**Survival time**		**Probability**
	Years	**SE**	**P**
Poor availability of food, any year during SGP			
Intercept	50.9	6.6	0.0001
Mother	-2.6	5.6	0.64
Father	5.5	5.7	0.34
Maternal grandmother	2.2	6.1	0.72
Maternal grandfather	-5.8	5.7	0.30
Paternal grandmother	10.8	6.3	0.09[1)]
Paternal grandfather	15.8	5.8	0.01
F-value = 2.945; p = 0.01			
Adjusted R^2 = 0.12			
Good availability of food, any year during SGP			
Intercept	76.1	6.9	0.0001
Mother	-6.3	6.1	0.30
Father	-6.8	6.0	0.26
Maternal grandmother	8.7	5.6	0.12
Maternal grandfather	-1.1	6.0	0.85
Paternal grandmother	-6.2	6.0	0.31[2)]
Paternal grandfather	-16.5	6.0	0.01
F-value = 3.043; p = 0.47			
Adjusted R^2 = 0.12			
Moderate availability of food during all SGP			
Intercept	62.2	4.3	0.0001
Mother	3.7	6.2	0.55
Father	4.0	7.6	0.59
Maternal grandmother	-16.4	8.1	0.05
Maternal grandfather	17.0	13.8	0.22
Paternal grandmother	-3.7	7.6	0.63
Paternal grandfather	4.3	10.6	0.68
F-value = 0.943; p = 0.47			
Adjusted R^2 =-0.004			

Ancestors are introduced into the model in this order: mother, father, maternal grandmother and grandfather, and paternal grandmother and grandfather. Availability of food classified from harvests and prices and other historical facts in poor (famines), good, and moderate availability.

[1)] The step before the paternal grandfather was introduced in the model, p measured with a T-test was = 0.02.

[2)] The step before the paternal grandfather was introduced in the model, p measured with a T-test was = 0.01.

4. DISCUSSION

We used a historical birth-cohort and ancient cohorts of parents and grandparents in the analysis. The register data dated far back into history, for 13 of the ancestors we found only the year of birth and there may be other defects we were unable to check afterwards. When we established their period of slow growth velocity, we used a modern cohort, determined the SGP out of the growth velocity in cm/year, and added one year, as puberty occurred about one year later for the ancestors. Furthermore their age at puberty is known to have had a more skewed distribution to the right for them but, we did not take this into consideration. Our delineation of the SGP consequently is approximative, which might mean that some differences between the groups could not be detected.

For thirteen of the grandparents the birth year was missing from the records. They were excluded from the analyses. In sensitivity analyses they were included in the analyses as negative, i.e. neither starving, overfed, nor moderately fed in the respective analyses. The results were then unaffected. Another analysis denoting them as starving, overfed or intermediate during the SGP did not markedly affect the results, except that poor availability during the paternal grandmother's SGP then had an effect as well ($p = 0.046$). In some instances the SGP included years of poor availability as well as years with a surfeit of food. A sensitivity analysis where only one of the two kinds was allowed to define the exposure gave slightly less distinct differences (data not shown).

Few of the parents in our cohort experienced famine and starvation during the SGP. Furthermore crop failures did not result in the same degree of catastrophe during the end of the 19th century as in the early decades. The reason was primarily the development of farming but also a better community organisation to master difficult times. These facts might explain why there was no detectable influence upon the probands when their fathers had starved or been overfed. Parents' longevity was however not significantly affected by the grandparents' access to food during the SGP (data not shown). The parental generation appeared to have been skipped.

We do not know what the ancestors actually received from the available food supplies. The individual's social class and area-based socio-economic indicators make independent contributions to health outcomes (Smith *et al*., 1998). Furthermore, availability of food, was determined for the province as a whole, and not just for our smaller research area. On the other hand this means that relief supplies within the nearest 200-300 kilometres were unlikely. Relief from further afield was an impossibility. At that time there was no railway and no roads and in the winter no transport by sea as the Baltic Sea freezes over.

The outcome parameter (mortality) is very aspecific. The impact of nutrition might however regard a wide range of cardiovascular and neoplastic diseases (Signorelli and Trichopoulos, 1988) only two of the deaths were accidental. The number of probands is regrettably small because of the elaborate follow-up and we have not checked the probands' own life experiences. This birth cohort however did not live through any famine during childhood. Death of parent(s) before the proband was 12 years old did not significantly influence longevity when introduced into the model (data not shown).

Good availability of food and poor availability of food during the paternal grandfathers SGP had opposite effects while moderate availability had hardly any effect on survival time of the probands. Nutrition affects ovaries and testes from the moment they form during fetal life up to maturity (Gosden *et al*., 1997). One might expect that an effect would be visible in the next generation. This was not the case, however. Fathers' or mothers' living in an environment with a surfeit of food or poor availability of food during their SGP had no effect on their children's longevity. Likewise such an environment during SGP of most of the grandparents had no impact on their children's longevity and did not affect their grandchildren either, but for the one important exception. The paternal grandfather's living in an environment with a surfeit of food during his SGP did affect his grandchild's longevity negatively and the other way round when the availability was poor.

The first interesting aspect of this finding is that over nutrition seems to have affected the DNA directly when it affected only the paternal grandfather and perhaps the paternal grandmother but no maternal ancestor. This was not seen for other childhood periods, but only uniquely seen for nutrition during the SGP. The second finding of interest is that the impact skipped the parent generation. This could be consistent with a genomic imprinting (Hall, 1997) and in effect an intergenerational "feedforward" control loop similar to the loop proposed by Pembrey (1996) linking grandparental nutrition with the grandchild's growth.

ACKNOWLEDGEMENTS

Lennart Bäckman, MD, is thanked for his contribution to the study, which was supported by a grant from the Swedish Council for Planning and Co-ordination of Research (FRN 940020:4).

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