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ORIGINAL ARTICLE

Birthweight—is it linked to minor illness in adulthood?

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Abstract

OBJECTIVE: The Barker's hypothesis states that poor nutrition *in vitro* is linked to low birthweight and major illness, in particular cardiovascular disease, in later life. Reported here is an investigation to establish links with birthweight and minor illness.
METHODS: 78 participants whose birthweight ranged from 1.93 kg to 4.88 kg with a mean to 3.31 kg completed a symptom checklist.
RESULTS: Analysis of variance indicates that those with a higher birthweight experience less minor illness. Regression analysis indicates that birthweight is significantly predictive of levels of some minor illnesses.
CONCLUSION: This investigation adds a new dimension to Barker's hypothesis and shows that early environment can also affect levels of minor illness. It is suggested that susceptibility to minor illness may be explained by coactions between structure, function and environment prior to birth.

Introduction

Babies are born in different sizes and forms. Size at birth is determined by coactions between the intrauterine environment and the fetal genome. The association between birthweight and later major disease such as coronary heart disease (CHD) has been confirmed by epidemiological studies [1]. However, the association of size at birth and minor illness, which is the main aim of our study, has not been hitherto investigated. Our interest is on a size of birth which has not attracted systematic investigation, i.e. babies born between 2.5 kg and 3.31 kg and the association with minor illness.

The relatively new interdisciplinary science of psychoneuroimmunology or PNI has been described as the relationship between behavioral, neuroendocrine and immune functions [2]. PNI investigates coactions and interactions between psychological and physiological factors, seeking to understand pathways between these systems. Minor illnesses such as the common cold, upper respiratory tract infection (URT) and 'flu' have frequently been investigated in psychoneuroimmunological research [3].

The baby in the womb: *in utero* coactions

Gottlieb's [4] theory of experiential canalization defends that epigenesis is probabilistic and views the individual as an "emergent, coactional, hierarchical system." The consequence of horizontal (e.g. cell to cell) and vertical (e.g. cell to environment) is the emergence of new structural and functional properties [5].

Examples of these new structural and functional properties are reported by Gupta [6] who discusses how hormones in pregnancy influence fetal and childhood development with the concept that hormones and neurotransmitters affect personality and physiology. Exposure of the fetus to maternal secretion of higher or lower levels of various hormones can effect fetal and neonatal brain development that may cause significant changes in adulthood. He presents evidence (from human and animal studies) suggesting that an imbalance of fetal neurotransmitter production can influence later life, e.g. possible gender identity influences, sterility in male rats, and anxious and depressed behavior in animals. Also, low secretions of hormones and neurotransmitters produced by the central nervous system and pineal gland can affect the immune system and leave person susceptible to many infections.

A further example of new structural and functional properties can be seen in the relationship between fetal and placental development. At an early stage, an embryo is comprised of two groups of cells. The outer cell mass develops into the placenta while the inner cell mass becomes the fetus. Distribution of cells between the two masses have been shown to be influenced by nutrition and hormones [7], and it appears that even short periods of under nutrition may permanently change bodily function and structure [1].

Nathanielsz [8] suggests that in an unfavorable environment the developing baby makes attempts to compensate for deficiencies. Following compensation, birthweight may be normal or only slightly decreased; however, the compensatory effort carries a price. Studies investigating the consequence of these early life coactions and changes in function and structure in later life will be discussed in the next sections.

Early environment and later disease

Epidemiological studies

Using archive material, Barker [1] reports a number of associations between birthweight and disease in later life. These associations are found independently of social group, behaviors such as smoking or maternal size and age. Furthermore, Barker reports that these associations between birthweight and CHD have been confirmed by studies in the UK, USA, and South India. One such study showed that it is people who are small at birth because they failed to grow, rather than being born too early, who are at increased risk of disease [9].

The association between birthweight and CHD is paralleled by trends in other major disease, i.e. hypertension and non-insulin dependent diabetes. For example, there is a higher incidence of non-insulin dependent diabetes in people who were small at birth but obese as adults [10, 11]. Evidence suggests the reason for this is that poor fetal growth results in reduced number of pancreatic β cells and a reduced capacity to make insulin.

Similarly, the association between birthweight and raised blood pressure has been extensively demonstrated in both adults and children [12]. Possible mechanisms for this association have been attributed to the effects of maternal glucocorticoid hormones [13, 14]. Also, expansion of the placenta has been associated with hypertension in later life. In one study [15] blood pressure was correlated with placental weight, with the highest blood pressure being in those who in fetal life allocated a greater proportion of resources to placental development than their own growth. Placental enlargement has also been associated with impaired glucose tolerance, disordered blood coagulation and CHD [1].

Comparative studies

Barker [1, 16] and Schmidt [17] report that in animal experiments, under nutrition *in utero* is associated with a number of health deficits including the reduction of immune functions. In animals poor nutrition can impair fetal growth at critical stages and permanently damage a range of organs such as the endocrine pancreas and liver.

Modest glucocorticoid excess has been shown to retard fetal growth and program for raised blood pressure. Excess may be a result of feto-placental stress or deficiency of the placental enzyme, which protects the fetus from the mothers' glucocorticoids. This deficiency has been experimentally induced in rats by under nutrition. In sheep, under nutrition in early pregnancy leads to placental enlargement, thought to be an adaptation to extract more nutrients, the effects of which have been identified in the previous section on epidemiological studies.

Minor illness

Minor illnesses have been subject to a number of investigations in psychoneuroimmunology research for a number of reasons. Firstly, they are particularly susceptible to psychological influence [18, 19, 20]. Secondly, they are common in the general population which allows study of small groups over a short period of time as opposed to lengthy studies involving large numbers of participants. Finally, retrospective self reports of minor illnesses over a period of up to three months have been shown to be stable and reliable.

This study

Literature reviewed suggests that emergent altered structure and function following unfavorable intrauterine coactions carry a price of increased susceptibility to major disease in later life. Barker's hypotheses [1] that poor nutrition *in vitro* permanently affects the fetus, resulting in LBW and disease in later life. Nathanielsz further suggests that even babies who are not officially LBW may also be programed for ill health.

It is generally recognised that LBW is 2.5 kg and under. Classification of normal birthweight, however, is somewhat more difficult, as Barker [1] writes. The diversity of size of human babies after normal pregnancies is remarkable; this diversity is essentially determined by the intrauterine environment.

The central nervous system and pineal gland produce a large number of hormones, any alteration in the synthesis or secretion of which can leave a person more susceptible to many infections [6]. Black [21] reviewed studies of psychoneuroimmunolgy which indicated that mutual interactions exist between the central nervous system and the immune system. We have cited studies which indicate the link between fetal environment and secretion of hormones and neurotransmitters, which can result in lowered immune function. Nevertheless, studies investigating the consequences of the relationship between size at birth and adult minor illness has hitherto not been investigated. We hypothesis that those with a lower birthweight will report more minor illness symptom days.

Methods

Design

Data were collected as part of a larger study. In the demographic details, participants were asked to state their birthweight, with an option of "don't know." This is a retrospective design, with participants reporting symptoms for the previous month.

Participants

An opportunity sample of 78 students (67 female, 15 male) with a mean age 25.33, standard deviation 8.96, took part in study. The sample was taken from a larger study, where participants were asked to either give their birthweight or state that they did not know.

Birthweight ranged from 1.93 kg to 4.88 kg., as this study is interested in participants who are not officially low birthweight. Those under 2.5 kg were excluded. The remaining 75 had a mean birthweight of 3.4 kg., median of 3.31 kg., and mode 3.18 kg.

Hypothesis

As immune function is one of the systems to be affected by intrauterine environment, it is anticipated that those with a lower birthweight will report more minor illness symptoms.

Measurements: Minor illness symptom checklist

The symptom checklist used here was developed by the author from other studies, Evans and Edgerton [18, 19] and Reifman, Bierinat, and Lang, [22]. It measures minor illness in eight categories: Common cold or upper respiratory tract infection (URT), digestive illness, skeletal problems, cough and sore throat, sinus problems, allergic reactions, sleep problems and miscellaneous illness.

Common cold or URT symptoms are as used by Evans et al. and Reifman et al. (op cite). For other minor illness categories Evans & Edgerton et al. used a seven item yes/no checklist, e.g. digestive problems

were dealt with as *"have you had an acute episode of illness involving stomach, bowels or digestive system?"* or *"Do you have an acute allergic reaction (skin weals, swelling, etc.)?"* In contrast Reifman et al. presented actual symptoms, e.g. digestive problems were presented as indigestion and diarrhea. They also recorded the number of symptom days "never, 1–2 days, 3–6 days, 7–14 days, 15 or more days." The symptom checklist used for this study adopted the measurement of symptom days and presented actual symptoms which were taken from both Evans et al. and Riefman et al. lists.

Data analysis

Since the median is a measure of central value, it was used as a cutoff point to identify two groups. Group 1 with a birthweight below the median of 3.31 kg had 36 participants; group 2 with a birthweight above the median had 39 participants. Analysis of variance (ANOVA) was used to establish whether membership in a birthweight group can account for the variance in reports of minor illness. A series of linear regressions was carried out to identify minor illnesses that could be predicted in a membership of birthweight group.

Results

Results of the ANOVA indicate that membership in a birthweight group accounts for the variance in reports of upper respiratory tract infection, [F (1,73) = 7.10, p = .009] cough and sore throat [F (1,72) = 4.22, p = .043] sinus problems [F (1,71) = 5.43, p = .023]. Figure 1 shows the mean number of reported illness days for each birthweight group. The lower birthweight group reported a mean of 5.36 days of URT symptoms, 3.14 days cough and sore throat and 2.45 days of sinus symptoms. The higher birthweight group reported less illness days with 3.30 days of URT symptoms, 2.07 cough and sore throat, and 1.47 of sinus symptoms.

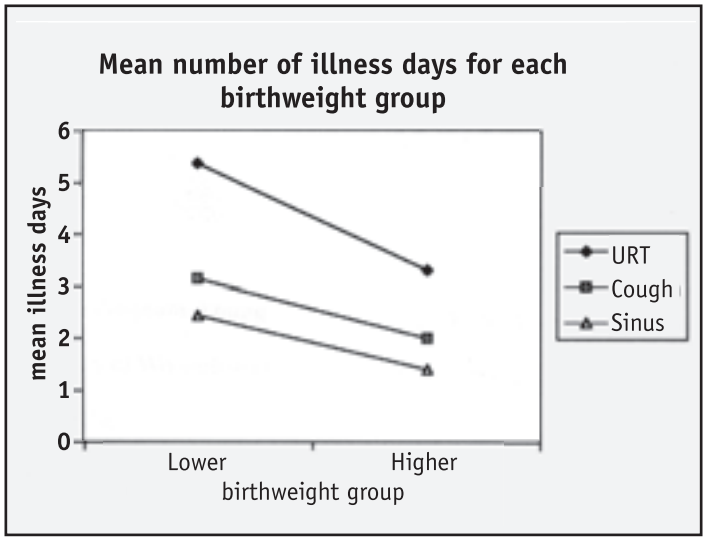

Fig. 1. Mean reported days of minor illness symptom category for each birthweight groups above and below the median weight.

Results of linear regression confirm that the variances revealed by the ANOVA can be predicted by membership in a birthweight group. Membership in the lower birthweight group is significantly predictive of higher incidence of URT illness (b = -.29, r^2 = .08, p = .009) cough and sore throat (b = -.23, r^2 = .05, p = .043) and sinus problems (b = -.26, r^2 = .07, p = .023). The other minor illness categories were not statistically significant, although the trend was for the lower illness group to report more symptoms.

Discussion

Results were as expected; participants with lower birthweights report more incidence of upper respiratory tract infections and sinus problems than those in the higher birthweight group. The predictive nature of this relationship is demonstrated by the regression results where membership in a higher or lower birthweight group is predictive of levels of minor illness symptoms.

These results add a new dimension to Barker's hypothesis that environment in the womb is associated with major disease and demonstrates that minor illness as well as major disease is also linked to birthweight. It supplies evidence which supports Nathanielsz' [8] concept of early programing, that even babies who were not officially low birthweight carry the health consequences of fetal compensatory actions into adulthood

PNI studies often focus on minor illnesses such as the common cold or upper respiratory tract infection (URT) as these have been shown to be particularly sensitive to psychological influence [20]. Here we are able to report that URT and other minor illness are also sensitive to birthweight. This is as expected since animal studies have shown that the immune system is affected by poor nourishment *in vitro*. Both Barker [1] and Nathanielsz [8] agree that variation in birthweight is essentially a result of the environment in the uterus. Although participants were not officially low birthweight, our data were able to demonstrate a linear and predictive relationship between size at birth and susceptibility to minor illness. As Nathanielsz states, birthweight may be normal or only slightly decreased. However, when a fetus diverts resources to compensate for an unfavorable environment, this compensation pays a price. It appears that prenatal growth is critical to health throughout life.

It is interesting to note that the minor illnesses

predicted by birthweight are of a similar nature, i.e. common cold (URT), cough, sore throat and sinus problems. Digestive illness, skeletal problems, allergic reactions, or sleep problems were not significantly related to birthweight. This indicates that fetal compensation and early programing is not a random act, but is rather focused on specific physiological systems.

This programing may be explained by Gottlieb's theory of experiential canalization. He argues that experiential canalization is a result of horizontal (e.g. cell to cell) and vertical (e.g. cell to environment) coactions. Within this framework which embraces PNI, horizontal and vertical coactions are suggested to explain our findings. Adverse uterine environment acts upon the fetus (environment to biological structure); fetal compensation occurs affecting organs responsible for neurotransmitter production and immune system (biological structure to biological structure); reduced immune function has the effect of more minor illness symptom days in adulthood (biological structure to health outcome).

Barker's hypothesis stems from an epidemiological perspective, seeking to understand the source of disease. To paraphrase him from Schmidt [17], we have spent years trying to understand why a car is broken; now we see that we need to understand how the heart is made and why some are built like a Rolls-Royce and others like a cheap car. By applying Gottlieb's theory of experiential canalization, where he sees epigenesis as being probabilistic, i.e. not determined, then we see that all is not lost. If well cared for, a cheap car can last as long a Rolls-Royce, and if left to run without oil or maintenance, the Rolls-Royce will not last so well.

Limitations of this study are that it relies upon self report of birthweight which is subject to accuracy of information from the memory of parents and participants. However, people remember what is important to them, and participants were given the option of stating birthweight was unknown. Social factors affecting birthweight have not been considered; however, epidemiological studies have demonstrated the link between size at birth and major disease when such factors have been controlled for. Participants' lifestyle has also not been controlled for; e.g. it is not known how many of the participants were smokers. Notwithstanding this limitation, these are important first findings linking minor illness with size at birth in a group that has not been previously studied, indicating that intrauterine environment affects health on different levels, not just major disease.

Further investigation with measures of immune function and where birthweight is obtained from records, and social and behavior factors are controlled for is required. Investigation is required to understand the trend for minor illnesses found to be not significant in this study, i.e. is there a relationship that would be uncovered by replication with larger numbers, or is there some other reason why they are not affected by size at birth.

In conclusion, this study identifies links between birthweight and adult minor illness in a group that is not officially low or normal birthweight. It would be presumptuous to speculate as to the mechanisms for this; indeed that was not the aim of this study, rather it was to investigate whether or not such a relationship existed. In keeping with the Barker's hypothesis, evidence is presented to support the concept that fetal compensation programs the immune system, resulting in increased susceptibility to some minor illnesses.

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