The fetal origins of adult disease: a narrative review of the epidemiological literature

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Summary

The fetal origins of adult disease (FOAD) hypothesis suggests that risk factors from intrauterine environmental exposures affect the fetus' development during sensitive periods, and increases the risk of specific diseases in adult life. This link was initially observed between prenatal exposures and adult coronary heart disease, but corresponding observations have later been published for a range of chronic conditions. Although the hypothesis has been praised as an essential shift in our understanding of determinants for health, the hypothesis has also been criticized on a number of accounts, both methodologically and theoretically. The aim of this paper is to critically discuss the FOAD-hypothesis, in relation to the epidemiological evidence. We conclude that much of the research literature on the FOAD-hypothesis finds support for the hypothesis. Despite this, it is still unclear if the effects are independent and what the public health relevance is. Notwithstanding the heart of the hypothesis – that environmental influences during gestation have an effect on later development – should be considered a major insight and constitutes a complement to a focus on genetic and more proximal factors (such as adult lifestyle) as causes of adult disease. As the search for determinants for disease and health continues, the FOAD-hypothesis is likely to remain an important perspective. It may however be better positioned as part of a broader life course perspective, rather than as an independent hypothesis.

Introduction

Epidemiologic research is key to identifying determinants of disease.[1] Over the last century, epidemiologic research in western societies has steadily turned its focus from communicable to non-communicable disorders, such as coronary heart disease, non-insulin dependent diabetes, asthma and chronic obstructive pulmonary disease, and a strengthened interest in lifestyle and social factors as determinants for disease.[1–3] The shift has also increased the focus on more distal factors, both socio-culturally (i.e. socioeconomic region) and temporally (i.e. events during earlier stages of life).[4]

The framework originally labelled 'the Barker hypothesis'[5] has become among the more important frameworks on distal temporal determinants,

suggesting that chronic illness is initiated by processes at prenatal stages.[6] The main feature of the model is that intrauterine environmental exposures and events affect the fetus' development, and thereby increases the risk of specific diseases in adult life. Initially, the potential intrauterine environmental exposures of interest were both malnutrition and infections,[7] but subsequent epidemiological studies have mainly focused on intrauterine nutrition.[8] Support for the general hypothesis was first documented for coronary heart disease,[9] but the framework has now been expanded to include a range of chronic conditions.[6] Following the expansion, the hypothesis has been dubbed the fetal origins of adult disease (FOAD), and an increased focus on the mechanisms behind the observed associations has entailed.[10] This narrative review will discuss the epidemiological evidence for the FOAD-hypothesis, and suggest future research directions within a broader framework of life course epidemiology.

Methods

This narrative review is based on a series of literature searches carried out over time during a PhD-project on associations between fetal and early life factors, and adult disease. The searches were done using several databases, including PubMed, Google Scholar and ISI Web of science. The reference lists of the identified research papers were inspected for further relevant literature (ancestry approach). The identified studies were read and assessed in accordance with the aims of the study.

The fetal origins of adult disease: biological basis and underlying mechanisms

In early studies investigating the origins of heart disease, Barker and colleagues linked the standardized mortality ratios for cardiovascular disease for 16,000 individuals, born in Hertfordshire from 1911–1930, to birth data for these individuals.[6] The data suggested that low weight, small head circumference and low ponderal index (mass/height^3) at birth was associated with an increased risk for coronary heart disease in adulthood.[11] These findings were considered the first evidence that an adverse intrauterine environment, as measured by individual anthropometric measurements at birth, had longstanding effects on the development of adult disease.

Elevated blood pressure, high serum cholesterol and diabetes mellitus are considered some of the major risk factors for coronary heart disease,[12] and was therefore studied as possible mediators of the low birthweight–FOAD link. In 1989, the first report of an inverse relationship between birthweight and blood pressure was published.[13] In a secondary analysis of the link between birthweight and blood pressure, the authors concluded that the elevated blood pressure continued to increase trough out the lifetime ('amplification').[14] Around the same time, an inverse relationship between birthweight and serum cholesterol was published.[15]

Insulin is important for gestational growth[16] and is associated with cardiovascular disease,[17] suggesting metabolic disease as a link between early growth and cardiovascular disease. The results of studies on this potential mechanism has nurtured the 'thrifty phenotype' hypothesis[18] Osmond and Barker claim that although obesity and low levels of physical activity are central in the development of non-insulin dependent diabetes, a pre-existing susceptibility is required.[6] Their argument further suggests that fetal malnutrition will lead to a down-regulation of numerous important developmental processes during gestation.[6,18] Importantly, this down-regulation leads to insulin resistance and impaired glucose tolerance which makes the individual able to retain as much nutritional energy as possible. But, if high-energy food becomes available and consumed later in life, the changes to secure fetal survival can in adult life, when faced with nutritional abundance on the contrary, increase the risk for developing non-insulin dependent diabetes. Support for this 'thrifty phenotype' has been found in many different populations, and across ethnic groups,[19] and Hales and Barker[18] claim it is now generally accepted that environmental impact during gestation increases susceptibility for non-insulin dependent diabetes. It is argued that the 'thrifty phenotype' model adds to our understanding of the diabetes epidemic,[20] beyond the previous relative unison focus on genetic determinants.

The concept of a fetal origin of adult disease have been extended well beyond coronary heart

disease and being a risk factor for coronary heart disease, and now includes investigations of the development of the central nervous system, early origins of adult mental health[21] and cognitive function.[22] Although the FOAD-hypothesis has been expanded, both in depth and breadth since its conception, the hypothesis remains controversial, and several objections have been raised.

Controversy concerning the fetal origins of adult disease hypothesis

The FOAD-hypothesis has been praised as a paradigmatic shift from proximal factors to include distal factors as determinants of disease.[23] Some now argue that the empirical support for the link between an adverse intrauterine environment and later specific disease is so strong, that our focus should be to search for mechanisms.[24] Others criticize the hypothesis on a number of accounts, both methodologically and theoretically.

Susser and colleagues[25,26] has argued that the original hypothesis is too vaguely and broadly defined. According to them, stating that a fetus' nutritional status during gestation will influence the disease risk in adulthood, allows researchers to test a near unlimited matrix of potential nutritional measures and any later disease. Such a setting is prone to produce 'Type-I' errors.[27] Secondly, due to the general formulation of the original hypothesis it could not be readily falsified, which is crucial in scientific theory testing.[28] Rather, as Paneth and Susser put it: *'example is piled on example, each somewhat consistent with hypothesis but none seriously testing it'*.[26] These criticisms have been met to a certain degree by a further refinement of the basic hypothesis,[6] as well as a elaboration of the hypothesis in relation to specific diseases (such as the 'thrifty phenotype'). Additionally, there has been an increased focus on potential mechanisms underlying the proposed causal relationship,[6,11] including research based on animal models and intervention studies involving human subjects.[29–31] Thus, through a more clear-cut formulation of the hypothesis (and disease-specific sub-hypotheses), development of a theoretical framework, identification of potential mechanisms and replication in animal models, some of the early criticism regarding the FOAD-hypothesis have been addressed.[27]

The FOAD-hypothesis has also been criticized on account of how one should interpret the statistical association between anthropometric measures at birth, and outcomes in adulthood. As for any observed association, the relationship could be a result of chance, bias, confounders, or it may be a genuine causal effect.[32]

Many of the early criticisms of the observed association between anthropometric measures at birth and later disease concerned the lack of adjustment for important third variables.[25] For example, socioeconomic status (SES) is associated with birthweight, coronary heart disease and lifestyle factors such as diet, cigarette smoking and physical exercise. This makes SES a plausible confounder, as it may influence birthweight and disease in adult life, but also lifestyle factors associated with adult disease such as smoking and physical exercise.[33] A few later studies have tried to adjust for candidate confounders and propose that the association remains.[6,34]

Further, critics have argued that some of the established associations between early factors and adult outcomes partly emerge through statistical over-adjustment.[35] This statistical phenomenon is called the 'reversal paradox', where a relationship between two variables becomes distorted when introducing a third variable, either through adjustments or stratification.[36] As an example, it is seen as inappropriate to adjust associations between birthweight and blood pressure for adult body weight, since adult body weight in part is a function of birthweight, and not necessarily a confounder.[30] Tu and colleagues[35] have through data simulation provided convincing evidence that adjusting for adult body size can alter conclusions, regardless of whether the datasets truly contain either no association, a modest inverse association or a modest positive association. As the impact of over-adjustment is difficult to assess retrospectively, the results of the simulation cannot invalidate the FOAD-hypothesis. It does, however, underline the importance of correct interpretations of statistical modelling and results. A suggested strategy is to specify four regression models when investigating the early origins hypothesis: (1) the first should investigate the bivariate association between early exposure and adult outcome, (2) the second should add information on intermediate exposures

to the first model, (3) the third should investigate the potential interaction between early exposure and intermediate exposures, and (4) the fourth should investigate to which degree intermediate exposure is related to the adult outcome.[30] In order to claim support for the FOAD-hypothesis, the first model should indicate a significant relationship between the early exposure and adult outcome before moving to test regression models 2–4.[30] Alternatively, structural equation modelling, with its synthesis of confirmatory factor analysis and regression analysis, enables investigation and estimation of proposed causal relationships.[25,36]

Attrition and selection bias has also been a major concern in relation to the FOAD-hypothesis,[25] especially in the early reports, where birth records of cohorts 50 years ago or more were used. Later, studies with high follow-up rates and information about social and economic status have emerged, reducing criticism concerning potential attrition, confounding and selection bias.[27,37]

In 2003, a meta-analysis reported evidence of publication bias regarding the inverse relation between birth-weight and blood pressure.[38] A re-analysis of the data, with control for the estimated bias, weakened the association but remained in support of the FOAD-hypothesis. Publication bias was also investigated in relation to 'the thrifty phenotype' association, but with no strong evidence.[19] Although meta-analyses have taken publication bias into consideration, the issue is not altogether resolved.

Despite major objections since the initial reports, evidence in support of the FOAD-hypothesis keeps accumulating, with better study designs and increased awareness of the possible caveats in analyzing and interpreting the findings.[27,29] Much of the criticism has been resolved or at least attended to, and the hypothesis maintains credence in the scientific community. What, then, are the possible implications of this framework for our understanding of development of chronic disease?

Implications of the FOAD hypothesis

Biological determinism and fatalism easily springs to mind with the notion that adult disease originates in the fetal stage.[39] If increased risk for adult disease is a direct consequence of irreversible structural and functional changes occurring during gestation, it has implications for public health initiatives. Strictly speaking, if changes in anatomy or function during gestation are irreversible, the window of opportunity for preventive intervention is limited to the first nine months of life.

How to structure public health interventions in this area, poses several dilemmas. Public health interventions can be either universal or targeted; universal interventions encompass all in a specified population, while targeted interventions are implemented in at-risk sub-populations. Within a FOAD-setting, universal interventions such as increasing birthweight may not be effective, and even harmful:[37] Increasing the population mean may help those at risk with low birthweight, but may at the same time increase the proportion of individuals with high birthweight, where other health risks are involved.[40] Therefore, targeted interventions, such as encouraging healthy eating habits for low birth weight individuals as well as supplementing diets for pregnant mothers likely to have low birth babies have been suggested, although only for those at risk in affluent areas to avoid increasing risks such as those outlined in the 'thrifty phenotype' model.[41] How to screen for and identify the target populations, and how to deliver the interventions, is not an easy task.[42] By extension, it has also been suggested to circumvent the focus on fetal development altogether, and rather focus on universal interventions of healthy lifestyle habits[34] and postnatal interventions such as encouraging breastfeeding.[43]

Even though early risk factors are linked to adult outcomes, it is necessary to differentiate between 'contributing' and 'sufficient' causes for any given disease.[44] A contributing cause merely increases the likelihood of disease to develop, while a sufficient cause always yields the disease. So even if the evidence for the FOAD-hypothesis accrues, and evidence seems to support a causal role of early influences on adult outcomes, it is unlikely that these early influences in themselves are sufficient causes for adult diseases. Especially since, so far, the size and relevance of the hypothesized effect of intrauterine influences on detrimental outcomes in adult life is unclear. Many reviews have concluded that the effects are small and of less public health

relevance than other risk factors.[45–47] As one author commented: *'a statistically significant relation does not necessarily mean there is any important implication for the population'*.[48]

The FOAD-hypothesis and the emerging life course perspective

The FOAD-hypothesis states that intrauterine environmental exposures will lead to specific changes in the fetus, which influences risk for disease in adulthood. Whether or not this risk leads to adult disease may, however, depend on environmental interaction.

According to the 'thrifty phenotype' hypothesis, there should not be an increased risk for non-insulin dependent diabetes among low birthweight babies who grow with a scarcity of food.[18,49] The same low birthweight babies would, however, be at increased risk growing up in an area of affluence – thus the intrauterine exposure will only actualize its inherent harmful potential in interaction with later exposures. This reformulation of the FOAD-hypothesis ties it in with epigenetics and the framework of 'life-course epidemiology'.[37,50]

The life-course perspective can be described as *'the study of long-term effects on chronic disease risk of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life'*.[50] Furthermore, the framework integrates elements from the individual's life, as well as inter-generational and history-specific elements to understand development of chronic disease.[50] By highlighting biological, psychological and social determinants of disease, a more contextualized view is advocated. A hallmark of the life-course perspective is the emphasis on the timing of exposure variables, as well as how they relate to each other in relation to the outcome of interest. This entails that life-events and biological, behavioural and socioeconomic processes during the entire lifespan (and across generations) can modify effects of intrauterine exposures, such as those highlighted by the FOAD-hypothesis.

The life-course perspective distinguishes between two main possible causal pathways between exposure and outcome:[50] The critical period model states that an exposure has lasting and specific effects on the anatomical or functional properties of organs, tissue and body systems at particular time-limited periods of development.[50] This model is further subdivided into whether later environmental triggers are necessary or not, or if later environmental influence can amend the effects. The FOAD-hypothesis resonates with the critical period model, with its focus on environmental influence during gestation. The other proposed model relates to accumulation of risk, or 'allostatic load',[51] where the number and duration of exposures adds up over the life-course, with cumulating damage to the organism and increased risk for specific diseases as result. The accumulation of risk can either be unclustered or clustered; the former relating to random exposures during life, while clustered accumulation of risk is not haphazard or equally distributed in the population, in the words of Ben-Shlomo and Kuh: *'…children living in adverse social circumstances are more likely to be of low birthweight, be exposed to poor diets, experience passive smoke exposure, and have worse educational opportunities'*.[50]

Positioning the FOAD-hypothesis within the broader life course perspective in line with the suggestion of Ben-Shlomo and Kuh, fetal growth becomes merely one out of many periods of development, which cannot be assessed independently and detached from other periods. Without incorporation into a more comprehensive scope of theorizing and investigation – supportive evidence of the fetal origins hypothesis are bound to be merely scientific fragments. This insight was exemplified by a study on blood pressure based on the 'Barry Caerphilly Growth Study'.[52] This study investigates the comparative predictive value of fetal growth versus early childhood growth for blood pressure in early adulthood. According to the authors, it was the first study with sufficiently detailed data on growth trajectories over the first five years of life, and also follow-up in adulthood (age ≈25). By modelling growth trajectories before and after birth, they concluded that both prenatal and postnatal developmental factors are important determinants for blood pressure in early adulthood – indicating more than one early critical period for the development of hypertension. Studies that include fetal growth as part of a life-course perspective can help identify the relative importance of fetal growth against other factors, and further

refine our insights into the aetiology of diseases in adulthood.[53]

Conclusion

The FOAD-hypothesis has expanded greatly during the past decades, and is influential in medicine and epidemiology. Recently, the World Health Organization included low birthweight as a risk for factor for cardiovascular disease.[54] The heart of the hypothesis – that environmental influences during gestation have an effect on later development – is a major insight and constitutes a complement to genetic and more proximal factors (such as adult lifestyle) as causes of adult disease. Whether there is an independent and direct public health impact of the associations reported within the FOAD-framework is however still unclear, even for outcomes such as blood pressure, non-insulin dependent diabetes mellitus and heart disease. As the search for determinants for disease and health continues, the FOAD-hypothesis is likely to remain an important perspective. It may however be better positioned as part of a life course epidemiology, than as an independent hypothesis.

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