# Fetal Programming and the Leningrad Siege Study

Sara A. Stanner[1] and John S. Yudkin[2]

[1]*British Nutrition Foundation, London*
[2]*International Health and Medical Education Centre, University College London*

The Leningrad Siege Study investigated the relationship between decreased maternal food intake and risk factors for coronary heart disease in adult life. The study screened 169 subjects exposed to intrauterine starvation during the Siege of Leningrad (now St Petersburg) 1941–4, 192 subjects born in Leningrad before the siege and 188 subjects born concurrently with these two groups but outside the area of the siege. No difference was found between the subjects exposed to starvation *in utero* and during infancy in glucose tolerance [*in utero*: 5.2 mmol/l (95% confidence interval 5.1 to 5.3; infancy: 5.3 (5.1 to 5.5), $p = 0.94$], insulin concentration, blood pressure, lipid concentration or coagulation factors. The intrauterine exposed group had evidence of endothelial dysfunction by higher concentrations of von Willebrand factor and a stronger interaction between adult obesity and blood pressure. Non-systematic differences in subscapular to triceps skinfold ratio, diastolic blood pressure and clotting factors were demonstrated compared to the non-exposed groups. In conclusion, this study did not find an association between intrauterine starvation and glucose intolerance, dyslipidaemia, hypertension or cardiovascular disease in adult life. These findings differ from studies of subjects exposed to maternal starvation during the Dutch Hunger Winter. However, the dissimilar effects of exposure to the two famines may contribute to our understanding of the mechanisms of the 'thrifty phenotype' and support the importance of catch-up growth during early childhood, a situation that occurred in the Netherlands but not in Leningrad.

Several studies in diverse populations have shown that retarded growth *in utero* predisposes to the development of Type II diabetes, coronary heart disease and hypertension in adult life (Barker, 1998). While there are a variety of proposed mechanisms to explain these observations, they may result from impaired development or vascularisation of particular organs, tissues or cells at different stages of fetal development, which predispose the individual to altered organ function, with consequent disease in later life (Barker, 1998). Hales and Barker (1992) have proposed the 'thrifty phenotype' hypothesis to suggest that many of the diseases in Western civilization may be the result of 'programming' of the metabolism and function of a tissue or organ as a result of diminished supply of certain nutrients during critical stages of development and poor maternal nutrition has been implicated as a common antecedent for many of these pathological conditions. This hypothesis is supported by animal experiments; for example, in rats maternal malnutrition during pregnancy retards fetal growth and raises blood pressure in the offspring (Langley-Evans et al., 1994). The 'fetal origins hypothesis' has, therefore, led to calls for improvements in maternal diet. However, most studies in humans of the long-term effects of adverse intrauterine environment have used body size at birth as an indirect measure of fetal nutrition and assumed that this is related to maternal, as opposed to fetal, supply of nutrients during pregnancy. To date, a limited number of studies in humans have directly investigated the relationship between maternal diet and either birth weight in the offspring or subsequent disease.

## Materials and Method

The hypothesis that intrauterine malnutrition increases the susceptibility to adult diabetes and cardiovascular disease was addressed by the Leningrad Siege Study. Details of study design and recruitment methods have been published elsewhere (Stanner et al., 1997). German armies besieged Leningrad (now known as St Petersburg), preventing food supplies from reaching the city, between September 1941 and January 1944. Around a half of the city's population of 2.4 million died, mostly as a result of starvation. The majority of these deaths occurred during the worst 'Hunger Winter' period (November 1941 to February 1942), when the average daily ration was around 300 calories, comprised almost entirely from carbohydrate. Although the situation improved when Lake Ladoga froze sufficiently to allow supplies to be transported across, it was April/May 1942 before food supplies increased substantially. Studies document a 75% reduction in the birth rate and a drop in male and female birth weights of 18% and 16% respectively during the Hunger Winter (Antonov, 1947).

The Leningrad Siege Study investigated 3 groups of subjects (Figure 1). The first consisted of 169 subjects (37 males, 132 females) who were *in utero* during the Hunger Winter period of the siege and were born in the City between 1st November 1941 and 30th June 1942. The second comprised a group of 192 subjects (62 males, 130 females) born in Leningrad between 1st January 1941 and 30th June 1941, so being at least 10 weeks old at the start of the siege and exposed to the siege during early infancy.

*Address for correspondence: Sara Stanner, British Nutrition Foundation, High Holborn House, 52–54 High Holborn, London WC1V 6RQ, United Kingdom. Email: s.stanner@nutrition.org.uk*



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Since historical records document the plentiful supply of food in the City until rationing was imposed on 18th July 1941 in preparation for the impending siege, the mothers of this group would be expected to have been adequately nourished during pregnancy. Both groups were identified from the register of the Society of Children of the Siege, which maintains an up-to-date and complete record of people living in, or born in, Leningrad during the siege. Nearly 70% of the subjects in both groups remained in the city until the end of the siege, with most evacuations occurring after July 1942. Therefore, subjects exposed to starvation *in utero* were additionally exposed to the siege in infancy.

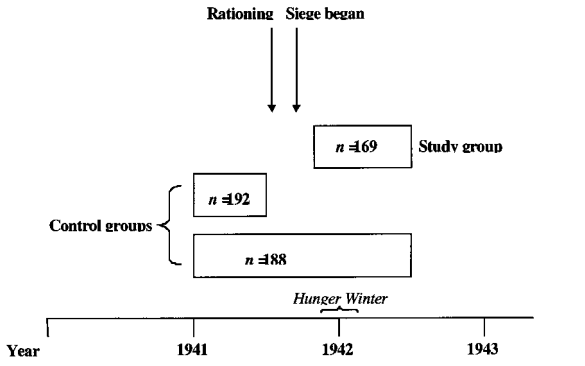


**Figure 1**
Study design.

The final group consisted of 188 adults (50 males, 138 females) who were born in the province of Leningrad but outside the city (and, therefore, the siege limits) during the same period as the other two groups (1st January 1941 to 30th June 1942). Subjects in this group were identified from two sources — a radial kerotomy clinic of a local hospital, where patients had been referred for surgery for refractice eye problems ($n$ = 102) and six local workplaces ($n$ = 86). This group provided subjects who were unexposed to starvation during the siege. However, initial comparisons of the distribution of variables was carried out between the *utero* and infancy exposed subjects, since the source of subjects for both groups was a register of Children of the Siege, while the control group was identified from separate sources. For the purpose of the analysis, subjects with diagnosed diabetes were excluded from all 3 groups.

## Results

A comparison of the subjects exposed to the siege *in utero* with those exposed in infancy showed no difference in height, degree or centrality of obesity (Table 1) or in concentrations of fasting or two hour plasma glucose (Table 2). There was no excess of known diabetes or glucose intolerance (Figure 2) in either of these study groups. The prevalence of coronary heart

**Table 1**
Anthropometric Variables

| | Exposed groups | | | |
|---|---|---|---|---|
| | Intrauterine ($n$ = 169) | Infant ($n$ = 192) | Significance ($p$ value)+ | Unexposed group ($n$ = 188) |
| Age (years) | 52.3 | 53.1 | | 52.8*** |
| Height (m) | | | | |
| Male | 1.72 (1.70-1.74) | 1.74 (1.72-1.76) | 0.43 | 1.73 (1.71-1.75) |
| Female | 1.58 (1.56-1.60) | 1.59 (1.57-1.61) | 0.50 | 1.60 (1.56-1.64) |
| Body mass index (kg/m$^2$) | | | | |
| Male | 24.6 (23.6-25.6) | 25.4 (24.2-26.6) | 0.39 | 25.2 (24.1-26.3) |
| Female | 26.9 (26.1-27.7) | 27.0 (26.2-27.8) | 0.89 | 26.7 (25.9-27.5) |
| Waist:hip ratio | | | | |
| Male | 0.86 (0.84-0.88) | 0.88 (0.84-0.92) | 0.66 | 0.87 (0.85-0.89) |
| Female | 0.79 (0.77-0.81) | 0.78 (0.76-0.80) | 0.49 | 0.79 (0.75-0.83) |
| Subscapular:triceps | | | | |
| Male | 1.26 (1.11-1.41) | 1.32 (1.20-1.44) | 0.50 | 1.41 (1.31-1.51) |
| Female | 1.01 (0.93-1.09) | 0.93 (0.87-0.99) | 0.17 | 0.88 (0.82-0.94)* |
| Ischaemia (%): | | | | |
| Confirmed | | | | |
| Male, Female | M: 2.7, F: 1.5 | M: 3.2, F: 2.3 | M: 0.88, F: 0.64 | M: 0, F: 2.2 |
| Definite or possible | | | | |
| Male, Female | M: 18.9, F: 20.0 | M: 16.1, F: 12.3 | M: 0.72, F: 0.10 | M: 14.3, F: 16.7** |
| Angina (on questionnaire) | | | | |
| Male, Female | M: 13.9, F: 27.5 | M: 29.5, F: 40.6 | M: 0.08, F: 0.03 | M: 14.0, F: 21.9 |
| Any abnormalities (ECG or questionnaire combined) | | | | |
| Male, Female | M: 25.0, F: 35.1 | M: 37.7, F: 41.4 | M: 0.20, F: 0.30 | M: 22.0, F: 31.9 |

Values are means (95% confidence intervals)
+Analysis of variance for continuous variables and $\chi^2$ test for categoric variables comparing intrauterine and infancy exposed groups (*$p < 0.05$ **$p < 0.005$ ***$p < 0.001$)



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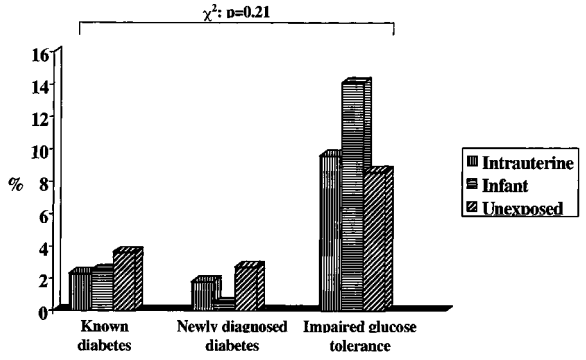
**Table 2**

Glucose Concentrations According to Siege

| Glucose levels (mmol/l) | Exposed groups: Intrauterine (*n* = 169) | Infant (*n* = 192) | Significance (*p* value)+ | Unexposed group (*n* = 188) |
|---|---|---|---|---|
| Fasting | 5.2 (5.1-5.3) | 5.3 (5.1-5.5) | 0.94 | 5.3 (5.1-5.5) |
| 30 minute | 8.0 (7.7-8.3) | 8.4 (8.1-8.7) | 0.29 | 7.9 (7.8-8.0) |
| 120 minute | 6.1 (5.8-6.4) | 6.0 (5.7-6.3) | 0.99 | 5.7 (5.4-6.0) |

Values are means (95% confidence intervals)

+Analysis of variance between intrauterine and infancy exposed groups




Subjects with diagnosed diabetes at initial screening were excluded from further study.

**Figure 2**

Glucose concentrations according to exposure to siege.

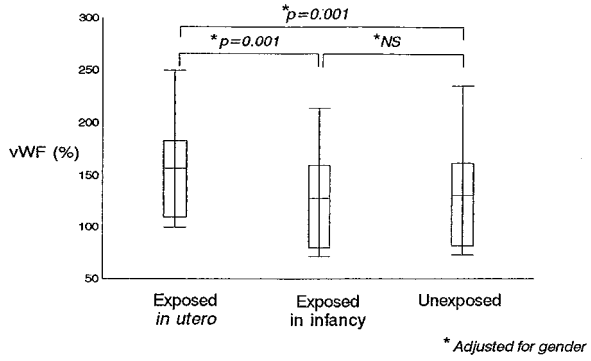



**Figure 3**

Effect of siege exposure on von Willebrand factor concentrations.

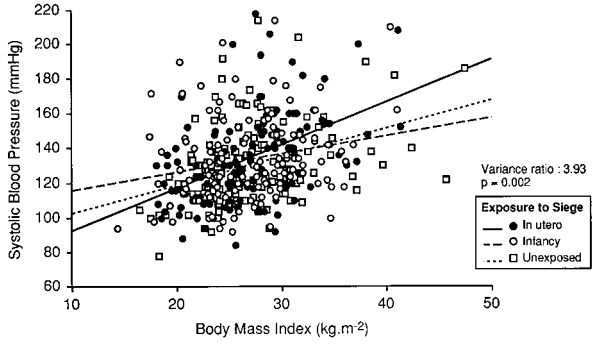



**Figure 4**

Interaction between siege exposure, obesity and blood pressure.

disease defined according to ECG abnormalities and/or angina, assessed by questionnaire (Rose & Blackburn, 1968), was similar (Table 1). Levels of fasting and 2 hour plasma insulin, proinsulin and des 31,32 proinsulin molecules, lipid concentrations and daytime albumin excretion rate did not differ, but the *in utero* exposed group had a significantly lower overnight albumin excretion rate. There was also no difference in the concentrations of several haemostatic and fibrinolytic variables (fibrinogen, factor VII, plasminogen activator inhibitor activity and antigen). However, subjects in the intrauterine group had a significantly higher concentration of circulating von Willebrand factor, a marker of endothelial dysfunction. This remained significant after further adjustment for obesity, smoking, and current coronary heart disease (Figure 3).

No difference in systolic or diastolic blood pressure or in the proportion of hypertensive subjects was found between the *in utero* and infancy exposed groups (Table 3). Since adult blood pressure has been shown to be more markedly affected by obesity in individuals with intrauterine growth retardation than those without growth retardation (Leon et al., 1996) the interactions with adult BMI were explored. In all subjects combined there was a positive association between blood pressure and adult obesity, but this relationship was significantly stronger in subjects who had been exposed to intrauterine starvation (Figure 4). This suggests that siege exposure and adult obesity act synergistically to increase susceptibility to hypertension.

Subjects in the unexposed group had significantly higher concentrations of factor VII and lower diastolic blood pressure and concentrations of plasminogen activator inhibitor antigen and activity than either of the exposed groups. Female subjects in this group had a lower subscapular to triceps ratio but all other variables were found to be similar.

In summary, the study found no evidence for a link between maternal malnutrition and glucose intolerance, dyslipidaemia, hypertension or cardiovascular disease in adulthood. However, endothelial dysfunction and a stronger relationship between obesity and blood pressure were more common in the subjects who were exposed to the siege *in utero*.



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**Table 3**

Effect of Siege Exposure on Blood Pressure

| Blood pressure | Exposed groups: Intrauterine ($n$ = 169) | Infant ($n$ = 192) | Significance ($p$ value)+ (adjusted for gender) | Unexposed group ($n$ = 188) |
|---|---|---|---|---|
| Systolic | 131.6 (127.9-135.3) | 133.1 (129.9-136.3) | 0.73 | 128.5 (125.3-131.7) |
| Diastolic | 80.9 (78.7-83.1) | 82.2 (80.0-84.3) | 0.67 | 77.3 (75.4-79.2)* |
| No. subjects taking antihypertensives | 23.0 (13.6%) | 19.0 (9.9%) | | 24.0 (12.8%) |

Subjects on antihypertensive treatment excluded from blood pressure comparisons

Values are means (95% confidence intervals)

+Analysis of variance between intrauterine and infancy exposed groups

*$P < 0.05$

## Discussion

### Contrasting Results With the Dutch Hunger Winter Study

Other traumas during times of war have, fortuitously, permitted other similar studies. In 1944–5 pre-natal exposure to the Dutch famine caused by a blockade in the Netherlands during the first half of pregnancy was associated with significantly higher obesity rates in 19-year-old men (Ravelli et al., 1976) and adult women (Ravelli et al., 1999). Adult men and women exposed to the blockade in early gestation were also found to have a more atherogenic lipid profile, including a significantly higher LDL to HDL cholesterol ratio, than those who were not exposed to the famine *in utero* (Roseboom et al., 2000a). The prevalence of coronary heart disease at age 50 was significantly greater in people exposed in early gestation than in those who were not exposed prenatally (8.8% vs 3.2%, OR 3.0, 95% CI 1.1 to 8.1) (Roseboom et al., 2000b). However, no affect was found on adult blood pressure (Roseboom, 1999) and in contrast to the Leningrad Siege Study, no interaction between blood pressure, obesity and intrauterine famine exposure was demonstrated (personal correspondence). Roseboom et al. (1999) have postulated that the lack of a relationship between famine exposure and adult blood pressure in the Dutch subjects suggests that poor maternal nutrition during pregnancy may be linked with higher blood pressure only when there are prolonged periods of undernutrition or deviations in the balance of micronutrients in the maternal diet. Whilst food rations in Russia consisted almost entirely of bread, so that calories were, therefore, derived predominantly from carbohydrate, calorie intake from protein, fat and carbohydrate was proportionally reduced in Holland. This hypothesis is supported by the study of Campbell et al. (1996) which found the balance between protein and carbohydrate in the maternal diet during late pregnancy to be associated with blood pressure in the offspring 40 years later. At either extreme of this balance, blood pressure was raised.

Subjects exposed to the Dutch famine during mid and late gestation had decreased glucose tolerance when compared with non-exposed subjects (Ravelli et al., 1998). Those exposed to maternal starvation during the last trimester of pregnancy showed a 2 hour plasma glucose concentration 0.5 mmol/l higher than that in unexposed subjects and significantly higher 2 hour insulin concentrations (Table 4). A further analysis of the Leningrad Siege Study data using similar definitions to classify trimester of exposure as those used by Ravelli and colleagues, namely the average food ration during the period in question being less than 1000 kcals, did not show any differences in concentrations of either fasting or 2 hour glucose (Table 5). Two hour insulin concentration again differed between the groups, but in this case were significantly lower in those exposed in later gestation than those born before the siege ($p$ = 0.05). Adjustment for gender or BMI had little effect on the results.

The contrasting findings of these two studies are unlikely to be a consequence of numbers of subjects. The Leningrad Siege Study had 91% of the power of the Dutch study. Although the former lacked data on maternal or birth weight, and, like the Dutch study, no record of maternal food availability, excluding subjects whose occupations might have allowed them access to additional food supplies

**Table 4**

Effect of Famine Exposure on Glucose and Insulin Concentrations in the Netherlands (14)

| | Exposure to famine: Born before famine ($n$ = 202) | Late gestation ($n$ = 110) | Mid gestation ($n$ = 100) | Early gestation ($n$ = 63) | Conceived after famine ($n$ = 63) | $p$ value |
|---|---|---|---|---|---|---|
| 120 min glucose (mmol/l) | 5.7 | 6.3 | 6.1 | 6.1 | 5.9 | 0.006 |
| 120 min insulin (pmol/l) | 160 | 200 | 190 | 207 | 181 | 0.04 |



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**Table 5**

Effect of Famine Exposure on Glucose and Insulin Concentrations in Leningrad

| | Exposure to famine | | | | |
|---|---|---|---|---|---|
| | Born before Siege ($n$ = 192) | Late gestation ($n$ = 64) | Mid gestation ($n$ = 75) | Early gestation ($n$ = 58)) | $p$ value |
| Fasting glucose (mmol/l) | 5.3 | 5.2 | 5.2 | 5.3 | 0.84 |
| Fasting insulin (pmol/l) | 35.0 | 35.4 | 34.7 | 34.3 | 0.98 |
| Fasting proinsulin (pmol/l) | 2.9 | 2.5 | 2.8 | 2.7 | 0.63 |
| Fasting des 31,32 proinsulin (pmol/l) | 1.2 | 1.0 | 1.6 | 1.2 | 0.18 |
| 120 min glucose (mmol/l) | 6.1 | 5.9 | 6.1 | 6.1 | 0.97 |
| 120 min insulin (pmol/l) | 149.8 | 117.5 | 167.5 | 128.3 | 0.05 |

did not affect the results. Moreover, while it is known that severe famine was responsible for a substantial increase in infertility and early pregnancy loss, allowing for some risk of selection bias for those surviving exposure in early pregnancy, it is less likely that such selection bias can explain the inability to find an effect of late gestation exposure.

One explanation for these discrepant findings might be that subjects in the Leningrad Siege Study were predominantly women. The effects of early growth retardation do appear to be stronger in men (Hales & Barker, 1992) than in women (Fall et al., 1995). An alternative explanation could be that it is not low energy or protein intake which influences fetal programming of insulin resistance, but a particular nutrient which was deficient in the Dutch diet but present in the Leningrad Siege rations, although this seems unlikely. A potentially important difference between the 2 studies was in the nutritional status of the women prior to pregnancy. Whilst the Dutch famine was preceded by adequate nutrition, people in Leningrad were likely to have been undernourished before the siege. A mother's ability to supply her fetus with nutrients in not only determined by what she eats during pregnancy but also by her own growth and physical development over the years and consequently maternal pre-pregnant body size is an important determinant of fetal growth (Stein et al., 1996).

### The Importance of Catch-up Growth

If there are indeed differences in the effects of exposure to the two famines, they might contribute to our understanding of the mechanisms of the 'thrifty phenotype'. Conditions before and after the famine period differed considerably in Leningrad and the Netherlands. In the Netherlands the siege lasted only 5 months and adequate nutrition was restored within 3 weeks of the end of the siege. By contrast, in Leningrad the siege lasted 28 months. The food ration for dependents fell below 1000 kcals with the imposition of rationing on July 18th 1941 and remained below this level for the duration of 1942. Those exposed in early or mid gestation were, therefore, exposed to at least 6 months postnatal malnutrition. It has been suggested that intrauterine starvation, or growth retardation, may be of greater impact when followed by a high nutrient intake at a later stage (Yajnik, 2000), a situation which occurred in the Netherlands but not in Leningrad. The effect of exposure to postnatal and intrauterine malnutrition appears to conflict, at least in terms of longevity. Hales and colleagues have demonstrated that 'catch-up' growth during the postnatal period of the offspring of animals exposed to a protein deficient diet in pregnancy, is associated with increased blood pressure and shortening of the life span (Hales, 1997).

Several studies have supported the possible interaction between early and postnatal growth. A large cohort study of Finnish men found that those with the highest rates of cardiovascular disease had low birth weight and were thin at birth, but were heavier at age 7 (Eriksson et al., 1999). Whincup et al. (1997) studied over 1000 children, with a mean age of 10 and demonstrated glucose tolerance and insulin resistance to be more strongly related to childhood growth than to size at birth. This study also showed an interaction between retarded fetal growth and accelerated weight gain during childhood, as the most insulin resistant children were those born small but who 'caught up'. Amongst South African children the combination of low birth weight and obesity at age 7 was strongly linked with glucose and insulin concentrations (Crowther et al., 1998). Growth velocity for weight was also a strong predictor of insulin resistance at age 7. Further support for the importance of catch-up growth comes from studies in Indian babies. In 4-year-old children in Pune plasma glucose and insulin concentrations were positively associated with weight and body fat measures and, following adjustment for current size, inversely related to size at birth (Yajnik et al., 1995). The children who were born small but were fatter during infancy had the highest plasma glucose and insulin concentrations 30 minutes after a glucose load. Similar observations were confirmed when the children were studied at the age of 8 (Bavdekar et al., 1999). The conclusion from these studies was that catch-up growth during childhood appears to increase the risk of insulin resistance more than poor intrauterine growth or childhood obesity alone (Yajnik, 2000).

## Conclusions

In conclusion, the Leningrad Siege Study did not find any evidence of a relationship between maternal malnutrition during pregnancy and glucose intolerance, dyslipidaemia, hypertension, or cardiovascular disease in adulthood. These findings contrast with those observed in subjects



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exposed to intrauterine malnutrition during the Dutch famine. Differences between the nutritional circumstances experienced in the Netherlands and Leningrad suggest that the long-term effects of acute and chronic malnutrition may differ significantly and that intrauterine malnutrition may be of greater impact when postnatal nutrition is sufficient.

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