Papers

Long term mortality after severe starvation during the siege of Leningrad: prospective cohort study

Pär Sparén, Denny Vågerö, Dmitri B Shestov, Svetlana Plavinskaja, Nina Parfenova, Valeri Hoptiar, Dominique Paturot, Maria Rosaria Galanti

Abstract

Objective To determine whether starvation during periods of increased growth after birth has long term health consequences.

Design Analysis of cardiovascular risk factors and mortality in a longitudinal follow up after the 1941-4 siege of Leningrad. Mortality measured from 1975 to the end of 1999.

Setting St Petersburg, Russia (formerly Leningrad).

Participants 5000 men born 1916-35 who lived in Leningrad, randomly selected to take part in health examinations in 1975-7. Of the 3905 men who participated, a third had experienced the siege.

Main outcome measures Relative risk of ischaemic heart disease and mortality from stroke by siege exposure. Odds ratios and means for several cardiovascular risk factors.

Results Three to six decades after the siege, in men who experienced the siege around the age of puberty blood pressure was raised (mean difference in systolic 3.3 mm Hg, in diastolic 1.3 mm Hg) as was mortality from ischaemic heart disease (relative risk 1.39, 95% confidence interval 1.07 to 1.79) and stroke (1.67, 1.15 to 2.43), including haemorrhagic stroke (1.71, 0.90 to 3.22). The effect on mortality was partly mediated via blood pressure but not by any other measured biological, behavioural, or social factor.

Conclusions Starvation, or accompanying chronic stress, particularly at the onset of or during puberty, may increase vulnerability to later cardiovascular disease.

Introduction

Famine and food shortage have both short and long term consequences for health. Results of studies on the effect of starvation are, however, inconsistent.[1–7] The focus on fetal malnutrition may have been too narrow. We studied the long term health consequences of involuntary starvation in a population of men who were aged 6-28 years at the peak of the period of severe food shortage. During the second world war German troops prevented supplies from reaching Leningrad from 8 September 1941 to 27 January 1944. Of a population of 2.9 million (including 0.5 million children), 630 000 died from hunger-related causes,[8] most during the winter of 1941-2. We investigated whether experience of the siege did in fact lead to an increased risk of mortality, particularly from cardiovascular disease.

Methods

Study base and data collection

As part of the 1973 US-Soviet collaborative programme, data were collected for the lipid research clinics programme.[9] A baseline survey was undertaken in Leningrad 1975-7, in which 5000 men born in 1916-35 were randomly selected from voting lists in the socially mixed Petrogradsky district; 3905 men (78%) participated. Data were collected on socioeconomic factors (education, occupation, and marital status), behaviour (smoking and alcohol consumption), anthropometric measures (weight, height, and skinfold thickness), and other biological measurements (blood pressure, cholesterol concentration, and a Rose questionnaire interview about cardiovascular dysfunction). Nearly a third (n = 1406) had lived in Leningrad during the siege, which normally meant that they spent the whole siege period there as most people were unable to leave.

We followed mortality from the time of the interview to 31 December 1999.

Food shortage

From 20 November 1941 bread rations in Leningrad were at their lowest: 250 g daily for manual workers and 125 g for other civilians. Children below the age of 12 belonged to the latter category, but children over 12 years received even less—for example, only 200 g of fat, 800 g of sugar, and 600 g of carbohydrate a month. If rations were received in full, which was not always the case, this amounted to about 460 calories a day.[8] The average daily ration was around 300 calories, containing virtually no protein.[3] This is extremely low, even compared with rations during the Dutch hunger winter.[10]

Statistical analyses

We used Poisson regression to calculate relative risks. Residence in Leningrad during the siege (yes/no) and age at siege (≤ 8, 9-15, 16-26 years *v* not in siege) were

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Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
Pär Sparén *senior researcher*
Centre for Health Equity Studies, CHESS, Stockholm University/Karolinska Institute, Stockholm, Sweden
Denny Vågerö *professor*
Institute of Experimental Medicine, Russian Academy of Medical Sciences, St Petersburg, Russia
Dmitri B Shestov *professor emeritus*
Svetlana Plavinskaja *senior researcher*
Nina Parfenova *researcher*
Valeri Hoptiar *programmer*
Södertörns högskola, University College, Huddinge, Sweden
Dominique Paturot *research assistant*
Unit of Clinical Epidemiology, Department of Medicine, Karolinska Hospital, Stockholm, Sweden
Maria Rosaria Galanti *senior researcher*
Correspondence to: P Sparén Par.Sparen@meb.ki.se

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introduced into successive regression models with other explanatory factors. We always controlled for birth year and attained age. We examined whether there was any difference in risk of mortality between those living in Leningrad during the siege and those who were not; whether any effect was modified by age at exposure; and whether any effect was of similar magnitude during the whole follow up period.

To assess socioeconomic confounding we adjusted risk estimates for marital status, education, and occupational class at baseline (interview). We also adjusted for smoking and alcohol consumption.

Intermediate outcomes—namely, adult body mass index, adult height, skinfold thickness measured at the arm, diastolic and systolic blood pressure, and the ratio of low to high density lipoprotein cholesterol—were considered as potential mediators between starvation and later cardiovascular disease. We used biological risk indicators as dichotomised outcome variables in logistic regression models[11] to estimate odds ratios by siege experience. They were also treated as continuous outcome variables in linear regression models to estimate mean differences.

Results

We analysed intermediate outcomes, measured before the start of the mortality follow up. There was a significant excess risk of high systolic and diastolic blood pressure in men who lived through the siege. Those who were around the age of puberty (9-15 years) at the peak of starvation (January 1942) were especially prone to high systolic blood pressure (odds ratio 1.56, 95% confidence interval 1.21 to 2.02) with a mean excess of 3.3 mm Hg (Wald test P = 0.03). Except for a tendency to have a greater skinfold thickness, all other indicators of cardiovascular risk were remarkably similar for exposed and non-exposed.

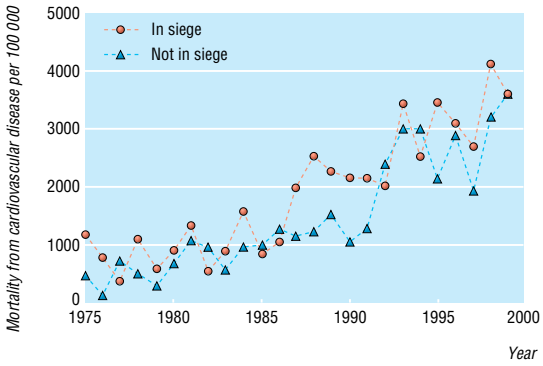
During follow up 2048 of the 3905 men died. Cardiovascular disease accounted for 1050 deaths (51%), 662 from ischaemic heart disease and 333 from stroke, 97 of which were haemorrhagic. The excess risk of dying (all causes) for those who experienced the siege was 21% (relative risk 1.21, 1.10 to 1.32). The excess risk of dying from ischaemic heart disease was 28% (1.28, 1.08 to 1.51) (table). Among those aged 9-15 at the peak of starvation this estimate was 1.39 (1.07 to 1.79). The effects of starvation around puberty were stronger still for stroke (1.67, 1.15 to 2.43), including haemorrhagic stroke (1.71, 0.90 to 3.22). For stroke, but not for other mortality, the siege effect was significantly stronger for those who experienced it around puberty than at other ages (Wald test P = 0.02).

Adjustment for occupation, education, marital status, smoking, or alcohol consumption had no impact on risk estimates, although all these variables were themselves strongly correlated with mortality. Among those aged 9-15 years adjustment for systolic and diastolic blood pressure changed risk estimates

Systolic and diastolic blood pressure measured at recruitment of cohort in 1975-7, and cardiovascular mortality 1975-99 for restricted sample* by age at siege exposure.

		Age at siege (years)				Tests for heterogeneity	
	Any age	≤ 8	9-15	16-26	Not in siege (reference)	Likelihood Ratio† P value	Wald‡ P value
Blood pressure§							
Systolic BP ≥160 mm Hg	1.30 (1.10 to 1.54)	0.64 (0.33 to 1.25)	1.56 (1.21 to 2.02)	1.22 (0.97 to 1.53)	1.00	0.0006	0.03
Difference in systolic BP (mm Hg)	1.88 (0.44 to 3.32)	−2.02 (−5.75 to 1.71)	3.26 (1.27 to 5.26)	1.32 (−0.95 to 3.59)	0.00	0.003	0.03
Diastolic BP ≥95 mm Hg	1.18 (1.03 to 1.35)	0.92 (0.63 to 1.35)	1.20 (0.99 to 1.45)	1.23 (0.99 to 1.52)	1.00	0.07	0.71
Difference in diastolic BP (mm Hg)	0.87 (0.07 to 1.67)	−1.35 (−3.41 to 1.32)	1.33 (0.23 to 2.44)	0.95 (−0.31 to 2.20)	0.00	0.02	0.14
Cause of death¶							
Ischaemic heart disease:							
Model 1	1.28 (1.08 to 1.51)	1.35 (0.76 to 2.38)	1.39 (1.07 to 1.79)	1.19 (0.95 to 1.50)	1.00	0.03	0.43
Model 2	1.24 (1.05 to 1.47)	1.33 (0.75 to 2.35)	1.37 (1.06 to 1.77)	1.14 (0.91 to 1.44)	1.00	0.06	0.35
Model 3	1.23 (1.04 to 1.46)	1.38 (0.78 to 2.44)	1.29 (1.00 to 1.68)	1.17 (0.93 to 1.47)	1.00	0.11	0.68
Model 4	1.22 (1.03 to 1.44)	1.44 (0.81 to 2.55)	1.25 (0.97 to 1.61)	1.17 (0.93 to 1.47)	1.00	0.14	0.87
Model 5	1.19 (1.00 to 1.41)	1.38 (0.78 to 2.44)	1.25 (0.97 to 1.62)	1.13 (0.89 to 1.42)	1.00	0.21	0.69
Stroke:							
Model 1	1.19 (0.93 to 1.51)	0.55 (0.13 to 2.31)	1.67 (1.15 to 2.43)	0.99 (0.72 to 1.35)	1.00	0.03	0.02
Model 2	1.15 (0.90 to 1.46)	0.54 (0.13 to 2.27)	1.65 (1.13 to 2.40)	0.94 (0.69 to 1.30)	1.00	0.04	0.01
Model 3	1.13 (0.88 to 1.43)	0.58 (0.14 to 2.43)	1.49 (1.02 to 2.17)	0.96 (0.70 to 1.33)	1.00	0.15	0.05
Model 4	1.11 (0.87 to 1.81)	0.57 (0.14 to 2.40)	1.44 (0.99 to 2.10)	0.96 (0.70 to 1.32)	1.00	0.20	0.06
Model 5	1.09 (0.85 to 1.39)	0.55 (0.13 to 2.30)	1.48 (1.02 to 2.16)	0.92 (0.67 to 1.27)	1.00	0.13	0.03
Haemorrhagic stroke:							
Model 1	1.28 (0.82 to 1.98)	0.94 (0.12 to 7.48)	1.71 (0.90 to 3.22)	1.01 (0.55 to 1.87)	1.00	0.44	0.22
Model 2	1.27 (0.82 to 1.97)	0.99 (0.12 to 7.94)	1.69 (0.90 to 3.20)	1.01 (0.55 to 1.87)	1.00	0.46	0.23
Model 3	1.18 (0.75 to 1.82)	0.99 (0.12 to 7.83)	1.51 (0.80 to 2.86)	0.96 (0.52 to 1.77)	1.00	0.66	0.30
Model 4	1.14 (0.73 to 1.77)	0.94 (0.12 to 7.42)	1.43 (0.75 to 3.42)	0.94 (0.51 to 1.75)	1.00	0.74	0.34
Model 5	1.14 (0.73 to 1.79)	0.95 (0.12 to 7.56)	1.44 (0.76 to 2.76)	0.95 (0.51 to 1.76)	1.00	0.73	0.33

*Excludes 672 men for whom information on socioeconomic and behavioural variables was missing.
†Likelihood ratio test that outcome was equally likely in each category (≤ 8, 9-15, 16-26, not in siege). Under the null hypothesis the test statistic has χ^2 distribution with 3 df.
‡Wald test that siege effect was same for those aged 9-15 at siege as for those aged ≤ 8 or 16-26. Under the null hypothesis the test statistic has χ^2 distribution with 1 df.
§Probability measures are odds ratios for dichotomous outcomes (estimated with logistic regression models) and mean differences for continuous outcomes (estimated with linear regression models), both with 95% confidence intervals. All estimates adjusted for birth cohort.
¶Relative risks and 95%% confidence intervals as estimated with Poisson regression models; model 1: birth cohort and attained age; model 2: model 1 + occupation, education, marital status, smoking, and alcohol intake; model 3: model 1 + systolic and diastolic blood pressure; model 4: model 1 + all biological risk indicators; model 5: model 1 + all factors from other models.



Cardiovascular mortality over time by exposure to Leningrad siege (mortality estimated from Poisson regression model)

downwards from 1.39 to 1.29 for ischaemic heart disease, from 1.67 to 1.49 for stroke, and from 1.71 to 1.51 for haemorrhagic stroke. Addition of other intermediate outcomes rendered small changes.

Throughout the follow up period there was a pattern of higher cardiovascular mortality for those who experienced the siege (figure). This was particularly pronounced in 1987-91, when those who did not experience the siege seemed to have a reduced risk. The period specific relative risk was 1.79, based on the main effect and a highly significant interaction (P = 0.004) effect (1.55, 1.16 to 2.08).

Discussion

Men who experienced the Leningrad siege have higher systolic and diastolic blood pressure and excess mortality from ischaemic heart disease and stroke. Blood pressure mediated part of the siege effect on mortality, while other biological risk markers (such as body mass index and cholesterol concentrations) did so to a lesser extent. Lifestyle and socioeconomic circumstances did not confound the association between cardiovascular mortality and siege exposure.

Starvation around puberty (ages 9-15) was more strongly associated with high systolic blood pressure and stroke in adult life than was starvation at other ages. This casts new light on the effect of severe malnutrition in early life. We used the age limit of 9 years on the basis of work by Marshall and Tanner, who considered "the fat spurt" to be the earliest manifestation, or trigger, of puberty that is visible before age 10.[12]

Literature on anorexia nervosa details several cardiovascular abnormalities in patients, including reduction of ventricular mass, valvular dysfunctions,[13] and electrocardiographic abnormalities.[14] Damage of the myocardial fibres has been documented in obese patients on very low calorie diets.[15] Furthermore, endocrine changes accompany self starvation around puberty.[16] At least two of these changes—increased circulating concentrations of growth hormone and cortisol—profoundly influence regulation of blood pressure. Increased secretion of growth hormone is linked with hypertension.[17 18] Critical stages in the process of regulating blood pressure may therefore occur during puberty,[19 20] and starvation may cause a permanent disruption of blood pressure regulation.

An early study of the siege concluded that the immediate effect of starvation was a lowering of blood pressure. However, overcompensation occurred on refeeding. In people who have to do hard physical work blood pressure may rise as a consequence of refeeding after starvation.[21 22] Limited food supplies reached Leningrad from the spring of 1942 across Lake Ladoga. Keys et al refers to the subsequent "refeeding after starvation" in 1943.[23] A sample of 10 000 healthy people in Leningrad examined in April 1943 showed that the distribution of blood pressure had shifted radically upwards compared with that in 1940. The prevalence of hypertension had increased fourfold among those under age 39 and twofold among those aged ≥ 40 years. This "Leningrad blockade hypertension epidemic" remains visible in our data over three decades after the blockade.

Possible biases

We considered several methodological problems to rule out any potential bias.

Selection—The death toll during the 1941-4 siege was extreme. Death rates of survivors in 1944-75 may also have been increased. Siege survivors examined in 1975-7 constituted a group of individuals selected for better genetic, constitutional, and social resources for health than other study participants. This selection should bias our estimates of the mortality effects of starvation downwards.

Narrow exposure contrast—Food shortage was common all over Russia during the war, especially in areas occupied by the Germans. Livestock and harvests were appropriated for German needs, and not distributing food to the Russian population was part of the German war strategy.[24] Therefore we are comparing boys and men exposed to protracted starvation with those who experienced less severe food shortage, including episodes of starvation, which results in conservative risk estimates.

Residual confounding—We assessed potential confounding factors at only one point in time (1975-7). Although all of them were strongly associated with mortality, they had little confounding effect. Residual confounding is therefore likely to be small.

Differential ascertainment of death—The researchers who traced the movements of cohort members and collected death certificates did not know the siege status of participants. After the last date of contact we excluded from the study individuals who moved from Leningrad. A bias could occur if this follow up was imperfect and if men who had not experienced the siege were more likely to leave Leningrad for some reason. We found no such evidence.

Conclusions

On balance, our estimates of risks caused by siege exposure are probably conservative, perhaps very much so. It is difficult to suggest pathways, other than raised blood pressure, by which starvation causes cardiovascular mortality. Other potential mediating factors (for example, endocrine changes[25 26]) were not measured at all, and thus remain hypothetical. The nutritional component of starvation is also entangled with the trauma of the siege.

Work predating the fetal origins hypothesis had a broader focus, which included childhood exposures. Our study indicates that puberty may also be a highly vulnerable period. Starvation in puberty today may have implications for future cardiovascular disease in

What is already known on this topic

Impaired growth in utero is linked to raised blood pressure and increased risk of ischaemic heart disease and stroke

Results of previous studies on the effect of severe starvation in utero, infancy, or childhood on cardiovascular outcomes are inconsistent, and few studies have assessed the long term effects of starvation at later ages

Anorexia in young people is thought to affect cardiovascular health

What this study adds

Starvation during the Leningrad siege, with its accompanying stress and trauma, resulted in raised systolic and diastolic blood pressure, which was evident even three decades after the event

In a further follow up to 25 years, men who had experienced the siege had increased mortality from ischaemic heart disease and stroke

Puberty may be a highly vulnerable period for the development of later cardiovascular disease

many developing countries. War is still a leading cause of starvation and this may have consequences for circulatory disease decades later.

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1 Leon DA, Lithell HO, Vågerö D, Koupilova I, Mohsen R, Berglund L, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915- 29. *BMJ* 1998;317:241-5.
2 Hyppönen E, Leon DA, Kenward MG, Lithell H. Prenatal growth and risk of occlusive and haemorrhagic stroke in Swedish men and women born 1915-29: historical cohort study. *BMJ* 2001;323:1033-4.
3 Stanner SA, Bulmer K, Andres C, Lantseva OE, Borodina V, Poteen VV, et al. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. *BMJ* 1997;315:1342-8.
4 Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Bleker OP. Plasma lipid profiles in adults after prenatal exposure to the Dutch famine. *Am J Clin Nutr* 2000;72:1101-6.
5 Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Schroeder-Tanka JM, et al. Coronary heart disease after prenatal exposure to the Dutch famine, 1944-45. *Heart* 2000;84:595-8.
6 Bygren LO, Edvinsson S, Brostrom G. Change in food availability during pregnancy: Is it related to adult sudden death from cerebro- and cardiovascular disease in offspring? *Am J Human Biol* 2000;12:447-53.
7 Kannisto V, Christensen K, Vaupel JW. No increased mortality in later life for cohorts born during famine. *Am J Epidemiol* 1997;145:987-94.
8 Pavlov D. *Leningrad 1941: the blockade.* Chicago: University of Chicago Press, 1965.
9 Abernathy JR, Thorn MD, Ekelund LG, Holme I, Stinnett SS, Shestov DB, et al. Correlates of systolic and diastolic blood pressure in men 40 to 59 years of age sampled from United States of America and Union of Soviet Socialist Republics Lipid Research Clinics populations. *Am J Cardiol* 1988;61:1071-5.
10 Stein Z, Susser M, Saengler G, Marolla F. *Famine and human development. The Dutch hunger winter of 1944-1945.* London: Oxford University Press, 1975.
11 Agresti A. *Categorical data analysis.* New York: John Wiley, 1990.
12 Marshall W, Tanner J. Puberty. In: Falkner F, Tanner JM, editors. *Human Growth. A comprehensive treatise. Part 2. Postnatal growth neurobiology.* New York: Plenum Press, 1986:171-209.
13 De Simone G, Scalfi L, Galderisi M, Celentano A, Di Biase G, Tammaro P, et al. Cardiac abnormalities in young women with anorexia nervosa. *Br Heart J* 1994;71:287-92.
14 Swenne I. Heart risk associated with weight loss in anorexia nervosa and eating disorders: electrocardiographic changes during the early phase of refeeding. *Acta Paediatr* 2000;89:447-52.
15 Garnett ES, Barnard DL, Ford J, Goodbody RA, Woodehouse MA. Gross fragmentation of cardiac myofibrils after therapeutic starvation for obesity. *Lancet* 1969;i:914-6.
16 Støving RK, Hangaard J, Hansen-Nord M, Hagen C. A review of endocrine changes in anorexia nervosa. *J Psychiatr Res* 1999;33:139-52.
17 Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. *Pituitary* 1999;2:29-41.
18 Bohlooly YM, Carlson L, Olsson B, Gustafsson H, Andersson IJ, Tornell J, et al. Vascular function and blood pressure in GH transgenic mice. *Endocrinology* 2001;142:3317-23.
19 Nelson MJ, Ragland DR, Syme SL. Longitudinal prediction of adult blood pressure from juvenile blood pressure levels. *Am J Epidemiol* 1992;136:633-45.
20 Zicha J, Kunes J. Ontogenetic aspects of hypertension development: analysis in the rat. *Physiol Rev* 1999;79:1227-82.
21 Kreipe RE, Harris JP. Myocardial impairment resulting from eating disorders. *Pediatr Ann* 1992;21:760-8.
22 Brozek J, Chapman C, Keys A. Drastic food restriction: effect on cardiovascular dynamics in normotensive and hypertensive conditions. *J Am Med Assoc* 1948:1569-74.
23 Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. *The biology of human starvation.* Minneapolis: University of Minnesota Press, 1950.
24 Beevor A. *Stalingrad.* London: Viking, 1998.
25 Melamed S, Ugarten U, Shirom A, Kahana L, Lerman Y, Froom P. Chronic burnout, somatic arousal and elevated salivary cortisol levels. *J Psychosom Res* 1999;46:591-8.
26 Rosmond R, Bjorntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. *J Intern Med* 2000;247:188-97.

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One hundred years ago

Gardening for women

Gardening must be looked upon, by those interested in the national physique, as a healthy and invigorating occupation for women. The Ladies' Branch of the Practical Gardening School of the Royal Botanic Society is interesting, inasmuch as most of the pupils trained there are School Board scholars, who have obtained scholarships from the London School Board, and who intend to adopt gardening as a profession. The pupils are nominated by the Technical Education Board of the London County Council. Among its Fellows the Society numbers many members of the medical profession, and Lord Lister is a member of its Council. It is satisfactory to feel that the gardening branch is of such definite use in opening up a healthy invigorating and interesting employment for women. The advantage to girls who attend this particular training school is that the Botanical Gardens in Regent's Park are usually within easy reach of their houses, and they can attend classes without living away from home. The students, under the superintendence of Mrs. Sowerby, are allowed to work in a particular portion of the grounds and also learn practical hothouse work in the conservatories. The longest course is three years. The first-year students are taught ground operations, flower and vegetable gardening, and everything connected with the operations. During the second year the subjects taught are outdoor work, indoor work, and theoretical work. The third year is devoted to pruning, mowing, care of conservatory, plant houses, frames and pits, etc., and to theoretical work, such as keeping accounts, elementary meteorology, landscape gardening, sprays and washes for insect pests, and to classes and laboratory work in botany and horticultural chemistry. . . .

Students readily find situations, and it is interesting to note how many people now employ lady gardeners in preference to men. (*BMJ* 1904;i:94)