Long-Term Health Effects in Adults Born during the Holocaust

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ABSTRACT: **Background:** Previous studies suggest that exposure to starvation and stress between conception and early infancy may have deleterious effects on health later in life; this phenomenon is termed fetal origin of adult disease.

Objectives: To determine whether exposure to the Holocaust from preconception to early infancy is a cause of chronic morbidity in adulthood.

Methods: This pilot study involved 70 European Jews born in countries under Nazi rule (exposed group) during the period 1940–1945 who were interviewed to determine the presence of chronic diseases. A control group of 230 Israeli-born individuals of the same descent, age, and gender distribution were extracted from the Israel National Health Interview Survey-2 (unexposed group). The prevalence of selected risk factors and chronic diseases was compared between the groups.

Results: The prevalence of cardiovascular risk factors and morbidity was significantly higher in the exposed group: body mass index (BMI) (29.06 ± 3.2 vs. 26.97 ± 4.42, $P = 0.015$), hypertension (62.9% vs. 43%, $P = 0.003$), dyslipidemia (72.9% vs. 46.1%, $P < 0.001$), diabetes (32.9% vs. 17.4%, $P = 0.006$), angina pectoris (18.6% vs. 4.8%, $P = 0.001$) and congestive heart failure (8.6% vs. 1.7%, $P = 0.013$). The prevalence of cancer (30.0% vs. 8.7% $P < 0.001$), peptic ulcer disease (21.4% vs. 7%, $P = 0.001$), headaches/migraines (24.3% vs. 12.6%, $P < 0.001$) and anxiety/depression (50.0% vs. 8.3%, $P < 0.001$) was also higher in the exposed group.

Conclusions: These results suggest that exposure to Holocaust conditions in early life may be associated with a higher prevalence of obesity, dyslipidemia, diabetes, hypertension, cardiovascular morbidity, malignancy and peptic diseases in adulthood. These findings set the stage for further research, which might define those exposed as a high risk group for chronic morbidity.

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KEY WORDS: Holocaust, late morbidity, hunger, fetal origin of adult disease, Holocaust survivors

It is now well established that environmental stress and malnutrition during gestation or early infancy may result in morbidity later in life [1-4]. This direct link was found in many studies; of particular interest are those performed on populations that suffered from hunger during World War II. The most important of these studies relate to the "Dutch famine" [5,6] and the siege of Leningrad [7]. Possible mechanisms attributed to this link are the "fetal programming theory" [7-10], the "thrifty phenotype hypothesis" [11], and the "epigenetic explanation" [12-14].

Different illnesses have been linked to fetal programming, including increased prevalence of coronary heart disease, stroke, diabetes, metabolic syndrome and osteoporosis in later life [11,15,16]. Numerous studies have described the link between coronary heart disease and its risk factors, including hypertension and diabetes, and in utero detrimental exposures [2,17]. Fetal growth has been shown to influence bone metabolism [15,16,18]. Ample evidence has demonstrated a direct relationship between birth weight and body mass index attained in later life [19].

There is a wealth of data describing higher morbidity rates among Holocaust survivors and their offspring, the vast majority of them relating to mental and behavioral aspects [20]. A higher prevalence of somatic later-life morbidity has also been described. These studies exposed the link between surviving the Holocaust and malignancy [21,22], osteoporosis and osteopenia [23]. However, the handful of studies undertaken to reveal a correlation between exposures to the horrors of the Holocaust and somatic disease did not focus on the unique group of survivors who were born around the time of the Holocaust, whose gestation occurred during a period of mental stress and who suffered different levels of malnutrition – to the verge of starvation. The current study was undertaken to investigate whether early developmental exposure to Holocaust conditions has later-life health and disease implications.

PATIENTS AND METHODS

This cross-sectional study involved two population groups. The exposed group comprised Israeli subjects born in Europe

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during the period 1940 to 1945 with definitive self-reported exposure to the Holocaust. Additional criteria included independent home living. Excluded were subjects who were unable to participate in a personal interview without assistance. The exposed group consisted of a convenience sample recruited between 2009 and 2012 through various voluntary assistance organizations and from study subjects' referrals ("snowball" approach). Seventy subjects met the inclusion criteria and agreed to participate in the study.

The control group (unexposed) comprised 230 Jews of European ancestry born during the same period (1940–1945) in the pre-state of Israel. The group was extracted from a representative sample of the Israel National Health Interview Survey-2, conducted by the Israel Center for Disease Control of the Ministry of Health in 2007–2009, with 10,331 interviewees in total [24].

STUDY TOOLS

The study questionnaire followed the INHIS-2 survey questionnaire, which is based on the European Health Interview Survey (EUROHIS). The questionnaire was administered by means of a personal and a telephonic interview in the exposed and non-exposed groups, respectively. The questionnaire collected self-reported demographic data, health behaviors, and current health status. The self-report data regarding current morbidity were further validated by additional questions on professional diagnoses and treatment of the disease. The exposed group interviews also referred to exposure ascertainment through information regarding the mother's exposure and personal history during the Second World War.

Two grouped variables were created: dyslipidemia (which included hypercholesterolemia and/or increased triglycerides) and "any cardiovascular disease," which included at least one of the following: myocardial infarction, cerebrovascular accident, congestive heart failure, angina pectoris, and any cardiac condition (i.e., any cardiac morbidity including arrhythmias or valvular disease).

STATISTICAL ANALYSIS

Frequencies of categorical variables or means and standard deviation in the case of continuous variables such as age were computed separately for the study groups. The frequencies were cross-tabulated and differences between the exposed and the unexposed were statistically assessed using the chi-square test. Continuous variables were statistically assessed using independent *t*-tests. Multivariate binary logistic regression models of selected morbidities that were found to significantly differ by exposure status were also carried out. The regression models used selected morbidities as the dependent variable (dichotomous) and assessed the exposure status as an explanatory variable, controlling for gender and obesity (BMI ≥ 30) as potential confounders. All analyses were performed with SPSS 18.0.0 for Windows 7 64bit (SPSS Inc., Chicago, IL, USA). The Ethical Board Committee of the University of Haifa approved the study.

INHIS-2 = Israel National Health Interview Survey-2

RESULTS

STUDY POPULATION CHARACTERISTICS

The mean year of birth in the exposed and unexposed groups was 1942.1 ± 1.7 and 1942.9 ± 2.2, and the corresponding gender distribution 45.7% and 46.5% males ($P = 0.508$) respectively. No significant differences in education, marital status, or existence of offspring were found between the groups, but those in the exposed group were more likely to report a higher income ($P < 0.001$). The exposed were also more likely to report current or past smoking, 48.6% compared to 16.1% of the unexposed group ($P < 0.001$). Mean BMI was significantly different between the groups ($P = 0.039$). Further analysis demonstrated that the difference in BMI between the groups was present mainly in the male population, with a significantly increased BMI in the exposed group compared to the unexposed group: 29.06 ± 3.2 kg/m^2 vs. 26.97 ± 4.42 kg/m^2 respectively ($P = 0.015$).

CHRONIC MORBIDITY

Cardiovascular risk factors were significantly higher in the exposed group, namely hypertension (62.9% vs. 43%, $P = 0.003$), dyslipidemia (72.9% vs. 46.1%, $P < 0.001$) and diabetes (32.9% vs. 17.4%, $P = 0.006$) [Figure 1]. Cardiovascular morbidity was significantly more prevalent in the exposed group as well, including angina pectoris (18.6% vs. 4.8%, $P = 0.001$), congestive heart failure (8.6% vs. 1.7%, $P = 0.013$), or any cardiovascular disease (37.1% vs. 19.1%, $P = 0.002$), all of which may be regarded as proxies or consequences of ischemic heart disease [Figure 2]. Other morbidities that were found to

BMI = body mass index

Figure 1. Prevalence of cardiovascular risk factors

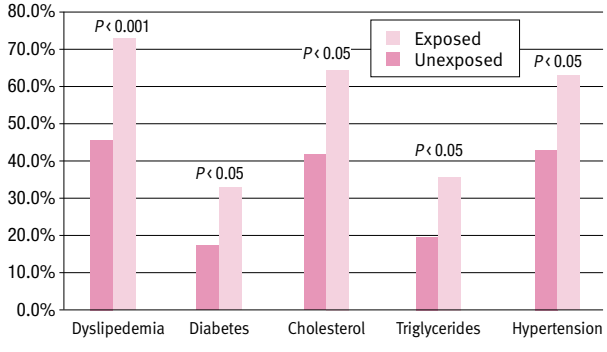
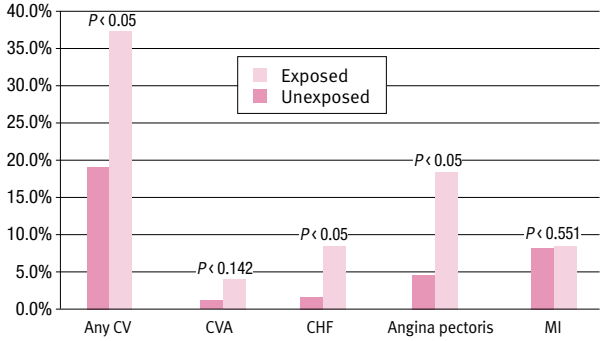


Figure 2. Prevalence of cardiovascular disease



CV = cardiovascular disease, CVA = cerebrovascular accident, CHF = congestive heart failure, MI = myocardial infarction

Table 1. Comparison of chronic morbidity

	Exposed		Unexposed		
	N	%	N	%	*P* value
Asthma	6	8.6	9	3.9	0.109
Hypertension	44	62.9	99	43.0	0.003
Triglycerides	25	35.7	45	19.6	0.005
Cholesterol	45	64.3	96	41.7	0.001
Myocardial infarction	6	8.6	19	8.3	0.551
Angina pectoris	13	18.6	11	4.8	0.001
Congestive heart failure	6	8.6	4	1.7	0.013
Other heart disease	16	22.9	13	5.7	< 0.001
Stroke	3	4.3	3	1.3	0.142
Lung disease	8	11.4	5	2.2	0.003
Osteoporosis	18	25.7	38	16.5	0.063
Peptic ulcer disease	15	21.4	16	7.0	0.001
Headache	17	24.3	29	12.6	0.017
Chronic pain	24	34.3	12	5.2	< 0.001
Anxiety or depression	35	50.0	19	8.3	< 0.001
Diabetes	23	32.9	40	17.4	0.006
Malignancy	21	30.0	20	8.7	< 0.001
Dyslipidemia	51	72.9	106	46.1	< 0.001
Any cardiovascular disease	26	37.1	44	19.1	0.002

be increased with statistical significance among the exposed compared to the unexposed were peptic ulcer disease (21.4% vs. 7.0%, $P = 0.001$) and frequent headaches or migraines (24.3% vs. 12.6%, $P < 0.001$). The proportion of participants reporting anxiety/depression was 50.0% vs. 8.3% ($P < 0.001$) in the exposed and non-exposed groups, respectively. The corresponding rates for malignancy were 30.0% and 8.7% ($P < 0.001$). Osteoporosis prevalence did not significantly differ between the study groups [Table 1]. However, following gender stratification, exposed females showed a statistically significant increased rate of osteoporosis compared to the unexposed group (39.5% vs. 17.9%, $P = 0.007$).

Lastly, we also applied several logistic regression models to study the independent effect of the exposure status on the prevalence of selected conditions (hypertension, dyslipidemia, diabetes, any cardiovascular disease, malignancy). In each of these models, the dependent variable in the regression was a selected chronic disease and the main independent variable was the exposure status. Obesity (BMI ≥ 30) and gender were added as potential confounders, while age, which did not differ between the groups, was not. It is clear from the results [Table 2] that the exposure status remained statistically significant following adjustment in all the above-mentioned morbidities examined in the regression, and that obesity also had an independent effect on hypertension, diabetes and dyslipidemia.

DISCUSSION

It is well accepted that Holocaust survivors of all ages suffered from severe starvation, extreme mental stress, exposure to infectious agents, and cold winter temperatures. The focus of this study was the unique group of survivors who were conceived, born, and partly raised during the Holocaust. Members of this group, who later immigrated to Israel, experienced a major environmental change during their life course. They shifted from a life of persecution and lack of resources to an environment with a relative abundance of food. This mismatch may have set the stage for late-life morbidities in those exposed to the Holocaust in their early life. This subgroup of survivors is similar in its exposure pattern to subjects of other famine studies from around the world [3,4,6,7]. Hence, the initial assumption of the current study is that since these individuals meet all the conditions of the thrifty phenotype hypothesis, they may suffer from late morbidity attributed to their early-life exposures. The results of the study support this assumption and show a statistically significant difference in late morbidity between the two investigated groups. Since the two study populations are well stratified and do not differ in gender distribution, age, descent and education, it is reasonable to assume that the differences found in morbidity may be attributed to the exposure variable. Nevertheless, several aspects of the study results and limitations warrant attention and are discussed below.

BMI: CAUSE OR EFFECT?

The comparison groups differed significantly in their BMI, which was higher in the exposed group. The higher BMI may be one of the causes for the increased morbidity in the exposed group, but it may also be an effect of the exposure as previously described [6,18,19]. In order to explore the independent effect of BMI on chronic morbidity, a regression analysis was carried out, using obesity (BMI > 30) as

Table 2. Logistic regression models for hypertension, diabetes, dyslipidemia, malignancy, and any cardiovascular disease

		Exposed (ref: unexposed)	Male (ref: female)	Obese (BMI > 30) (ref: BMI < 30)
Hypertension	OR (95%CI)	2.2 (1.2–3.8)	1.2 (0.7–1.8)	3.2 (1.7–6.1)
Diabetes	OR (95%CI)	2.2 (1.2–4.2)	0.9 (0.5–1.6)	2.9 (1.5–5.5)
Dyslipidemia	OR (95%CI)	3.1 (1.7–5.7)	1.0 (0.6–1.6)	1.9 (1.1–3.7)
Malignancy	OR (95%CI)	4.3 (2.1–8.7)	0.9 (0.4–1.8)	0.5 (0.2–1.5)
Any cardiovascular disease	OR (95%CI)	2.6 (1.4–4.7)	1.2 (0.7–2.1)	1.7 (0.9–3.3)

OR = odds ratio, CI = confidence interval

an independent categorical variable [Table 2]. The results indicated that both exposure status and obesity are statistically significant factors in the prevalence of hypertension, dyslipidemia and diabetes. These results strongly suggest that perinatal environmental exposures have a role in morbidity. The question whether obesity is an additional risk factor that exacerbates the effects of uterine environmental exposures, or an intervening factor, remains unanswered. Based on the current literature we believe that obesity may be both. Whether a cause, effect or both, increased BMI is one of the factors leading to the observed late morbidity.

CARDIOVASCULAR RISK FACTORS AND MORBIDITY

An unexpected result in the current study was that while the rates of hypertension, dyslipidemia, smoking, BMI and diabetes were significantly higher in the exposed group, rates of myocardial infarction and stroke were almost identical. Previous studies have described increased cardiovascular morbidity among those who had been exposed to detrimental environmental effects during the fetal period [2,17]; a similar result would have been expected in the current study as well. Lack of statistical study power may be the reason. Another possible explanation is that earlier mortality due to cardiovascular or other reasons may account for the discrepancy between the increased cardiovascular risk factors and lack of cardiovascular morbidity. Unfortunately, mortality data were beyond the scope of this pilot study, for obvious reasons. Yet, when examining the previously described variable of "any cardiovascular disease," which aggregates the prevalence of several cardiovascular conditions, a statistically significant difference between the groups does exist. This difference hints at an alternative explanation to the observed phenomenon and not to the non-existence of cardiovascular morbidity that might be mistakenly taken at face value.

OTHER MORBIDITIES

Since the study participants reported on a wide range of morbidities, several interesting observations were noted, including the finding that anxiety or depression, chronic headache, and chronic pain were all significantly higher in the exposed group and may be regarded as a marker for the effects of mental stress on late morbidity in this group of survivors. Previous studies suggest that the mental stress of exposure to the Holocaust affects both the survivors and their offspring, including those born after the Holocaust [20]. The results of the present study also show a statistically increased prevalence of anxiety or depression in the exposed group. This observation is important for further validating the existence of concurrent mental morbidity [1,20] and as a supplemental factor when examining later-life morbidity in Holocaust survivors.

Osteoporosis did not significantly differ between the groups; however, when stratified by gender, the prevalence of osteoporosis was significantly higher in women in the exposed group compared to the non-exposed ($P = 0.007$). This observation corresponds with previous work [15,16] which emphasized the importance of early detrimental exposure on the female's lifetime risk of developing osteoporosis. Prevalence of cancer was also found to be significantly increased in the exposed group. This study continues the line of previous research [21,22] demonstrating a link between surviving the Holocaust at an early age and increased rates of malignancy.

STUDY LIMITATIONS

This was a pilot study that for the first time addressed the subject of fetal programming and its consequences on Holocaust survivors. One of the advantages of this cross-sectional study is the fact that exposure was asserted, i.e., through the use of interviews, and not assumed based solely on demographic determinants such as year and place of birth. Nonetheless, this study has several limitations. The first is the snapshot nature of cross-sectional studies, which does not provide a good basis for establishing causality. However, the main independent variable – being born during the Holocaust – is in fact predetermined and undoubtedly preceded the other dependent variables. In addition, being a pilot study, the population was a convenience sample and we cannot positively rule out selection bias. This bias might have exaggerated the difference in results, especially when taking into account the fact that the exposed group members were recruited in a "snowball" fashion and interviewed person-to-person while the unexposed individuals were derived from a national health survey based on a representative sample of the population and interviewed by telephone.

In addition, it is impossible to distinguish between different periods of exposure and to determine whether the exposure that affected late morbidity occurred prenatally or in fact took place during early infancy and childhood. Scientific data and literature support the idea that the meaningful exposure and programming plasticity periods occur during pregnancy [2,12]. In the Dutch famine study [6], significant exposure had a precisely defined time window relating to the prenatal period. This defined period induced late-life morbidities that resemble current results. The participants of the present study endured, to

some extent, extreme exposures that were also shared by individuals in the Leningrad study where fetal exposure emerged as a noteworthy factor in late morbidity [7]. Epigenetic studies in animal models and humans have also demonstrated that significant windows of plasticity open during the prenatal period [2,12,14]. There is an obvious difficulty in recruiting individuals who were born during the Holocaust and whose exposure ended abruptly. Nevertheless, the wealth of previous publications and data gathered on the effects of perinatal exposure lead us to believe that perinatal exposures play a crucial role in the emergence of later morbidity in these individuals.

SUMMARY AND FUTURE DIRECTIONS

The results of the current study demonstrate a link between exposure and late morbidity that may have grave importance for screening this unique population. Since different causes of late-life morbidity can converge, it is impossible to distinguish the mental from the biological influence. Future studies in both fields – biology and epidemiology – may address this issue using novel genetic markers to demonstrate crucial changes in the fetal period. These studies should include objective measurements of morbidity, early mortality, and biomarkers of epigenetic changes, together with the effects on subsequent generations.

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"Life cannot be classified in terms of a simple neurological ladder, with human beings at the top; it is more accurate to talk of different forms of intelligence, each with its strengths and weaknesses. This point was well demonstrated in the minutes before last December's tsunami, when tourists grabbed their digital cameras and ran after the ebbing surf, and all the 'dumb' animals made for the hills"

Brian Reynolds Myers (born 1963), American associate professor of international studies at Dongseo University in Busan, South Korea, best known for his works regarding North Korean history