Holocaust Survival and the Long-term Risk of Cardiovascular Disease in the Elderly

Nadya Kagansky MD[1], Hilla Knobler MD[3], Marina Stein-Babich[1], Hillary Voet PhD[4], Adi Shalit[1], Jutta Lindert PhD MPH[5,6] and Haim Y. Knobler MD[3,7]

[1]Sherutei Briut Clalit (Clalit Health Services), Central region, Israel
[2]Institute of Diabetes, Endocrinology, and Metabolism, Kaplan Medical Center, Rehovot, Israel
[3]Hebrew University–Hadassah Medical School, Jerusalem, Israel
[4]Department of Environmental Economics and Management, Smith Faculty of Agriculture, Food and Environment, School of Nutritional Sciences, Hebrew University of Jerusalem, Rehovot, Israel
[5]University of Applied Sciences Emden, Emden, Germany
[6]Women's Research Center, Brandeis University, Waltham, MA, USA
[7]Peres Academic Center, Rehovot, Israel

ABSTRACT: **Background:** Reports of longevity in Holocaust survivors (HS) conflict with excess prevalence of chronic diseases described among them. However, data on their long-term risk of cardiovascular diseases (CVD) are limited. Clinical data on large representative groups of HS who were exposed to severe persecution are also limited.

Objectives: To determine the prevalence of CVD and the risk factors in a large cohort of elderly HS compared to elderly individuals who were not exposed to the Holocaust (NHS).

Methods: CVD prevalence rates and data on risk factors from the computerized system of the central district of Clalit Health Services, the largest Israeli health maintenance organization in Israel, were evaluated in a retrospective observational study. The study was comprised of 4004 elderly HS who underwent direct severe persecution. They were randomly matched by identification numbers to 4004 elderly NHS.

Results: HS were older than NHS and 51% of them were older than 85 years. The prevalence rate of ischemic heart disease (IHD) was significantly higher among HS. HS underwent significantly more cardiac interventions (20% vs. 15.7%, $P < 0.05$). HS status was an independent risk factor for increased IHD and for more coronary interventions.

Conclusions: Despite having a higher prevalence of CVD, a substantial number of HS live long lives. This finding may imply both unique resilience and ability to cope with chronic illness of the survivors as well as adjusted medical services for this population. These findings may help in planning the treatment of other mass trauma survivors.

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KEY WORDS: cardiovascular disease, elderly, Holocaust survivors

The impact of the Holocaust on the morbidity and mortality of the survivors has been evaluated by several studies, yet these reports have provided conflicting results [1-6]. Several studies showed excess prevalence of chronic diseases and mortality. However, some were conducted soon after the end of World War II (WWII). Others were limited due to small and/or convenience samples and by self-reported medical data [1-3]. In addition, Holocaust survivors are often compared to ex-prisoners of war, who in general reveal premature aging and a significantly increased prevalence of chronic diseases and early mortality [7-9]. It has been assumed that they shared the same medical consequences.

However, more recent studies conducted several decades after the end of WWII challenge this assumption and suggest that Holocaust survivors represent a selective resilient group. This resilience not only enabled them to survive the Holocaust, a period of extreme physical and mental trauma that lasted several years, but may have also favorably affected their ability to cope with lifelong medical problems. Data from the large Israeli Ischemic Heart Disease study published in 1993, a study that included male Israeli government employees, did not find a difference in mortality between Holocaust survivors and non-survivors [4]. Another study published a decade later confirmed this lack of excess mortality [5]. The most intriguing data were found in an Israeli population-based retrospective cohort study, which showed that survivors lived, on average, longer than non-survivors [6]. The possibility of special resilience among survivors was recently supported by a study comparing elderly survivors and controls presenting with acute myocardial infarction. The report showed a tendency for reduced long-term mortality in survivors [10].

Jews who lived in Nazi occupied Europe during the Holocaust period were exposed to extreme physical and

psychological stress. Psychological stress included torture, humiliation, separation from loved ones, and daily fear. Numerous studies have provided evidence that psychological stress increases the occurrence of cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia, and leads to increased cardiovascular disease (CVD) as reported by Rozanski et al. [11]. However, there are only limited data on the long-term risk of CVD among survivors. Two recent small cross-sectional studies conducted among adults born during the Holocaust showed a higher prevalence of CVD as well as CVD risk factors [12,13].

The aim of the present study was to estimate, seven decades after the end of WWII, the prevalence of CVD and CVD risk factors in a large cohort of elderly individuals who were exposed to direct severe persecution during the Holocaust, and to compare them to non-survivors, all of whom were residing in the same central area of Israel.

PATIENTS AND METHODS

We conducted a retrospective, matched controlled study.

POPULATION

The definition of Holocaust survivors used in the current study is based on the criteria used by the Israeli Holocaust Rights Authority in accordance with Israeli law. These criteria aim to provide financial benefits to individuals who underwent Nazi persecution. Holocaust survivors are divided into two main groups: survivors who underwent direct severe persecution (e.g., living in ghettos, concentration camps, labor or death camps) and other survivors.

In Israel, Clalit Health Services, is the largest health maintenance organization. Clalit social workers who specialize in caring for elderly survivors are responsible for the detection of the survivors' Holocaust status. According to this process, group 1 included 4004 from the central region. Data related to their year and place of birth as well as Holocaust status were gathered from the Clalit's Central Region's computerized database, which provides care for approximately 600,000 individuals, including 57,796 who are age 70 years and older. The control group of non-survivors included 4004 living Jewish elderly individuals, older than 70 years who were randomly selected from Clalit's computerized database from the same geographic region, and were born before 1945, either in Israel or Europe (and immigrated to Israel before 1939). The randomization process of eligible non-survivors was based on identification numbers, without further age-adjustment.

Demographic and medical information was obtained from Clalit's computerized medical records and included age, gender, smoking status, and medical diagnosis.

The study was approved by Kaplan Medical Center's institutional review board.

MEASURES

The following data were gathered from medical records of diagnoses recorded by family physicians: hypertension, hyperlipidemia, diabetes, ischemic heart disease (IHD), and stroke. Diagnoses were based on the ICD-10 system. The definition of IHD included the diagnoses of IHD, angina pectoris, myocardial infarction, and cardiac interventions, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). The definition of stroke included non-hemorrhagic stroke.

STATISTICAL ANALYSIS

Descriptive statistics were presented for all continuous and categorical variables as proportions or means with standard deviations.

The prevalence of each medical condition was age-corrected, using the age distribution of the non-survivors as representative of the age distribution in the general population. Confidence intervals for prevalence were calculated for differences between survivors and non-survivors using the normal approximation to the binomial distribution. To estimate whether there was an association between Holocaust status and the prevalence of IHD, myocardial infraction, cardiac intervention, and stroke, logistic regression analysis was performed using models including Holocaust status and additional variables, which either showed a significant bivariate association with the outcome or were considered relevant in the medical literature. These differences included gender, hypertension, hyperlipidemia, diabetes, age, and smoking habits. Results are presented as odds ratios (OR) with respective 95% confidence intervals (95%CI).

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $P < 0.05$ (2-tailed).

RESULTS

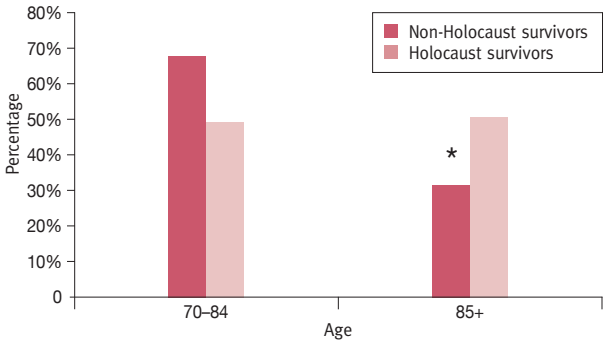
In the final analysis, the survivors and the non-survivors groups each included 4004 individuals.

Survivors were significantly older. The mean age of this group was 84.0 ± 6.6 years vs. 81.3 ± 6.6 years ($P < 0.001$). In addition, 51% of survivors were 85 years old and older vs. 32% of the non-survivors ($P < 0.0001$) [Figure 1].

Both groups included more women than men, but this finding was less prominent in the survivor group than in the non-survivor group (56/44% vs. 59/41%, respectively, $P = 0.022$).

Comparing age-adjusted CVD risk factors in survivors vs. non-survivors [Table 1], we found that hyperlipidemia was less prevalent in male survivors compared with male non-survivors, but there were no statistically significant differences in the prevalence of other CVD risk factors, namely diabetes, hypertension, and smoking.

Figure 1. Age distribution of Holocaust survivors vs. non-survivors



*Comparing age distribution of survivors vs. non-survivors, $P < 0.001$

With regard to the prevalence of CVD, we found that the prevalence of IHD was higher in the survivor group compared to the non-survivors (42.6% vs. 34.9%) and the difference was statistically significant in both men and women. Angina pectoris was also more prevalent among survivors than non-survivors and the difference was significant in both men and women. The prevalence of myocardial infarction was 9.3% in the survivor group vs. 8.0% in the non-survivor group, but the difference was not statistically significant. Survivors underwent significantly more cardiac interventions (PCI and CABG) than non-survivors (20% vs. 15.7%) and the difference was significant in both men and women. In contrast, stroke was less prevalent among survivors than non-survivors, and the difference was statistically significant in women.

Logistic regression analysis was performed for factors possibly associated with IHD, myocardial infarction, coronary intervention, and stroke [Table 2]. As shown, survivor status remained an independent risk factor for increased IHD (OR 1.46, 95%CI 1.33–1.61) and ongoing coronary interventions (OR 1.36, 95%CI 1.20–1.54) and was associated with reduced prevalence of stroke (OR 0.46, 95%CI 0.30–0.68). Age, male gender, diabetes, and hyperlipidemia were also independently associated with IHD, myocardial infarction, and coronary interventions. Hypertension was strongly associated with all events including stroke.

Table 2. Logistic regression analysis of cardiovascular diseases and cardiac intervention

	Odds ratio (95% confidence interval)			
	Ischemic heart disease	**Myocardial infarction**	**Stroke**	**Cardiac intervention**
Male gender	2.60 (2.36–2.87)	3.02 (2.56–3.56)	1.27 (0.87–1.86)	2.89 (2.57–3.26)
Hypertension	2.99 (2.56–3.50)	1.65 (1.26–2.17)	2.75 (1.26–5.99)	2.13 (1.73–2.62)
Hyperlipidemia	3.16 (2.68–3.72)	6.34 (4.03–9.99)	1.80 (0.86–3.74)	3.45 (2.70–4.40)
Diabetes	1.35 (1.22–1.49)	1.20 (1.02–1.41)	1.07 (0.72–1.57)	1.32 (1.17–1.49)
Holocaust status	1.46 (1.33–1.61)	1.16 (0.98–1.36)	0.46 (0.30–0.68)	1.36 (1.20–1.54)
Older age	1.05 (1.04–1.06)	1.03 (1.01–1.04)	1.02 (0.99–1.05)	1.03 (1.02–1.04)
Smoking	1.17 (0.94–1.47)	1.28 (0.91–1.78)	1.64 (0.79–3.43)	1.20 (0.92–1.56)

DISCUSSION

The current study evaluated the prevalence of CVD risk factors and the prevalence of IHD, cardiac interventions, and stroke in a large cohort of Holocaust survivors who underwent severe persecution compared to non-survivor elderly individuals (aged 70 years and older) living in the same geographic area and treated by the same health system.

The main result of the study is that male and female survivors of the Holocaust had statistically significant higher prevalence

Table 1. Age-adjusted prevalence rates of cardiovascular diseases and risk factors

	Men (%)			Women (%)			All (%)		
	Non-survivors	**Survivors**	**95%CI**	**Non-survivors**	**Survivors**	**95%CI**	**Non-survivors**	**Survivors**	**95%CI**
Hypertension	81.1	80.6	-2.31–3.33	82.4	84.2	-4.13–0.46	81.9	82.6	-2.49–1.07
Hyperlipidemia	87.1	82.7	1.90–6.92	87.3	87.0	-1.72–2.29	87.2	85.1	-0.58–3.72
Diabetes	38.4	39.8	-4.87–2.04	34.7	34.9	-3.16–2.59	36.2	37.1	-3.15–1.26
Current smoking	7.0	6.3	-1.03–2.61	3.8	4.5	-1.96–0.57	5.1	5.2	-1.18–0.93
Ischemic heart disease	46.2	53.2	-10.50– -3.55*	27.0	34.2	-9.87– -4.50*	34.9	42.6	-9.83– -5.47*
Angina pectoris	22.7	27.7	-8.00– -1.94*	9.3	12.8	-5.41– -1.71*	14.8	19.3	-6.22– -2.82*
Myocardial infarction	13.0	13.8	-3.19–1.6	4.5	5.5	-2.33–0.25	8.0	9.3	-2.54–0.01
Cardiac intervention	24.1	28.8	-7.77– -1.61*	9.8	13.2	-5.31– -1.54*	15.7	20.0	-6.06– -2.60*
Stroke	1.9	1.4	-0.41–1.4	1.8	0.5	0.63–1.90*	1.8	0.9	0.41–1.46

*Statistically significant ($P < 0.05$)
95%CI = 95% confidence interval

rates of IHD. Moreover, Holocaust status remained an independent risk factor for increased prevalence of IHD and cardiac interventions in a logistic regression analysis adjusted for age, gender, and CVD risk factors. These data confirm previous data, mostly based on smaller convenience samples, which found increased rates of various illnesses among survivors [1-3,12,13]. This excess rate may be attributed to the extreme physical and mental torture, poor hygiene, malnutrition, and lack of preventive medical and health services during the Holocaust.

The increased risk of IHD observed in the current study can be attributed to the known impact of chronic stress exposure on the circulatory system. Studies conducted in animals and humans established that both acute and chronic forms of psychosocial stress contribute to the pathogenesis of coronary atherosclerosis by mechanisms such as activation of the hypothalamic-pituitary-adrenal axis and increased sympathetic nervous activity [11,14].

A population with reported high rates of increased physical morbidity, early mortality, and post-traumatic stress disorder (PTSD), and depression includes ex-prisoners of war (ex-POWs) [4-6]. In a study of Israeli ex-POWs compared to combat veterans 18 and 35 years after war [5], captivity was associated with premature mortality (the relative risk of mortality in ex-POWs was 2.95 higher than that of controls) and more health-related problems. Further analysis found that PTSD and depression partly mediated the association between captivity and health problems. Intriguingly, although numerous studies have shown higher rates of anxiety disorders, sleep disorders, and emotional distress among Holocaust survivors, these studies did not show an excess risk of major depression and PTSD [15,16] in survivors in contrast to several other groups that underwent atrocities in other parts of the world [17,18]. This discrepancy in the rates of PTSD in Holocaust survivors and POWs is remarkable considering the incomparable degrees of horrors and atrocities experienced by the Holocaust survivors who were both prisoners of war and civilians rather than trained soldiers.

Although the current study did not measure the longevity of the Holocaust survivors, we found a higher percentage of aged survivors in a cohort of survivors 70 years of age and older who experienced severe persecution, including those 85 years of age and older. This finding relates to the results of Sagi-Schwartz and colleagues [6], who found in a large study based on Israeli general population data, that Holocaust survivors lived an average 6.5 months longer than non-survivors. Furthermore, male survivors who were aged 10 to15 years at the onset of the Holocaust lived 10 months more, while male survivors who were 16 to 20 years at the time lived 18 months longer.

Taken together, these findings suggest that survivors represent a special group that manifest increased prevalence of IHD, but demonstrate a unique ability to cope with their medical condition. Furthermore, this coping ability continues even when they get older.

Our findings are supported by a smaller study that compared 305 age-matched pairs of Holocaust survivors and non-survivors presenting with acute myocardial infarction. Although the survivors had a higher rate of depression than controls, no excessive (and possibly even mildly improved) risk of mortality was found among them [10]. Notably, survivors in our current study underwent considerablely more cardiac interventions compared with non-survivors, implying that survivors seek medical treatment more often.

In contrast to the increased prevalence of IHD among survivors, we found a reduced prevalence of stroke even after adjusting for known risk factors. This finding, to the best of our knowledge, was not previously reported, however, it has to be confirmed by additional studies due to the small number of events.

The strength of this study is that it included a large cohort of elderly individuals, who were all being treated by the same HMO organization and living in the same geographic area. A computerized database system enabled gathering of detailed medical information. Another strength is that Holocaust status was based on strict national criteria carefully examined by well-informed and trained social workers.

Limitations in this study include the lack of survival data in the region studied and information on those who did not survive to the age of 70 years. We also lack data on the medications taken by our cohort. Further limitations include no knowledge on proximal risk factors, including psychological factors.

CONCLUSIONS

The data from the current study demonstrate that elderly Holocaust survivors who underwent severe trauma are a unique group of individuals who show an increased prevalence of IHD risk factors and IHD but reach longevity. These data suggest resilience and a special ability to cope with medical problems among survivors that are not shared by other groups who experienced severe trauma [19]. However, more data, especially longitudinal data, are needed to understand better the long term impact of the Holocaust on survivors.

Correspondence
Dr. H.Y. Knobler
Peres Academic Center, Rehovot 7610202, Israel
Phone: (972-8) 946-2069
Fax: (972-8) 936-3304
email: haim.knobler@gmail.com

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Capsule

MiR-135 suppresses glycolysis and promotes pancreatic cancer cell adaptation to metabolic stress by targeting phosphofructokinase-1

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human cancers. It thrives in a nutrient-poor environment; however, the mechanisms by which PDAC cells undergo metabolic reprogramming to adapt to metabolic stress are still poorly understood. **Yang** et al. showed that microRNA-135 is significantly increased in PDAC patient samples compared to adjacent normal tissue. Mechanistically, miR-135 accumulates specifically in response to glutamine deprivation and requires ROS-dependent activation of mutant p53, which directly promotes miR-135 expression. The authors found that, functionally, miR-135 targets phosphofructokinase-1 (PFK1) and inhibits aerobic glycolysis, thereby promoting the utilization of glucose to support the tricarboxylic acid (TCA) cycle. Consistently, miR-135 silencing sensitizes PDAC cells to glutamine deprivation and represses tumor growth in vivo. Together, these results identify a mechanism used by PDAC cells to survive the nutrient-poor tumor microenvironment, and also provide insight regarding the role of mutant p53 and miRNA in pancreatic cancer cell adaptation to metabolic stresses.

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Eitan Israeli

Capsule

The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans

Two main proteins accumulate in the brain in Alzheimer's disease (AD), β-amyloid (Aβ) and tau. Aβ appears to instigate AD, but tau appears to drive brain damage and cognitive decline. Sleep deprivation is known to increase Aβ acutely and chronically. **Holth** et al. showed that chronic sleep deprivation strongly increased tau acutely over hours and also drives tau pathology spreading in the brains of mice and humans. The sleep–wake cycle regulates interstitial fluid (ISF) and cerebrospinal fluid (CSF) levels of β-amyloid (Aβ) that accumulates in Alzheimer's disease. Furthermore, chronic sleep deprivation (SD) increases Aβ plaques. However, tau, not Aβ, accumulation appears to drive AD neurodegeneration. The authors tested whether ISF/CSF tau and tau seeding and spreading were influenced by the sleep–wake cycle and SD. Mouse ISF tau was increased ~90% during normal wakefulness versus sleep and ~100% during SD. Human CSF tau also increased more than 50% during SD. In a tau seeding-and-spreading model, chronic SD increased tau pathology spreading. Chemogenetically driven wakefulness in mice also significantly increased both ISF Aβ and tau. Thus, the sleep–wake cycle regulates ISF tau, and SD increases ISF and CSF tau as well as tau pathology spreading.

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Eitan Israeli