Chronic Health Conditions in Jewish Holocaust Survivors Born during World War II

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ABSTRACT: **Background:** Findings of studies addressing outcomes of war-related famine in non-Jewish populations in Europe during the Second World War (WWII) confirmed an association between prenatal/early life exposure to hunger and adult obesity, diabetes, hypertension, cardiovascular disease and the metabolic syndrome. Fetal programming was suggested as the explanatory mechanism.

Objectives: To study the association between being born during WWII in Europe and physical long-term outcomes in child Holocaust survivors.

Methods: We conducted a cross-sectional study on all Jewish Clalit Health Services (CHS) North District members born in 1940–1945 in Europe ('exposed', n=653) or in Israel to Europe-born parents ('non-exposed', n=433). Data on socio-demographic variables, medical diagnoses, medication procurement, laboratory tests and health services utilization were derived from the CHS computerized database and compared between the groups.

Results: The exposed were significantly more likely than the non-exposed to present with dyslipidemia (81% vs. 72%, respectively), hypertension (67% vs. 53%), diabetes mellitus (41% vs. 28%), vascular disease (18% vs. 9%) and the metabolic syndrome (17% vs. 9%). The exposed also made lower use of health services but used anti-depressive agents more often compared to the non-exposed. In multivariate analyses, being born during WWII remained an independent risk marker for hypertension (OR = 1.52), diabetes mellitus (OR = 1.60), vascular disease (OR = 1.99) and the metabolic syndrome (OR = 2.14).

Conclusions: The results of this cross-sectional study based on highly validated data identify a high risk group for chronic morbidity. A question regarding potential trans-generational effects that may impact the 'second generation' is also raised.

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The theoretical framework of Fetal Origin of Adult Diseases (FOAD) [1] focused on prenatal growth patterns reflected in low birth weight, and suggested that fetal experiences may determine the long-term risk for a variety of chronic diseases (coronary artery disease, hypertension, obesity and insulin resistance) through fetal programming [1]. The FOAD theory was later expanded to include not only conditions associated with the metabolic syndrome but also nervous system diseases, mental health and cognitive function [2]. This theory is based on the biological fact that one genotype may give rise to different phenotypes, depending on environmental and other influences during development. Therefore, poor nutritional conditions of the pregnant mother cause biologic and metabolic – but not genetic – adaptations of the fetus that serve to prepare it for survival in an environment in which resources are scarce [3]. The benefit of this phenotypic plasticity is that under changing environmental conditions it ensures the development of a phenotype that is best matched to the current environment [4].

When malnutrition occurs during fetal development it may be compensated for by accelerated growth thereafter. In animals, rapid/compensatory growth responses include shortening of the protective ends of the chromosomes (the telomeres) and increased cell death and organ degradation, which offer a potential explanation for certain associations between low birth weight and morbidity observed in humans [4]. Other explanatory mechanisms have been proposed:

- lower birth weight may indicate less functional capacity in key organs, such as the kidney, explaining the association with hypertension [5]
- consequential changes in the setting of certain hormones and metabolic pathways following prenatal and early life malnutrition also change the long-term susceptibility to chronic conditions [5]
- elevated oxidative stress associated with malnutrition and experienced in critical time windows during early devel-

opment may affect, directly or indirectly, growth patterns and gene expression [6]
- societal and environmental factors associated with fetal malnutrition, such as lower attained education and socio-economic status, indirectly impact late-onset morbidity [7].

Some of the data that support this hypothesis were derived from studies addressing outcomes of war-related famine exposures, such as those occurring during the Second World War (WWII) in Europe, i.e., the Dutch cohort [8], the Siege of Leningrad cohort [9] and the British Channel Islands cohort [10]. The findings of the studies conducted on these cohorts confirmed a relationship between prenatal and early life exposure to famine and later-life higher susceptibility for adult obesity, impaired glucose metabolism, hypertension, cardiovascular disease and the metabolic syndrome. These results were further supported by more recent publications referring to the great Chinese famine in 1959–1961 [11] and to maternal and child under-nutrition in low- and middle-income countries [7]. However, only a few studies so far [12-16] referred to Jewish Holocaust survivors who were born during the War years, even though this unique population was often exposed to pre- as well as postnatal severe malnutrition and horrific conditions. Most of these studies [12-15] focused on mental morbidity while, to the best of our knowledge, only two [15,16] addressed the issue of long-term physical consequences.

The aim of the current study was to investigate the association between being conceived and born during the Holocaust and later chronic conditions in a non-convenience sample of Jewish residents in northern Israel.

SUBJECTS AND METHODS

All Israeli citizens are covered by the National Health Insurance Law and health services are delivered to the entire population by four health maintenance organizations (HMOs). The Clalit Health Services (CHS) is the second largest HMO worldwide and the largest one in Israel, covering over 4,000,000 Israeli subjects (52.3% of the total population in 2011), about 900,000 of them living in the northern district of Israel (69.4% of the total population in this area). The study population of the current survey was derived from the Jewish members of CHS, northern district.

This was a cross-sectional study. Through the CHS northern district computerized database, all 2007–2012 Jewish members born between 1940 and 1945 were identified. The members' place of birth was used as a proxy for the exposure status: those born in European countries that had been occupied by the Nazis during WWII were defined as born during the Holocaust, or 'exposed'. Those born in Israel in the same time period, whose parents (mother and/or father) were born in one of these European countries, were defined as 'non-exposed'. In total, 808 exposed and 505 non-exposed eligible subjects were identified. Of them, 155 (19.2%) in the exposed group and 72 (14.2%) in the non-exposed group ($P = 0.02$) died before 2012. The mean (± SD) age at death was 59.4 ± 9.3 years and 58.0 ± 8.9 in the exposed and non-exposed groups, respectively ($P = 0.284$). The CHS electronic medical records (EMRs) are available since 2000 and are kept for 5 years following death; therefore, most clinical data for deceased persons were missing and were excluded. Thus, 653 exposed and 433 non-exposed participants were included in the analyses. The study was approved by the CHS Ethics Board Committee.

STUDY VARIABLES

Demographic variables included gender, date and place of birth, personal status, and having children or not. Fee exemption, which meant lower or no payment on medications and extra services, was initially planned to be used as a proxy for a lower socioeconomic status. However, it was later clarified that fee exemption is determined according to being defined as belonging to a "special population" (Holocaust survivors included), or being diagnosed with certain diseases, or both, and does not necessarily reflect socioeconomic status. Thus it was mostly used as a validation for the exposure status. Smoking (current, past, none), height and weight were determined from the EMRs, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters, squared.

The prevalence of certain medical conditions was determined by a physician's diagnoses in the EMR in 2007 through 2012: hyperlipidemia/hypercholesterolemia, hypertension, diabetes mellitus, coronary heart disease, myocardial infarction (MI), valvular heart disease, congestive heart failure (CHF), cerebrovascular accident (CVA), carotid artery disease (CAROD), peripheral vein disease (PVD), osteoporosis, hip fracture, cancer (breast, prostate, colorectal), asthma and chronic obstructive pulmonary disease (COPD). In addition, we used the medical prescription database of the CHS to confirm some of these diagnoses by repeated purchases (i.e., in the last 5 years) of certain drugs, for example, statins (dyslipidemia), bisphosphonates (osteoporosis), insulin and oral diabetes medications (diabetes mellitus). Information regarding repeated purchases of anxiolytics and anti-depressive agents was collected as well. We also used laboratory results of low density lipoprotein (LDL) and hemoglobin A1C levels to further validate the diagnoses of dyslipidemia and diabetes, respectively. Consecutively we created variables reflecting the prevalence of certain conditions based on a combination of a physician's diagnosis and appropriate medication and/or biochemical test, for example, dyslipidemia diagnosis combined with statin treatment, diabetes diagnosis combined with use of oral medications or insulin, osteoporosis diagnosis combined with bisphosphonates treatment, etc.

We grouped the diagnoses: coronary artery disease and/or MI and/or CHF were grouped into "ischemic heart disease" (yes/no). Likewise, we grouped the diagnoses of CVA and/

or CAROD and/or PVD into "vascular disease" (yes/no). In addition, we created a variable expressing the level of chronic morbidity, referring to the prevalence of any of nine health conditions (hypertension, diabetes, coronary artery disease, CAROD, CHF, osteoporosis, cancer, asthma, COPD), its values ranging between "0" (none) and "9" (all of these conditions) – the chronic morbidity indicator. Unfortunately, we were unable to directly evaluate the prevalence of the metabolic syndrome, and therefore created a proxy variable based on the simultaneous occurrence of diabetes (as a proxy for fasting hyperglycemia), hypertension, obesity and dyslipidemia (as a proxy for hypertriglyceridemia). Participants with all four conditions were considered as potentially having the metabolic syndrome.

Last, we also had data on the use of health services and compliance, including uptake of cancer screening (mammography and fecal occult blood test), immunizations, and visits to the family physician, to medical specialists and to the emergency room in 2011–2012, as well as the number of days of hospitalization in general and in the internal medicine ward in particular, the number of prescriptions issued and the number of prescriptions purchased.

DATA ANALYSES

We compared the demographic variables, the risk factors, clinical conditions and health services utilization indicators between the exposed and the non-exposed groups, using chi-square test, Fisher's test or independent Student *t*-test, as needed. A subanalysis examined the differences between "exposed" and "non-exposed" born in 1940–44 and in 1945 separately. Multivariable logistic regression models, using prevalence of certain chronic conditions as the dependent variable, were used to assess the independent association with the exposure variable following adjustments to potential confounders. All models were adjusted for gender, age, obesity and dyslipidemia. Fee exemption, which was based, among others, on being a Holocaust survivor, was closely related to the main exposure variable and was also found to be closely related to gender. Among the northern district CHS Jewish female members, 43.7% were fee-exempted as compared to 38.6% of the males ($P = 0.017$). Therefore, in order to avoid overmatching, this variable was not included in the models. Smoking rates did not differ significantly between the groups and in fact seemed to be underestimated. Therefore, this variable was not included in the models either. The models referring to ischemic heart disease and vascular disease were further adjusted to the prevalence of diabetes and hypertension.

Significance level was set at 0.05 and all analyses were carried out using the IBM-SPSS Statistics 21 package.

RESULTS

A total of 1086 subjects, 653 exposed and 433 non-exposed, took part in this study. A quarter (26.2%) and a fifth (20.1%) of the exposed and the non-exposed, respectively, were born in 1945 while the rest were born in 1940–44 ($P < 0.001$). The exposed were more likely than the non-exposed to be fee-exempted (62.2% vs. 18.5%, respectively, $P = 0.001$); however, among the fee-exempted exposed subjects, 90% were defined as a "special population" (a category that includes Holocaust survivors), 4% had certain diseases and 6% had both. The relevant proportions among the non-exposed were 66%, 30% and 4% (data not shown).

The gender distribution was significantly different ($P = 0.002$) between the exposed (males, 45.8%) and non-exposed (males, 55.4%) groups. The exposed were also somewhat older and had fewer children. In addition, the exposed were significantly more likely to be shorter, heavier and have a higher BMI compared to the non-exposed; however, for the variable ever-smoking the difference between the groups was statistically insignificant [Table 1].

Dyslipidemia, dyslipidemia combined with statin treatment, hypertension, diabetes, diabetes combined with use of oral medications or insulin, coronary artery disease, CVA, CAROD, COPD, and the use of anti-depressive agents were all more prevalent and the "chronic morbidity" indicator was significantly higher in the exposed compared to the non-exposed group [Table 2]. No significant differences were noted with respect to the prevalence of MI, CHF, valvular heart disease, PVD, osteoporosis, osteoporosis combined with bisphosphonate treatment, cancer (in general, and breast, prostate and colorectal cancer in particular), asthma and use of anxiolytics (data not shown). The combined variable of ischemic heart disease (coronary artery disease/MI/CHF) was more prevalent in

Table 1. Demographic and health-related characteristics of the study population

	Exposed (n=653)	Non-exposed (n=433)	*P* value*
Gender, % (n)			
Males	45.8 (299)	55.4 (240)	0.002
Females	54.2 (354)	44.6 (193)	
No. of children, % (n)			
0	37.8 (247)	24.7 (107)	< 0.001
1–2	49.9 (326)	55.4 (240)	
3–4	10.8 (70)	19.1 (83)	
5+	1.6 (10)	0.7 (3)	
Smoking, % (n)**			
Current or past	3.5 (15)	1.6 (5)	0.077
Never	96.5 (416)	98.4 (315)	
Age (years, mean ± SD)	69.4 ± 1.9	69.2 ± 1.7	< 0.001
Height (cm, mean ± SD)	163.7 ± 9.1	166.5 ± 9.1	< 0.001
Weight (kg, mean ± SD)	78.3 ± 14.6	76.4 ± 14.5	0.040
Body mass index (kg/m^2, mean ± SD)	29.2 ± 5.1	27.5 ± 4.3	< 0.001

*Chi-square test for categorical variables; independent *t*-test for continuous variables

**Data are partial and available for 431 (66%) of the exposed and 320 (73.9%) of the non-exposed

Table 2. Prevalence of chronic conditions in the study population

Chronic condition % (n)	Exposed (n=653)	Non-exposed (n=433)	*P* value*
Dyslipidemia	80.7 (527)	72.4 (322)	0.013
Dyslipidemia combined with statin treatment	74.4 (486)	67.2 (291)	0.017
Hypertension	67.2 (439)	53.3 (231)	‹ 0.001
Diabetes	41.0 (268)	27.7 (120)	‹ 0.001
Diabetes combined with use of oral medications or insulin	31.2 (204)	22.8 (99)	‹ 0.001
Coronary artery disease	26.8 (175)	21.5 (93)	0.046
CVA	9.5 (62)	3.5 (15)	‹ 0.001
CAROD	5.4 (35)	2.1 (9)	0.007
COPD	5.5 (36)	2.1 (9)	0.005
Use of anti-depressive agents	29.6 (193)	23.8 (103)	0.037
Chronic morbidity indicator**			
0	16.7 (109)	23.6 (102)	0.001
1–2	54.9 (358)	59.2 (256)	
3–4	25.6 (167)	15.7 (68)	
5+	2.9 (19)	1.6 (7)	
Ischemic heart disease***	27.8 (178)	22.2 (96)	0.059
Vascular disease^	17.6 (115)	8.8 (38)	‹ 0.001
Metabolic syndrome (proxy) ^^	17.2 (112)	8.8 (38)	‹ 0.001

*Chi-square test or Fisher's test when cell numbers were smaller than 10

**Based on the prevalence of any of these conditions: hypertension, diabetes, coronary artery disease, CHF, osteoporosis, cancer, asthma and COPD

***Ischemic heart disease = coronary artery disease and/or MI and/or CHF

^Vascular disease = CVA and/or PVD and/or CAROD

^^Metabolic syndrome proxy = the simultaneous occurrence of diabetes, hypertension, obesity and dyslipidemia

CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, CVA = cardiovascular accident, PVD = peripheral vascular disease, CAROD = carotid artery disease

Table 3. Logistic regression models to study the independent association of the exposure with selected chronic conditions, adjusted for potential confounders (OR, 95%CI)

Variable	Model 3a: Hypertension	Model 3b: Diabetes	Model 3c: Ischemic heart disease*	Model 3d: Vascular disease**
R^2	0.166	0.192	0.259	0.127
Exposure (yes vs. no)	1.524 (1.167–1.992)	1.604 (1.210–2.127)	1.132 (0.818–1.565)	1.992 (1.326–2.994)
Age, years (continuous)	1.085 (1.009–1.166)	1.051 (0.977–1.130)	1.108 (1.020–1.204)	1.049 (0.953–1.155)
Gender (males vs. females)	1.215 (0.933–1.581)	1.335 (1.019–1.749)	3.235 (2.354–4.4445)	1.714 (1.191–2.468)
Obesity (yes vs. no)	2.663 (1.998–3.549)	2.075 (1.576–2.733)	1.449 (1.055–1.991)	1.240 (0.858–1.794)
Dyslipidemia (yes vs. no)	3.668 (2.683–5.015)	8.427 (5.192–13.677)	5.420 (2.955–9.941)	3.802 (1.859–7.777)
Diabetes (yes vs. no)			1.525 (1.114–2.089)	1.092 (0.754–1.581)
Hypertension (yes vs. no)			3.181 (2.175–4.654)	2.466 (1.549–3.926)

*Ischemic heart disease = coronary artery disease and/or MI and/or CHF

**Vascular disease = CVA and/or PVD and/or CAROD

CVA = cardiovascular accident, PVD = peripheral vascular disease, CAROD = carotid artery disease

the exposed (borderline significance). The combined variable of vascular disease (CVA/PVD/CAROD) was significantly more prevalent in the exposed as compared to the non-exposed, as was the proxy variable for the metabolic syndrome [Table 2].

When health services utilization was compared between the groups, it was clear that the exposed were less likely than the non-exposed to undergo cancer screening tests (mammography 86.7% vs. 91.2%, fecal occult blood test 63.6% vs. 67.4%), but these differences did not reach statistical significance. The exposed were also less likely than the non-exposed to undergo adult immunizations: 83.6% vs. 89.8% ($P = 0.004$). The exposed had fewer visits to their family physician in 2011–2012: 18.9 ± 14.0 as compared to 20.9 ± 13.5 in the non-exposed ($P = 0.021$), but no major differences were noted with respect to visits to medical specialists, emergency rooms, total number of hospitalization days (as well as total number of days in the internal medicine ward), number of prescriptions issued and number of prescriptions purchased (data not shown).

A sub-analysis of those born in 1940–44 and those born in 1945 yielded similar findings to those of the total study population with respect to a higher prevalence of risk factors and chronic conditions in the exposed compared to the non-exposed, although in the smaller group of those born in 1945 (a total of 258) these results did not reach statistical significance while in those born in 1940–44 (n=828) they did (data not shown).

In order to estimate the independent association between the exposure and the chronic conditions studied, we used logistic regression models adjusted for potential confounders, where certain health conditions (diabetes, hypertension, ischemic heart disease, vascular disease) were the dependent variables [Table 3]. Being born during the Holocaust (exposure) remained significantly associated with hypertension [odds ratio (OR) = 1.52] and with diabetes (OR = 1.60) later in life, even after adjusting for age, gender, obesity and dyslipidemia. Obesity and dyslipidemia were significant covariates in both conditions. Age (OR = 1.08) was independently associated with hypertension but not with diabetes while gender was independently associated with diabetes (OR for males 1.33) but not with hypertension [Table 3, models 3a, 3b]. Following adjustments, being born during the Holocaust was no longer significantly associated with ischemic heart disease. However, significant covariates were age (OR = 1.11), gender (OR for males 3.23), obesity (OR = 1.45), dyslipidemia (OR = 5.42), diabetes (OR = 1.52) and hypertension (OR = 3.18) [Table 3, model 3c]. In the case of vascular disease, being born during the Holocaust had an independent effect (OR = 1.99), as did gender (OR for males 1.71), dyslipidemia (OR = 3.80) and hypertension (OR = 2.47) [Table 3, model 3d].

We also studied the relationship between being born during the Holocaust and (proxy) metabolic syndrome, and found it to

be independently associated [OR = 2.14, 95% confidence interval (CI) 1.48–3.47], following adjustment for gender and age (which were both statistically insignificant) (data not shown).

DISCUSSION

This cross-sectional study focused on the association between fetal and early-life exposures and long-term chronic morbidity in a unique population of Holocaust survivors whose pregnancy, infancy and at times also early childhood took place during WWII in Europe. The study findings indicate that the exposed were more likely to present with a heavy burden of chronic conditions, including dyslipidemia, hypertension, diabetes mellitus, vascular disease and the metabolic syndrome. They also exhibited lower use of health services but used anti-depressive agents more often compared to the non-exposed.

The results of the current study on fetal and early childhood exposure to malnutrition and hunger and the subsequent long-term outcomes are in accordance with previously published data from research on non-Jewish populations [8-11]. So far, only two studies referred to the late-term physical health of Jewish Holocaust survivors. Barel et al. [15], in 2010, published a thorough meta-analysis of 71 samples involving thousands of Holocaust survivors, focusing on whether the Holocaust experience affects survivors across different mental, cognitive and physical health domains. They reported that in non-selected samples Holocaust survivors did not show poorer physical health than their counterparts, but in the set of six selected samples which included 1067 participants a significant difference was found in physical health between Holocaust survivors and comparisons [15]. However, this meta-analysis was not limited to those exposed during pregnancy or at early infancy and childhood, but included all Holocaust survivors. Sperling et al. [16] reported in 2012 on differences in the physical health of a small sample of patients with Holocaust- and non-Holocaust-related post-traumatic stress disorder (PTSD). The results disclosed an increase in myocardial infarction, chronic degenerative diseases, and cancerous changes in the group of Holocaust-related PTSD patients compared to the non-Holocaust-related PTSD comparison group. The small sample size and the fact that all participants had PTSD make interpretation of these results difficult [16]. A very recent Israeli pilot study [17], which compared chronic morbidity in a convenience sample of Holocaust survivors born during the Holocaust and their origin-matched counterparts, disclosed a significantly higher prevalence of obesity, dyslipidemia, diabetes, hypertension, cardiovascular morbidity, malignancy and peptic diseases in the exposed [17]. These results are very similar to the results reported here. In both studies, the main differences between the exposed and the non-exposed were noted for disease risk factors (e.g., obesity, dyslipidemia) and related chronic morbidity (diabetes mellitus, ischemic heart disease, vascular disease, hypertension, metabolic syndrome) [17].

Holocaust survivors of all ages suffered from severe starvation, extreme mental stress, exposure to infectious agents, and cold winter temperatures [18,19]. It is reasonable to assume that those born during this time period were exposed to these conditions in utero and following birth, and shifted, at a certain point in their life course, from a life-long lack of resources to an environment abundant with food. This mismatch may have set the stage for late-life morbidities through the aforementioned developmental plasticity, which is mediated, at least partly, by epigenetic processes such as DNA methylation and histone modification. The interaction between the genome and the epigenome determines the mature phenotype and the susceptibility to adult diseases [20].

This study refers to the first generation of Holocaust survivors and adds information to the body of evidence regarding the relationship between early exposures and adult diseases. However, the question whether these effects are trans-generational and also affect the next generations of Holocaust survivors remains open. Studies of laboratory animals were able to show that epigenetic changes induced by stress to a pre-pregnant or pregnant mother are carried forward to the next generations [21-23]. Several previous studies on offspring of non-Jewish survivors of WWII addressed this point [4-6], but research on the offspring of Holocaust survivors is still scarce. Recently, Flory at al. [24] investigated self-reported health complaints of 82 offspring of Holocaust survivors and 55 comparisons, and found that maternal but not paternal exposure was associated with greater use of psychotropic (23% vs. 6%, $P = 0.01$) and other (57% vs. 38%, $P = 0.03$) medications, a higher proportion of having two or more conditions of the metabolic syndrome (15% vs. 2%, $P = 0.01$), and significantly lower self-rating of emotional and physical health [25]. Shrira et al. [25] also studied the potential trans-generational effects of trauma in Holocaust survivors' offspring and reported that the offspring had significantly more major health problems and symptoms and used more medications than their counterparts. However, more data are needed.

The results of the current study should be interpreted cautiously, keeping in mind its limitations. Although great efforts were made to use a random sample, we had no access to the medical data of the deceased and therefore had to exclude them from the analyses. The proportion of deceased among the exposed (19.2%) was significantly higher than among the non-exposed (14.2%), which may indicate a selection bias. As said, we had no information regarding background morbidity of the deceased or their cause of death and thus comparisons across the study groups were not possible. However, the average age at the time of death was similar in both groups, implying that for the most part these were not premature deaths. Since the exposed group was slightly older than the

non-exposed group, the higher proportion of deceased in the former may in fact reflect the age distribution in the exposed group in general, that is, slightly older within the birth cohort limits (48.5% of the exposed compared to 41.6% in the non-exposed were born in 1940–1942), thus partially explaining the higher mortality rate. At any rate, even if the mortality rate in the exposed group is indeed higher due to the exposure studied, the results observed are probably attenuated, and the differences may be even larger in reality.

Another concern may be the gender distribution in the study groups. The gender distribution in Israel in the age groups paralleling those of the study participants is obviously in favor of females: 53% females to 47% males in the 64–69 age group and 55% females to 45% males in the 70–74 age group. While the gender distribution of the exposed group (54% females to 46% males) reflects that expected according to the general population data, the distribution in the non-exposed group is different (45% females to 55% males). We are unable to offer a substantial explanation for this observation, since the non-exposed group subjects were born in Israel and therefore were not subjected to a potential gender selection which may have influenced the immigration prospects of their parents. Thus, the possibility of a selection bias should be kept in mind.

Furthermore, we included in the study only participants who were insured in the CHS for 5 consecutive years (2007–2011). Participants transferring to other HMOs were excluded since their EMRs became unavailable shortly after the transfer. However, in the last years the proportion of transfers between HMOs is negligible (around 1.5% per year) and in the last few years, the CHS has a positive balance of members, that is, a higher number of newly arrived members compared to members leaving [Health Economics and Data Division, Israel Ministry of Health].

Another limitation is the cross-sectional nature of the study, which does not allow for causal inference. In other words, the associations observed are not necessarily the direct result of the exposure studied. Indeed, the exposed group subjects had parents who were probably Holocaust survivors themselves while the non-exposed subjects did not, by definition (as their parents immigrated to Israel prior to WWII). This, in itself, may have impacted the socioeconomic status of the household, the attained education of the subjects, the lifestyle and upbringing, which in themselves could have accounted for or heavily attributed to the results. Nevertheless, the current results are consistent with the results of previous studies in this field.

Additionally, the data studied are available in the form of EMRs only since 2000, and data on smoking, self-reported and collected by the physicians only in recent years, seemed unreliable and therefore were not used.

On the other hand, this study has some advantages that should not be overlooked. We conducted the study on the member population of the CHS, which is the largest HMO in Israel in general and in the northern district in particular (covering about 70% of the total population in this geographic area). Since the analyses involved data mining of a computerized database, non-participation and non-response biases were avoided. Furthermore, since the CHS makes special efforts to improve the data quality especially with respect to certain chronic conditions such as dyslipidemia and diabetes mellitus, the validity of these diagnoses is high.

In conclusion, this is one of very few studies addressing the issue of adult health and diseases in Holocaust survivors born during World War II. Its results identify a high risk group for chronic morbidity, and call for higher clinical attention of health caretakers in this respect.

These results need to be consolidated in large prospective studies which, in turn, will provide policy makers with the evidence needed to plan tailored strategy for the primary and secondary prevention of these conditions in this population. Such intervention programs may involve specific outreach strategies, taking into account the fact that this population tends to utilize health system services less frequently than do non-Holocaust survivors.

Another urgent matter is the question of higher susceptibility to chronic morbidity in the next generations, which also calls for appropriate large-scale cohort studies. This should be placed high on the list of national health priorities because of the high burden of these chronic conditions that can be avoided through primary prevention as well as early detection.

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