Holocaust Experience and Mortality Patterns: 4-Decade Follow-up in a Population-based Cohort

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Abstract

Study of mortality associated with exposure to the Holocaust is relevant for better understanding the effects of man-made massive killings on survivors. Previous studies did not investigate long-term *cause-specific* mortality of Holocaust survivors. We compared mortality rates of Israelis born in European countries controlled by the Nazis to Israelis of European descent without this exposure. Records of 22,671 people (5,042 survivors, 45% women) from the population-based Jerusalem Perinatal Study (1964-1976) were linked to the Population Registry updated through 2016. Cox models were used with two-sided tests of statistical significance. Risk of all-cause mortality was higher in the exposed women (hazard ratio (HR) = 1.15; 95% confidence interval (CI): 1.05, 1.27) as compared to unexposed. No association was found between the exposure and male all-cause mortality. In both sexes, the survivors had higher cancer-specific mortality (HR=1.17; CI: 1.01, 1.35 in women and HR=1.14; CI: 1.01, 1.28 in men). The exposed men also had excess mortality due to coronary heart disease (HR=1.39; CI: 1.09, 1.77) and lower mortality due to other known causes combined (HR=0.86; CI: 0.75, 0.99). In summary, Holocaust experience was associated with excess of all-cause and cancer-specific female and cancer- and coronary heart disease -specific male mortality.

Keywords: Mortality**,** Cancer**,** Cohort study, Coronary heart disease**,** Holocaust, Survival analysis

Abbreviations
CHD, coronary heart disease
CI, confidence interval
HR, hazard ratio
ICD, International Classification of Diseases
JPS, the Jerusalem Perinatal Study
SD, standard deviation
SEP, socio-economic position
SHARE-IL, the Israeli component of the Survey of Health, Ageing and Retirement in Europe

The Holocaust undoubtedly stands out as an extraordinary outburst of extreme violence in the human history. Tragically, genocides continue to occur and they are not diminishing in frequency (1). In order to better understand long-term effects of extreme violence on human biology, study of mortality and morbidity associated with the Holocaust is as relevant in the 21st century as ever.

Epidemiological literature has demonstrated that the social environment at different stages of life can have substantial health consequences over the life-course (2-6). Whether as captives in concentration/death camps or escapees, Jewish survivors of the Holocaust have faced a combination of severe multifaceted stress conditions, e.g. extreme physical and emotional abuse, sleep deprivation, exposure to infectious diseases, toxic waste and strenuous physical activity (7-9). Many of them died quite soon in the aftermath of the Holocaust (10) or became too weak to resume a 'normal' life (11). While a considerable number of survivors nevertheless managed to rebuild their lives (12, 13), it is a reasonable hypothesis that the Holocaust may have a profound long term impact on survivors' health.

At the time this research was conducted, studies on health consequences of the Holocaust yielded conflicting findings, particularly with respect to mortality (14, 15). While some recent research in Israel found that the Holocaust did not affect old-age all-cause mortality (13, 16, 17), other showed it was even lower among the survivors (18, 19).

Several explanations have been proposed to account for the conflicting evidence (15, 16, 20), yet a recent study notes that more research is warranted to understand the Holocaust-related death hazards (19). Moreover, we are not aware of a study that investigated long-term cause-specific mortality in Holocaust survivors. Using data from a population-based cohort with mortality records spanning the period from the 1960's to 2016, this study aims to assess whether exposure

to the Holocaust affected all-cause and cause-specific mortality of survivors who have been able to immigrate to Israel and to have offspring.

METHODS

Study design and data source

The Jerusalem Perinatal Study (JPS) is a population-based cohort of 92,408 live- and stillbirths that occurred in Jerusalem in 1964–1976, and their parents (21). The current analysis focuses on the parents' generation, baseline data on whom included detailed sociodemographic characteristics (e.g. date and country of birth, education), as well as health-related and perinatal factors in mothers (21). Using unique Israeli identity numbers, vital status and dates of death (up to December 31, 2016) were obtained by linkage of the cohort members' baseline records to the Israeli Population Registry. For a very small number of the participants (0.06%) these data were verified through April 1, 2005. Underlying causes of death were available through the end of 2015 via record linkage with the Ministry of Health. The cohort was also linked to the Israel National Cancer Registry established in 1960 and updated through December 31, 2014. Deceased subjects, for whom the cause of death was unknown, were determined to have died from cancer if they were diagnosed with cancer and passed away within 5 years following the 1st diagnosis. The remaining cases with unknown cause of death were combined and analyzed below as a separate category. This study was approved by the Institutional Review Board of the Hadassah-Hebrew University Medical Center in Jerusalem.

Selection of the study sample and definition of exposure status

This work relies on a definition of a Holocaust survivor used by Israel's research and

governmental institutes, according to which a Holocaust survivor is a person who lived in one of the countries occupied by or under the influence of the Nazi regime for any length of time between 1933 and 1945. According to this definition, the survivor population also includes those who were forced to leave their place of residence because of the Nazi regime (22).

Figure 1 shows how exposed, unexposed and excluded groups were defined based on the initial sample. As in similar studies (e.g. (12, 17, 23)), to minimize biases related to cultural, environmental and genetic differences between survivors and unexposed, we only included individuals of European descent born before or during 1945. Following the approach used in Lurie *et al.* (2018) (23), survivors were further defined as being born in a Nazi-occupied country and immigrating to Israel during or after the year when Nazi persecutions in this particular country have started (Web Table 1). The comparison group was defined as either a) persons born in the same countries who immigrated to Israel *before* the Nazi persecutions or b) persons of European decent born in any other country (including Israel) before or during 1945. Since for the immigrants from the Union of Soviet Socialist Republics the country of birth variable did not specify particular republics, we could not establish whether they were born under the occupation and therefore excluded these participants (about 2% of the sample) from all analyses. The resulting exposure variable was coded as a dummy (1, exposed; 0, unexposed). Following this exposure definition, 10,210 women and 12,461 men that comprise 25% and 30% of the respective original samples were included in the reported analyses, of which 2,133 female and 2,909 male were Holocaust survivors (Figure 1).

We tested this exposure definition using data from the Israeli component of the Survey of Health, Ageing and Retirement in Europe (SHARE-IL) (24-26), which includes self-reported

information about subjects' Holocaust experiences (e.g. see (27)). Applying our definition of exposure to the SHARE-IL data and comparing it with the self-report demonstrated high reliability of our definition: 93% overall agreement and Cohen's Kappa=0.72 including countries of the Union of Soviet Socialist Republics (Belarus, Estonia, Latvia, Lithuania, Moldova and Ukraine) and 94% agreement, Kappa= 0.75 excluding these countries.

Key Variables

Outcomes studied in this paper were all-cause and cause-specific mortality. The underlying causes of death that have occurred in the period 1960's - 1997 were categorized according to codes of International Classification of Diseases, Ninth Revision (ICD-9), and those that have occurred from 1998 onwards according to ICD-10 codes (28). Causes of deaths were categorized into the following groups: deaths due to all circulatory conditions (ICD-9 codes: 390–459; ICD-10 codes: I0–I99); of them, deaths specifically due to coronary heart disease [CHD] (ICD-9 codes: 410–414, 427.4, and 427.5; ICD-10 codes: I20–I25, I46, and I49); deaths due to all neoplasms (ICD-9: 140–239; ICD-10: C0–C99 and D0–D48); deaths due to unnatural causes (ICD-9: 80–99; ICD-10: S0–T88, V0–Y99); deaths due to all other known causes taken together; and a separate category for unknown cause of death.

The following variables were included in the analyses as covariates in addition to the main explanatory variable: sex (unless stated otherwise, all the analyses were performed separately in strata of men and women), a six-point socioeconomic position scale (SEP: from 1 = highest to 6 = lowest) based on men's occupation, and education level in years (0, 1–4, 5–8, 9–12, ≥13). For women, we were also able to control for their parity (reported number of children born before the first registration in the JPS cohort plus those born within the cohort [categorized as 1, 2-4, 5-9

and ≥10]), having any of the obstetric conditions (toxemia, heart disease, diabetes or pre-diabetes) (1, yes; 0, no), and average birthweight of a woman's offspring registered in the cohort in grams (categorized as <2500, 2500-2999, 3000-3499 and ≥3500). The values for SEP and education were copied from the record of a person's last offspring born in the cohort. Although some people could have later increased their achievements, it is reasonable to assume that these variables reflect well the participants' life-time social position.

Statistical Analysis

To investigate death hazards we employed survival analysis based on age scale. In the current study we faced a statistical issue of left truncation (also known as delayed entry). In particular, we have no information on Holocaust survivors who have died before the JPS cohort was initiated, January 1st 1964. Hence, the risk-set correction method (29) is adopted, where at any age t, the risk set consists of those observations that were ascertained before age t and were right censored or died after age t. For an unbiased comparison between the exposed and unexposed survival distributions, it is assumed that the minimal recruitment ages in the two groups are similar (29). This assumption is verified in Web Table 2.

Cox proportional hazards regression models were used to assess the association between exposure to the Holocaust and all-cause and cause-specific mortality, controlling for educational level and SEP. A separate Cox model with a multiplicative interaction term (exposure times sex) was fitted to the pooled sample of women and men to formally test whether difference in male and female all-cause mortality is statistically significant. Cox models that also controlled for obstetric conditions (toxemia, heart disease, diabetes or pre-diabetes), parity and the offspring's birthweight were fitted to the subsample of women. Tests of statistical significance were two

sided and we report hazard ratios (HR) and 95% confidence intervals (CI) obtained from the Cox regressions. The models' goodness of fit was evaluated and confirmed graphically using plots of Cox-Snell residuals (29), as well as numerically, using Gronnesby and Borgan test (30). Finally, we examined the proportional hazards assumption using Grambsch and Therneau test (31), as well as -log(-log (S(t))) against log(t) plot, and did not find evidence for time-dependency in the reported results.

Data on education were missing for 4% of women and 3% of men and the obstetric data were missing for a slightly higher percentage of women (12%). Individuals with the missing information were excluded from the analyses. The analyses were repeated also using multiple imputation by chained equations (MICE) algorithm and yielded similar estimates. Analyses were performed in Stata 12 (Stata Corporation, College Station, TX).

RESULTS

Descriptive statistics

Table 1 shows that at the (country-specific) time when the Holocaust persecutions began, most of the survivors were young children or teenagers, and male survivors were older than female. SEP was slightly lower among the Holocaust survivors, as was the number of years of education. In women, obstetric conditions, parity and offspring's birthweight were roughly similar among the exposed and unexposed.

Table 2 shows that during the time of follow up (i.e. from the 1st offspring registered in the JPS until December 31st 2016) women contributed 471,316 person-years of observation, and 2,270 (22%) of them have died. Men contributed 539,876 person-years, and 4,665 (37%) of them have died. For those, who died the mean age at death was 69 years old for women and 71 for men.

All-cause mortality rate per 1,000 person-years was 4.8 in women and 8.6 in men. With the exception of mortality due to unnatural causes, for both sexes all-cause and cause-specific mortality rates were higher among the Holocaust survivors as compared to the unexposed (Table 3).

The leading cause of death for both women and men was cancer (Table 4), however while 43% of the deceased women died due to cancer, in men this percentage was lower (29%). Except for the 2 composite categories (any other known cause of death and unknown cause), the second largest cause of death among both sexes was circulatory disorders, yet while among women it was the cause of 14% of the deaths, among men this cause accounted for a higher percentage of the deaths (22%).

Cox proportional hazards models

Table 4 shows that after controlling for the sociodemographic variables, exposure to the Holocaust was associated with a significant increase of all-cause mortality in women yet had no relationship to male all-cause mortality. Specifically, compared with unexposed women, the HR for the female Holocaust survivors was 1.15 (CI: 1.05, 1.27). The differential association between the exposure to the Holocaust and survival in men and women was formally examined

using a multiplicative interaction term (i.e. Holocaust exposure times sex) and yielded significant results ($P_{interaction} = 0.028$).

In the female subsample, we also fitted a model (Web Table 3) that controlled for perinatal and obstetrical characteristics at baseline as well as for socioeconomic variables. This further adjustment attenuated only slightly the effect of exposure on the all-cause mortality produced by the model in Table 4 (HR = 1.12; CI: 1.01, 1.24).

Next, we examined relationships between the Holocaust and specific causes of death (Table 4). In women excess risk was found only for mortality due to cancer (HR=1.17; CI: 1.01, 1.35). This risk somewhat decreased after the model was further adjusted also for perinatal and obstetric conditions (HR=1.12, CI: 0.95, 1.31) (Web Table 3). In men, among Holocaust survivors we observed statistically significant excess in mortality due to CHD (HR=1.39; CI: 1.09, 1.77) and cancer (HR=1.14; CI: 1.01, 1.28) compared with non-exposed men. Mortality due to "any other known cause" was significantly lower in male Holocaust survivors as compared to the unexposed (HR=0.86, CI: 0.75, 0.99). To further investigate this observed relationship, we broke down this composite category into 7 subcomponents of diseases based on ICD-10 codes and analysed each of them separately. This analysis did not yield HRs significantly different from 1 in any one of the 7 categories (Web Tables 4 and 5), probably due to small number of observations in each of the categories.

We conducted several sensitivity analyses that all produced similar results. First, models were fitted using 1939 as the year the Holocaust has begun instead of the country-specific years. Additional models were run in a sample that also included the immigrants from the Union of Soviet Socialist Republics. In a further analysis we used a sample that excluded the Israeli-born

group and ran Cox models with and without control for participants' age at immigration. Finally, we conducted an analysis, where instead of counting time from own birth and correcting for the left truncation, we counted time from the moment a participant entered the study while controlling for her or his age at that moment.

DISCUSSION

Strikingly, our findings show that in persons, who have sired/gave birth to children in their midlife, the exposure to the Nazi regime early-in-life was associated with excess of all-cause and cause-specific mortality later in life. Differences in mortality rates were also found by survivors' sex. Overall, compared to women who were not exposed to the Holocaust, women survivors exhibited higher all-cause mortality rates. Furthermore, in survivors of both sexes we detected statistically significant excess in mortality due to cancer, and in the exposed men also due to CHD. It is noteworthy that in men, death due to other known causes combined was the 2nd largest category accounting for almost one-quarter (24%) of deaths. Since in this category mortality rate among male survivors was significantly lower than among the unexposed, it likely explains why there was no significant excess in the all-cause mortality in male survivors, even though mortality risks due to cancer and CHD were significantly increased.

These results have several implications. First, they differ from other studies on mortality among Holocaust survivors in Israel. As was noted above, previous research did not find excess all-cause mortality among the Holocaust survivors (13, 15-19). Our analyses point out to the importance of considering specific causes of deaths. Indeed, although in the male subsample there was no excess in all-cause mortality rate among Holocaust survivors, when broken down into specific causes of death, it appeared that the survivors were in fact affected by higher

mortality rates due to some, but not other causes. In addition, some studies that did not find excess in all-cause mortality among the survivors, studied only those who lived long enough (e.g. conducting interviews in late 1990's or 2000's), or used relatively late mortality data (i.e. only records from the late 1980's onwards, e.g. (16, 17, 19)). However, many frail survivors might have died much earlier. Instead, our mortality data spanned several decades.

The excess mortality due to cancer and CHD is in line with the recent research that showed higher prevalence of cancer (7, 9, 32, 33) as well as of cardiovascular morbidity and associated risk factors (8, 12, 14, 33, 34) among Holocaust survivors. Several mechanisms have been proposed to explain the survivors' vulnerability to these ailments. Apart from studies that found detrimental health effects of undernutrition around birth (3-6, 9), others have suggested that the abrupt increase in amount of caloric intake upon arrival in Israel might be responsible for late-life morbidities (34). Furthermore, acutely stressful events were also shown to affect cancer and cardiovascular morbidity by distressing various physiological systems, such as the hypothalamic-pituitary-adrenal axis or the immune systems (7, 12, 14, 28). Additionally, researchers pointed at the exposure of survivors to such carcinogens as infectious diseases (e.g. hepatitis) (7) or toxic waste (33).

Second, it is important to note that in women survivors mortality due to other known causes of death combined was not higher than among the unexposed and in the exposed men it was even lower. Breaking the category "other known causes of death" down into its separate components yielded non-significant results in both sexes. Although this lack of findings might be attributed to the small number of subjects who died due to these causes, previous research has suggested that the lack of excess in all-cause mortality might hint at survivors' resilience (e.g. (18)). Indeed, a theoretical model has suggested that Holocaust survivors can be characterized by general health

resilience combined with specific vulnerabilities (15, 20). Thus, although the vulnerabilities to cancer and CHD had persisted throughout the survivors' lives, they had not necessarily precluded the possibility of a normal life after the trauma.

Third, we note the aforementioned differences in mortality patterns by sex. It should be kept in mind though that on average our female survivors were younger than the male. This dissimilarity in the age structure could explain some of the observed sex differences in mortality patterns, both by differential timing of exposure to the Holocaust as well as by differential risks for CHD mortality by age and sex (35). It is therefore possible that a future follow up in this population might show an increased CHD mortality also in women.

Several limitations of this study should be mentioned. One shortage was the inability to adjust for risky health behaviors (e.g. diet or sedentary lifestyle) or psychological variables (e.g. personality characteristics or mental health). In addition, some scholars claimed that the ecological definition of a Holocaust survivor used in this paper might be inferior to respondents' self-report or to using Israeli state codes that designate survivors, because it does not provide adequate details on individual exposure (e.g. (7)). However, authors who mainly relied on the Israeli codes admit that their exposure definition, too, might be subject to some misclassification (7, 8). Furthermore, researchers who used self-report, suggest that their 'unexposed' participants were in fact persecuted due to residing as Jews in the Nazi-occupied countries (13). Finally, we found a substantial degree of agreement between our definition and the self-report in SHARE-IL dataset.

A further limitation was the lack of information on Holocaust survivors not included in the cohort. To account for the lack of records on survivors who died before the study was initiated, we corrected the risk-set for left truncation (29). Nevertheless, the absence of information about

survivors who immigrated elsewhere or did not have children might affect the generalizability of our results. While country of immigration might affect adaptation and thus mortality, a meta-analysis found no difference between elderly survivors living in Israel and those living elsewhere with respect to physical health (36). In addition, individuals without offspring might on average have worse health and shorter life span due to both, a causal effect (e.g. social support from the children in the old age) and/or selection (e.g. not having children due to health reasons). Based on these considerations we believe that while settling in Jerusalem possibly did not affect mortality, the absence of data on those without offspring might lead to underestimation of the survivors' mortality rates.

Our study has several strengths. This is one of the rare works to evaluate cause-specific mortality in Holocaust survivors. Our high-quality data span the period from 1960's to 2016 thus allowing estimation of mortality during 4-5 decades. The rich dataset also enabled us to control for several important covariates collected between 1964 and 1976, such as education and SEP, and in women also for perinatal and obstetrical characteristics.

In summary, this study contributes to understanding consequences of extreme adversity early-in-life for long-term mortality among parous Holocaust survivors. Our results suggest that sex-specific intervention strategies may be warranted to treat and prevent cancer and cardiovascular ailments in Holocaust survivors. Besides, our findings are relevant for understanding and predicting life-course mortality of survivors in more-recent genocides for whom less long-term data are currently available (9).

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Table 1. Sample Characteristics, by Sex and Exposure Status, Jerusalem Perinatal Study, Israel, 1964–1976

	Women				Men			
	Unexposed		Holocaust survivor		Unexposed		Holocaust survivor	
Characteristics	N	%	N	%	N	%	N	%
Age at exposure (in years)[a]								
Unexposed	8,077	100			9,552	100		
Newborn, <1			873	40.9			774	26.6
Child, 1-12			1,172	54.9			1,652	56.8
Adolescent, 13-19			88	4.1			421	14.5
Adult, 20+			0	0			62	2.1
Total	8,077	100	2,133	100	9,552	100	2,909	100
SEP[b]								
Low	661	8.2	212	9.9	821	8.6	304	10.5
Middle	2,932	36.3	770	36.1	3,548	37.1	1,029	35.4
High	4,484	55.5	1,151	54.0	5,183	54.3	1,576	54.2
Total	8,077	100	2,133	100	9,552	100	2,909	100
Own years of education								
0	29	0.4	10	0.5	18	0.2	5	0.2
1-4	33	0.4	22	1.0	15	0.2	16	0.6
5-8	1,060	13.1	277	13.0	728	7.6	274	9.4
9-12	2,553	31.6	725	34.0	3,038	31.8	903	31.0
13+	4,136	51.2	997	46.7	5,469	57.3	1,600	55.0
Unknown	266	3.3	102	4.8	284	3.0	111	3.8
Total	8,077	100	2,133	100	9,552	100	2,909	100
Ever diagnosed with an obstetric condition[c]								
No	6,690	82.8	1,802	84.5				
Yes	416	5.2	104	4.9				
Unknown	971	12.0	227	10.6				
Total	8,077	100	2,133	100				
N of live births								
1	954	11.8	254	11.9				
2-4	5,586	69.2	1,454	68.2				
5-9	1,334	16.5	346	16.2				
10+	190	2.4	75	3.5				
Unknown	13	0.2	4	0.2				

Total	8,077	100	2,133	100
Average offspring's birthweight (in grams)				
<2500	406	5.0	119	5.6
2500-2999	1,518	18.8	392	18.4
3000-3499	3,599	44.6	907	42.5
3500-3999	2,075	25.7	551	25.8
4000+	449	5.6	149	7.0
Unknown	30	0.4	15	0.7
Total	8,077	100	2,133	100

SEP – Socioeconomic position

[a] At the beginning of Nazi persecutions (country-specific year)

[b] By husband's occupation for women and own occupational status for men

[c] Toxemia, heart disease, diabetes or pre-diabetes

Table 2. Age and Follow-up Time by Sex, Jerusalem Perinatal Study, Israel, 1964–1976

	Women		Men	
Variable	N	Mean (SD)	N	Mean (SD)
Age (in years) at death or end of follow up	10,210	75.4 (8.0)	12,461	75.4 (9.3)
Age (in years) at death (among those who died)	2,270	68.7 (12.3)	4,665	70.7 (12.3)
Person-years from birth of 1st offspring in the cohort until death or end of follow up	471,316		539,876	

SD – Standard deviation

Table 3. Number of Deaths, Percentage and Mortality Rates by Cause, Sex and Exposure to the Holocaust, Jerusalem Perinatal Study, Israel, 1964–1976[a]

	Women				Men			
	Unexposed		Holocaust survivor		Unexposed		Holocaust survivor	
Cause of death	Deaths	Rate[b]	Deaths	Rate[b]	Deaths	Rate[b]	Deaths	Rate[b]
CHD	58	0.2	27	0.3	220	0.5	105	0.9
All circulatory disorders[c]	223	0.6	95	1.0	703	1.7	309	2.5
Cancer	729	1.9	244	2.5	950	2.3	397	3.2
Unnatural causes	31	0.1	11	0.1	117	0.3	32	0.3
Any other known cause	341	0.9	123	1.3	815	2.0	313	2.6
Unknown cause	338	0.9	135	1.4	743	1.8	286	2.3
All-cause mortality	1,662	4.4	608	6.3	3,328	8.0	1,337	10.9

CHD – Coronary heart disease
[a] Causes of death updated through the end of 2015
[b] Rate (/1000 person-years)
[c] Including CHD

Table 4. All-Cause and Cause-Specific Mortality as Functions of Exposure to the Holocaust (Cox Models) and the Number of Deaths, Jerusalem Perinatal Study, Israel, 1964–1976, causes of death updated through the end of 2015

Causes of death	Women[a] (*n* = 9,842 observations)				Men[a] (*n* = 12,066 observations)			
	Deaths	% of deaths	HR	95% CI	Deaths	% of deaths	HR	95% CI
All-cause mortality	2,137	100.0	1.15	1.05, 1.27	4,448	100.0	1.02	0.95, 1.09
Specific causes								
CHD	77	3.6	1.28	0.78, 2.12	306	6.9	1.39	1.09, 1.77
All circulatory disorders[b]	298	13.9	1.22	0.94, 1.57	960	21.6	1.12	0.97, 1.29
Cancer	930	43.5	1.17	1.01, 1.35	1,282	28.8	1.14	1.01, 1.28
Unnatural causes	40	1.9	1.34	0.67, 2.70	141	3.2	0.77	0.51, 1.16
Any other known cause	425	19.9	1.06	0.85, 1.32	1,087	24.4	0.86	0.75, 0.99
Unknown cause	444	20.8	1.17	0.95, 1.45	978	22.0	1.00	0.87, 1.15

CHD – Coronary heart disease
CI – Confidence Interval
HR – Hazard Ratio
[a] The models are adjusted for participants' education and SEP
[b] Including CHD

Figure 1. Description of study populations

Jerusalem Perinatal Study, Israel, 1964–1976