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Health Status of Vietnam Veterans

III. Reproductive Outcomes and Child Health

The Centers for Disease Control Vietnam Experience Study

The Vietnam Experience Study was a multidimensional assessment of the health of Vietnam veterans. From a random sample of enlisted men who entered the US Army from 1965 through 1971, 7924 Vietnam and 7364 non-Vietnam veterans participated in a telephone interview; a random subsample of 2490 Vietnam and 1972 non-Vietnam veterans also underwent a comprehensive medical examination. During the telephone interview, Vietnam veterans reported more adverse reproductive and child health outcomes than did non-Vietnam veterans. However, children of Vietnam veterans were not more likely to have birth defects recorded on hospital birth records than were children of non-Vietnam veterans. The rates of total, major, minor, and suspected defects were similar among children of Vietnam and non-Vietnam veterans (odds ratios, 1.0, 1.1, 1.0, and 0.9, respectively). These results are consistent with the findings of three epidemiologic studies conducted since 1981 on the relationship of Vietnam service and birth defects in children of male veterans.

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THE CENTERS for Disease Control has undertaken a congressionally mandated health study of Vietnam veterans called the Vietnam Experience Study (VES). In the VES, the health of a sample of male US Army Vietnam veterans was compared with that of a similar group of Vietnam-era veterans who served elsewhere. This is the third of three reports in this issue of THE JOURNAL summarizing the results of the VES. In it, we present data on reproductive outcomes and child health, including adverse pregnancy outcomes, birth defects, major childhood health problems, cancer, and mortality. The first report[1] focuses on the psychosocial characteristics of the veterans after discharge from the army and the second report[2] describes their physical health.

See also pp 2701 and 2708.

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SUBJECTS AND METHODS

Data Collection and Study Participants

In the VES, we identified a random sample of men who met certain eligibility criteria based on data from military records, traced them to their present locations, conducted telephone interviews, and invited a random sample of interviewees to participate in an extensive physical, laboratory, psychological, and neuropsychological examination. Subject selection, participation rates, and comparability of the study cohorts are described in the first article.[1]

Two sources of data were used to examine reproductive outcomes and child health: reports by veterans during the telephone interview and hospital birth records of selected veterans' children. During the telephone interview, veterans were asked questions about their offspring covering the following areas: (1) pregnancies that ended early, including miscarriages, induced abortions, and tubal pregnancies; (2) date of birth, sex of child, and status for all births (live birth or stillbirth); (3) types of birth defects; (4) types of major health problems or impairments occurring in the first five years of life; (5) leukemia or other type of cancer; and (6) infant and child mortality. The 15 288 veterans who completed the telephone interview reported fathering 28 724 pregnancies, 24 698 of which resulted in a birth (Table 1). Reported pregnancies that were conceived before the veteran was assigned to Vietnam or another duty location are not included in Table 1 or in the analyses presented herein.

An interim analysis of preliminary VES interview data showed differences in the rates of total birth defects and cerebrospinal malformations (CSMs) (anencephaly, spina bifida, and hydrocephalus) between children of Vietnam and non-Vietnam veterans. As a result of these findings, two substudies were added to the VES at the time of the interim analysis. The objective of the main substudy was to compare the rates of total birth defects recorded on hospital birth records for children of Vietnam and non-Vietnam veterans to verify the reported cohort differences found in the interview data. All veterans whose medical examinations were scheduled from Jan 1, 1986, to Sept 30, 1986, were asked to participate in this substudy. The interview results were not used in selecting veterans or offspring. In addi-

Table 1.—Numbers of Veterans, Eligible Pregnancies and Births, and Birth Records Received

Population	Vietnam	Non-Vietnam	Total
Interview Study			
No. of veterans	7924	7364	15288
No. of eligible pregnancies	16009	13715	28724
No. of eligible births	12780	11910	24698
No. of eligible live births	12650	11777	24436
Birth Defects Substudy			
No. of veterans	1237	1045	2282
No. of eligible births	1945	1738	3683
No. of birth records received	1791	1575	3366
Cerebrospinal Malformations Substudy			
No. of eligible births	154	140	294
No. of birth records received	127	94	221

tion to studying total birth defects, we used this population to examine other outcomes, such as birth weight.

Of the 4462 veterans who participated in both the interview and the medical examination components of the VES, 2282 were examined after Jan 1, 1986, and were asked to give detailed birth and hospital information for each of their children (live born and stillborn) so that birth records could be obtained. The 2282 veterans reported a total of 4122 offspring (Table 1). We tried to obtain birth records for all reported offspring to confirm reported birth dates and determine eligibility for inclusion in the final substudy population. Of the 4122 reported offspring, 381 were conceived before the veterans' assignments to Vietnam or other primary duty locations, 41 were 18 years of age or older at the time of record retrieval (veterans' adult children were considered ineligible), six were not the biologic children of the veterans, and 11 were miscarriages (birth weight, <500 g). When these ineligible offspring were omitted, the population for the main substudy of total birth defects was 3683 (1945 offspring of Vietnam veterans and 1738 offspring of non-Vietnam veterans).

In a second substudy, hospital birth records were sought for a small, select group of offspring with possible CSMs. Eligible offspring for this substudy were obtained from the entire VES interview population. Birth records for three types of children were sought: those with a reported CSM, so stated by the veteran; those with a reported condition that suggested a possible CSM; and all children reported as stillborn. These children were selected in an attempt to identify all CSM cases in the offspring of interviewed veterans and to verify those cases by using hospital birth records.

Of the children reported during the interview, 403 met one of the three criteria listed above for inclusion in the CSM substudy. Veterans were recontacted by telephone and asked for additional birth and hospital information about these children so that records could be obtained. Of the 403 reported children, 58 were conceived before the veterans' assignments to Vietnam or other primary duty locations and 51 were miscarriages (birth weight, <500 g), resulting in an eligible group of 294 potential CSM cases (Table 1).

For both substudies, hospitals were asked to send a copy of the child's entire medical record, covering the birth and associated hospital stay. Medical records were abstracted by a team of nurses and physicians, and the quality of the abstraction process was closely monitored throughout the study. To minimize bias, staff members who obtained and abstracted medical records were blinded to the military history status of all veterans.

Hospital birth records were obtained for more than 91% of the 3683 births that were eligible for inclusion in the main substudy of total birth defects (Table 1). Among offspring of Vietnam veterans, 1791 birth records (92.1%) were obtained; among offspring of non-Vietnam veterans, 1575 birth records (90.6%) were obtained.

In the substudy of potential CSM cases, the success rates for retrieving hospital records varied considerably by cohort status (Table 1); records were obtained for 127 eligible children of Vietnam veterans (82.5%) and for 94 eligible children of non-Vietnam veterans (67.1%). Non-Vietnam veterans were more difficult to locate and contact and much more likely to refuse participation than were Vietnam veterans.

Definitions of Birth Defects

For all analyses, a birth defect was defined as a condition that was coded within the range of 740.0 to 759.9 of the ninth revision of the *International Classification of Diseases*.[3] In addition, we classified the birth defects documented on hospital records as major or minor, using the general method of Erickson et al.[4] A third class, suspected defects, was used when a defect was described in the record as "suspected" or "rule out" but was not otherwise confirmed by available records. Details of this classification system are presented elsewhere.[5]

Analysis

Crude rates of outcomes among veterans' offspring were computed. The denominator of the rates varied, depending on the outcome; total pregnancies, total births, and live births were the denominators most often used. The primary measure used to assess the association of the Vietnam experience with reproductive outcomes was the odds ratio (OR). The precision of the OR estimate was evaluated by computing 95% confidence intervals (CI). Odds ratios were adjusted simultaneously for the following veteran characteristics by using multiple logistic regression methods[6]: age of the veteran at the birth of the child (or at the time of the adverse pregnancy outcome), race, year of entry into the army, enlistment status, general technical aptitude test score, primary military occupational specialty, and number of years between enlistment and the birth of the child (or the time of the adverse pregnancy outcome). Two additional covariates were included in analyses of record-based outcomes: maternal age and gravidity. Interactions between Vietnam service and each of the covariates were assessed.[7] If an interaction was found, a standardized OR was computed by using the covariate distribution of both cohorts combined.[8,9]

Since many veterans reported more than one pregnancy or child, we had to evaluate the possible impact of correlation among offspring within a family. We compared the results of the standard logistic regression method with results of a modified logistic method that accounted for correlation among the offspring.[5,10] These comparisons indicated that intrafamily correlation had virtually no effect on our estimates of the regression coefficients or their SEs; consequently, standard logistic regression techniques are presented herein.

RESULTS

Birth Defects

During the telephone interview, Vietnam veterans reported significantly more birth defects in their children than did non-Vietnam veterans; the

Table 2.—Birth Defects Reported in the Interview Study Among Children of Vietnam and Non-Vietnam Veterans

Organ System (ICD-9 Codes*)	Children of Veterans: Vietnam (N=12 788) Rate†	Vietnam No.	Non-Vietnam (N=11 910) Rate†	Non-Vietnam No.	Odds Ratio‡	95% Confidence Interval
Total anomalies (740-759)	64 6	826	49 6	590	1.3	1 2-1.4
Nervous (740-742)	2 6	33	1.1	13	2.3	1.2-4.5
Anencephaly (740.0)	0.2	3	0 0	0		
Spina bifida (741.0-741.9)	0.7	9	0.4	5	1.7§	0.6-5.0
Hydrocephalus (742.3)	0.9	11	0.2	2	5.1§	1.1-23.1
Eye (743)	1.6	20	1.1	13	1.3	0.7-2.8
Ear, face, and neck (744)	2.9	37	1.9	22	1.6	0 9-2 8
Circulatory (745-747)	6.7	86	6 1	73	1 1	0.8 1.6
Respiratory (748)	1.2	15	0.8	10	1.5	0.6-3.5
Digestive (749-751)	8.4	108	6.8	81	1.2	0.9-1.6
Genital (752)	2.7	35	2.3	27	1.3	0 8-2.2
Urinary (753)	3.6	46	2.4	28	1.4	0.9-2.3
Musculoskeletal (754-756)	33.3	426	25 9	309	1 2	1.1-1 5
Integument (757)	3 2	41	1.4	17	2.2	1.2-4.0
Chromosomal (758)	0.8	10	1.0	12	0.8§	0.3-1.8
Other unspecified (759)	1.6	20	0.8	10	1.7	0 8-3.9

*ICD-9 indicates *International Classification of Diseases—Ninth Edition;* the range of codes includes all the fourth digit codes contained within that range.
†Crude rates per 1000 total births.
‡Adjusted for veterans age at birth, race, year of entry into the army, enlistment status, general technical test score, primary military occupational specialty, and number of years between entry and birth.
§Crude odds ratio presented because the number of cases is not sufficient for multivariate modeling.

Table 3.—Birth Defects Noted on Hospital Birth Records Among Children of Vietnam and Non-Vietnam Veterans

Type of Defect	Children of Veterans: Vietnam (N=1791) Rate*	Vietnam No.	Non-Vietnam (N=1575) Rate*	Non-Vietnam No.	Odds Ratio†	95% Confidence Interval
Major	28.5	51	23.5	37	1.1	0.7-1.8
Minor	32.4	58	34 3	54	1.0	0.7-1.5
Suspected	11 7	21	13.3	21	0.9	0.5-1.7
Total	**72.6**	**130**	**71.1**	**112**	1.0	0 8-1.4

*Crude rates per 1000 total births.
†Adjusted for veterans age at birth, race, year of entry into the army, enlistment status, general technical test score, primary military occupational specialty, years between entry and birth, maternal age, and gravidity.

rates for each cohort are 64.6 and 49.5 per 1000 total births, respectively, and the adjusted OR is 1.3 (95% CI, 1.2 to 1.4) (Table 2). The excess is present for virtually every major organ system and does not seem to be explained by a single type (or category) of defect. The ORs for nervous system anomalies, hydrocephalus, anomalies of the integument, and musculoskeletal deformities are significantly greater than 1.0. While there was a positive association between Vietnam service and reported birth defects among children of both white and black veterans (adjusted ORs, 1.3 and 1.2, respectively), the reverse was true for children of Hispanic veterans and veterans of other races (OR = 0.7).

In the main substudy, the rates of total birth defects recorded on hospital birth records were similar in the two cohorts. As shown in Table 3, the crude rates per 1000 total births are 72.6 and 71.1, respectively, and the adjusted OR is 1.0 (95% CI, 0.8 to 1.4). When defects were classified as major, minor, or suspected, the adjusted ORs are 1.1, 1.0, and 0.9, respectively.

An analysis of total, major, minor, and suspected defects stratified by race shows that ORs vary considerably.[5] The adjusted OR for total defects among offspring of black veterans is 3.3 (95% CI, 1.5 to 7.5) compared with 0.9 (95% CI, 0.7 to 1.3) for offspring of white veterans and 0.4 (95% CI, 0.2 to 1.3) for offspring of Hispanic veterans and veterans of other races. This variability in the OR also is present for major and minor defects. The OR is statistically significant for total and minor defects among offspring of black veterans.

We examined the types of abnormalities in black infants more closely.[5] No single type of major defect occurred more than once in either veteran group. None of the infants with major defects had identical anomalies or any patterns of multiple anomalies suggestive of a syndrome. Of the 13 infants of black Vietnam veterans with minor defects, four had polydactyly (two of whom were siblings) and two other siblings had supernumerary nipples. No other minor anomalies occurred more than once.

The analysis of potential CSM cases was done separately for stillbirths and live births in each cohort (Table 4). Among reported stillbirths, birth records documented five CSMs in offspring of Vietnam veterans and six in offspring of non-Vietnam veterans. Ten of these 11 cases had no report of a defect by the veteran during the interview. Among live-born offspring, birth records documented 21 CSMs in children of Vietnam veterans and six in children of non-Vietnam veterans. Because record retrieval rates varied considerably by cohort status and because negative responses were not verified, we did not calculate or compare rates of CSM cases in the two cohorts; the results are expressed as numbers of verified cases.

Low Birth Weight—Hospital Birth Records Substudy

Rates of low birth weight (<2500 g) were similar in offspring of Vietnam and non-Vietnam veterans (5.6% and 5.5%, respectively; adjusted OR = 1.1; 95% CI, 0.8 to 1.4). The mean birth weights of offspring of Vietnam and non-Vietnam veterans were 3366 g and 3370 g, respectively.

Other Pregnancy and Child Health Outcomes—Interview Study

Vietnam veterans were more likely to report having fathered a pregnancy that ended in a miscarriage than were non-Vietnam veterans (adjusted OR = 1.3; 95% CI, 1.2 to 1.4). This relative excess appeared regardless of the trimester in which the miscarriage was reported to have occurred, and the magnitude of the ORs varied little across trimesters. The other reproductive outcomes examined—pregnancies ending in an induced abortion, tubal pregnancies, and stillbirths—were no more likely to be reported by Vietnam veterans than by non-Vietnam veterans.[6]

Among children of Vietnam and non-Vietnam veterans, 25 and 17 cancers were reported, respectively (adjusted OR = 1.5; 95% CI, 0.8 to 2.8). When

Table 4.—Cerebrospinal Malformations Noted on Hospital Birth Records Among Children of Vietnam and Non-Vietnam Veterans

	All Stillbirths		Live Births With a Reported or Possible CSM*		Total	
	Vietnam	Non-Vietnam	Vietnam	Non-Vietnam	Vietnam	Non-Vietnam
No. reported in interview	99	114	55	26	154	140
No. of birth records received	78	74	49	20	127	94
CSM on record, No.						
Anencephaly	3	4	7	3	10	7
Spina bifida	1	0	8	2	9	2
Hydrocephalus	1	2	6	1	7	3
Total	5	6	21	6	26	12

*CSM indicates cerebrospinal malformation.

childhood cancers were examined by site, the preponderant type reported among both groups of veterans was leukemia, with 12 cases among children of Vietnam veterans and seven cases among children of non-Vietnam veterans (crude OR = 1.6; 95% CI, 0.6 to 4.1).

More than half of the reported childhood health problems were attributed to respiratory diseases (mostly asthma and pneumonia) and diseases of the ear (primarily otitis media). The adjusted OR for all reported conditions is 1.3 (95% CI, 1.2 to 1.4). For most disease categories, Vietnam veterans reported more health problems in their children than did non-Vietnam veterans.[5]

Analyses of reported infant mortality (the proportion of all live-born children who die before reaching their first birthday) and child mortality (the proportion of children surviving until 1 year of age who subsequently die) showed no appreciable differences between children of Vietnam and non-Vietnam veterans.[5]

Table 5.—Observed and Expected Numbers of Cerebrospinal Malformations Among Children of Vietnam and Non-Vietnam Veterans

	No. of Cerebrospinal Malformations			
	Vietnam		Non-Vietnam	
Cerebrospinal Malformation	Observed	Expected*	Observed	Expected*
Anencephaly	10	5.0-9.0	7	4.6-8.4
Spina bifida	9	7.2-12.2	2	6.7-11.4
Hydrocephalus	7	6.1-11.2	3	5.7-10.5
Total	26	18.3-32.4	12	17.0-30.3

*Expected numbers are based on total rates from the nationwide Birth Defects Monitoring Program (lower estimates) and race-specific rates from the Metropolitan Atlanta Congenital Defects Program (upper estimates).[14,15]

COMMENT

For most reproductive and child health outcomes studied, Vietnam veterans were more likely to report an adverse event than were non-Vietnam veterans. The exceptions to this pattern were induced abortions, tubal pregnancies, stillbirths, and mortality. The tendency to report more adverse events for their children is consistent with the Vietnam veterans' reporting more adverse events with regard to their own health status.[9,10] For the many reproductive and child health outcomes (other than birth defects) examined in the interview, verification on this large sample using objective data sources was not feasible. Consequently, the possibility of differential recall and/or reporting must be considered when interpreting the interview results.

For birth defects, a second source of information not subject to differential reporting was available for a subgroup of children who were included in the main birth records substudy. This substudy had 80% power to detect a relative risk of 1.4 for total birth defects in the subgroup of children for whom birth records were received. However, the substudy was not large enough to assess cohort differences for specific birth defects. For all races combined, there were no differences between children of Vietnam and non-Vietnam veterans in the prevalence of total, major, minor, or suspected birth defects documented in hospital birth records. This finding supports the explanation of differential reporting in the interview and the conclusion that (at least for birth defects evident at birth) children of Vietnam veterans were not at increased risk.

The reasons for the apparent racial variation in the association between Vietnam service and total birth defects found in the hospital records substudy are unclear. The findings in black offspring may be explained, in part, by the multiple occurrence of polydactyly and supernumerary nipples in two families; both have been suggested to have a strong genetic component, most likely autosomal dominant inheritance.[11] Also, the results are based on small numbers of offspring among black and Hispanic veterans and may be due to sampling variability.[5]

The veterans in the main substudy of total birth defects were selected from those veterans who completed the physical examination. Detailed analyses of the examination participants relative to the telephone interview participants did not show different characteristics or health histories.[12] In addition, participation in this substudy was high in both cohorts, and, moreover, the two cohorts were similar with respect to various demographic and military covariates.[5] Thus, there is no evidence of selection bias or participation bias in this substudy. Also, the selection of participants in this substudy was independent of interview reports and, consequently, was unlikely to be biased by potential differential reporting among the two veteran cohorts.

One limitation of these studies is the lack of data about the mothers of the children studied. Only limited maternal information (age and gravidity) was uniformly recorded in the hospital birth records. Other maternal behaviors and exposures, such as tobacco, alcohol, and drug use, may be important for a more complete assessment of the outcomes studied. However, given the similarity of sociodemographic and behavioral characteristics between the fathers in the two cohorts, it seems unlikely that maternal characteristics would differ greatly. While we have extensive information on paternal characteristics in

this study, little is known about the association of paternal behaviors or exposures and birth defects in their children.

The CSM substudy was designed to identify possible CSM cases, based on interview reports, and to verify them using birth records. No attempt was made to verify negative responses (ie, children with no reported CSM) because these defects are rare, occurring at a rate of only 1.4 to 2.5 per 1000 total births.[14,15] The total number of verified CSMs in the Vietnam cohort is similar to the number that would be expected in the interview population on the basis of rates of these defects from two US birth defect surveillance systems (Table 5).[14,15] In contrast, the number of record-based CSM cases among children of non-Vietnam veterans is much lower than would be expected. This suggests a deficit of ascertained CSMs among children of non-Vietnam veterans rather than an excess among children of Vietnam veterans. These data may reflect true differences between the cohorts or may be due to differences in the opportunity to identify and verify probable CSM cases. There is evidence to suggest the latter explanation, since selection of participants for this substudy was based on fathers' interview reports and, hence, was subject to differential reporting in the two cohorts. Also, there were appreciable differences in participation rates in this substudy: Vietnam veterans were much more likely to participate than were non-Vietnam veterans.[5]

Our results for total birth defects can be compared with three previous epidemiologic studies of Vietnam service and reproductive outcomes of male veterans. The first two, conducted by the Australian government[16] and the Centers for Disease Control,[4,17] were large case-control studies of children born with congenital malformations. In the first study,[16] defects were identified through hospital and cytogenetic laboratories; in the second,[4,17] through a population-based registry. The third study was a cohort follow-up study of air force personnel who conducted the defoliation missions in Vietnam and a comparison cohort of cargo-mission personnel who flew to Vietnam but were not involved in spraying operations.[18] Information about reproductive outcomes in this study was obtained mainly through spouse interviews. Both the Australian study and the Centers for Disease Control study showed no difference in the odds of Vietnam service among case and control fathers for all types of defects combined (ORs = 1.0 and 0.97, respectively). However, even these large-scale studies could not adequately address whether Vietnam veterans, or a subgroup of Vietnam veterans, were at increased risk of fathering babies with specific rare malformations. In the air force cohort follow-up study, there was a significant excess of total reported birth defects among children of personnel conducting the defoliation missions. This reported excess prompted the collection of birth and medical records for all children, an effort that is currently ongoing.

In summary, Vietnam veterans reported more adverse reproductive and child health outcomes in the telephone interview than did non-Vietnam veterans. However, results of a substudy of birth defects documented on hospital birth records showed that Vietnam veterans were not at increased risk of fathering children with birth defects evident at birth. These results are consistent with the findings of three epidemiologic studies conducted since 1981 on the relationship of Vietnam service and birth defects in children of male veterans.

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