

Prevalence of Birth Defects Among Infants of Gulf War Veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989–1993

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BACKGROUND: Epidemiologic studies of birth defects among infants of Gulf War veterans (GWV) have been limited to military hospitals, anomalies diagnosed among newborns, or self-reported data. This study was conducted to measure the prevalence of birth defects among infants of GWVs and nondeployed veterans (NDV) in states that conducted active case ascertainment of birth defects between 1989–93. **METHODS:** Military records of 684,645 GWVs and 1,587,102 NDVs were electronically linked with 2,314,908 birth certificates from Arizona, Hawaii, Iowa, and selected counties of Arkansas, California, and Georgia; 11,961 GWV infants and 33,052 NDV infants were identified. Of these, 450 infants had mothers who served in the Gulf War, and 3966 had NDV mothers. **RESULTS:** Infants conceived postwar to male GWVs had significantly higher prevalence of tricuspid valve insufficiency (relative risk [RR], 2.7; 95% confidence interval [CI], 1.1–6.6; $p = 0.039$) and aortic valve stenosis (RR, 6.0; 95% CI, 1.2–31.0; $p = 0.026$) compared to infants conceived postwar to NDV males. Among infants of male GWVs, aortic valve stenosis (RR, 16.3; 95% CI, 0.09–294; $p = 0.011$) and renal agenesis or hypoplasia (RR, 16.3; 95% CI, 0.09–294; $p = 0.011$) were significantly higher among infants conceived postwar than prewar. Hypospadias was significantly higher among infant sons conceived postwar to GWV women compared to NDV women (RR, 6.3; 95% CI, 1.5–26.3; $p = 0.015$). **CONCLUSION:** We observed a higher prevalence of tricuspid valve insufficiency, aortic valve stenosis, and renal agenesis or hypoplasia among infants conceived postwar to GWV men, and a higher prevalence of hypospadias among infants conceived postwar to female GWVs. We did not have the ability to determine if the excess was caused by inherited or environmental factors, or was due to chance because of myriad reasons, including multiple comparisons. Although the statistical power was sufficient to compare the combined birth defects prevalence, larger sample sizes were needed for less frequent individual component defects. *Birth Defects Research (Part A) 67:246–260, 2003.* Published 2003 Wiley-Liss, Inc.[†]

Key words: aortic valve stenosis; birth defects; Gulf War veterans; hypospadias; Persian Gulf War; renal agenesis or hypoplasia; tricuspid valve insufficiency; tricuspid valve regurgitation

INTRODUCTION

A 1994 report by the U.S. General Accounting Office identified that 21 reproductive toxicants and teratogenic agents were present in the Gulf War environment (United States General Accounting Office, 1994). The teratogenic effects of myriad exposures, including petroleum solutions, insecticides, arthropod-borne pathogens, sarin, mustard gas, prophylactic drugs such as pyridostigmine bromide, and other medications and vaccines administered to Gulf War veterans (GWV) are unclear (NIH, 1994). Concerns regarding adverse reproductive outcomes precipitated several investigations to measure the risk of birth defects among military progeny (Penman et al., 1996; Cowan et al., 1997; Araneta et al., 1997; Goss Gilroy Inc., 1998; Araneta et al., 2000; Kang et al., 2001). American and Canadian GWVs reported a higher prevalence of birth

defects among their infants compared to infants of nondeployed veterans (NDVs) (Goss Gilroy Inc., 1998; Kang et al.

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al., 2001); however, data were limited to self-reported diagnoses and were not validated against medical records. The remaining studies showed no differences in birth defects prevalence by parental deployment, but were limited to births occurring in military hospitals or small military units, or had small sample sizes. Further, the hospitalization studies were based on birth defects diagnosed at delivery, which accounts for just half of all birth defects (Hexter et al., 1990). Such studies did not include births in nonmilitary facilities, births to members of the U.S. Reserves, National Guard, or those who separated from the military.

Epidemiologic studies of maternal exposure to selected agents during gestation, as well as biological, behavioral and demographic factors have identified various teratogens (Trasler and Doerksen, 1999). The role of and mechanisms for male-mediated teratogenesis, however, requires further evaluation. Distinguishing the effect of paternal exposures from confounding variables, particularly related maternal risk factors remains a methodologic challenge in epidemiologic studies. Thus, it is important to consider paternal and maternal Gulf War exposures separately. The study by Kang et al. (2001) showed that male GWVs reported infants with "moderate to severe" birth defects at nearly twice the rate of infants of male NDVs, whereas female GWVs were almost 3 times as likely to have a child with "moderate to severe" birth defects than female NDVs. The study by Cowan et al. (1997) found a statistically significant increase in the risk of any birth defect for infants of female GWVs compared to female NDVs. After adjustment for marital status, ethnicity, and branch of service, however, there were no significant associations between Gulf War service and the risk of birth defects among infants of female GWVs.

Active case ascertainment of birth defects is carried out currently in 11 of the United States (Centers for Disease Control and Prevention, 2001) and was conducted in six states between 1989–93, the period immediately before and after the Gulf War. They included Arizona, Hawaii, Iowa, and selected counties of Arkansas, California, and Georgia (metropolitan Atlanta). Case ascertainment of birth defects is population based, and is conducted through the first year of life for infants born in Arizona, Hawaii, and Iowa, or whose mothers are residents of participating counties in Arkansas, California, and Georgia (Centers for Disease Control and Prevention, 2001).

The objectives of this investigation were to enumerate infants of military personnel born between January 1, 1989, and December 31, 1993 in Arizona, Iowa, Hawaii, and participating counties of Arkansas, California, and Georgia, and to compare the prevalence of selected congenital anomalies between 1) GWV and NDV infants conceived before the war, 2) GWV and NDV infants conceived during or after the war, and 3) GWV infants conceived before and after the war.

MATERIALS AND METHODS

Data Sources and Study Population

The Defense Manpower Data Center provided information on individuals who were in military service on February 1991, the peak of the Gulf War mobilization. The Defense Eligibility Enrollment Reporting System provided data on spouses and children. Birth certificate data were provided by state health departments of the six participating states, and included information on all live births,

including personal identifiers, demographic characteristics, and selected pregnancy-related information. Personal identifiers available on birth certificate tapes varied by state. All six states recorded infant's name and date of birth; mother's first name, maiden name, and date of birth; and father's last name and date of birth; five states recorded father's first name, and three states recorded parents' social security numbers.

The six birth defects surveillance programs provided birth defects data. Active case ascertainment is conducted for all major congenital anomalies, as defined by the CDC (Metler et al., 1993). Case ascertainment methods in each state have been previously described (Centers for Disease Control and Prevention, 2001). Birth defects diagnostic data were abstracted by trained staff of the surveillance programs from multiple sources, including hospital discharge indexes, medical records at military and nonmilitary hospitals, pediatric, surgery, and autopsy logs, outpatient facilities, physician reports, fetal diagnostic clinics, cytogenetic and molecular biology laboratories, genetic service and specialty clinics, and vital records (Lynberg et al., 1992; Centers for Disease Control and Prevention, 2001). Diagnostic data for birth defects, including specific written diagnoses, cytogenetic data, and a six-digit diagnostic code developed by the CDC for reportable congenital anomalies (Metler et al., 1993) are reported in the birth defects surveillance case record. The six-digit diagnostic code is a modification of the World Health Organization's International Classification of Diseases, 9th Revision, Clinical Modification, and the British Pediatric Association codes (Metler et al., 1993).

Statewide birth defects surveillance data were available for all live births in Hawaii from 1989–93, all Arizona births from 1989–92, all Iowa births from 1989–90, and two-thirds of Iowa's births from 1991–93. Birth defects surveillance data from 1989–93 were available from counties that participated in birth defects surveillance in Arkansas (26 counties in 1989; 14 counties from 1990–92; statewide in 1993), Georgia (Metropolitan Atlanta, 5 counties), and California (nonmilitary hospitals in 57 counties in 1989, 13 counties from 1990–93, including Los Angeles County from July 1990 to December 1993).

Linkage software (LinkPro, Manitoba, Canada), an integrated system for deterministic and probabilistic record linkage, was used to identify births common to the military data set and state birth certificate records (Wajda, 1992). Linkage of military and birth certificate files for five states was carried out at the Naval Health Research Center (NHRC), and the sixth at the Arkansas Department of Health, for Arkansas births, using identical software and matching algorithms.

The military data set was stratified by gender of the parent who served in the military to maximize identification of births to military personnel with multiple sex partners and to separate paternal from maternal GWV exposures. Infants whose biological parents both served in the military during the study period were categorized as infants of military mothers. Several matching algorithms were developed to maximize identification of matches and to compensate for missing or incomplete data, transpositional and typographical errors, and to accommodate changes in last name resulting from marriage or divorce. A pilot study was conducted to test the feasibility of the linkage process (Araneta et al., 2000a,b).

Infants with records common to the military and state birth certificate files were defined as "military infants." NHRC provided each state birth defects surveillance program with a data file of their state's military infants containing birth certificate and military data. The birth defects programs matched records of these "military infants" files against their birth defects surveillance data, by state birth certificate number or infant and maternal identifiers. State birth defects programs appended birth defects diagnoses codes to birth certificate information and military data. Personal identifiers of infants, parents and physicians were removed, and anonymous files were forwarded to NHRC for statistical analysis.

Statistical Analysis

There are approximately 850 diagnostic codes for reportable congenital anomalies (Metler et al., 1993) but CDC and other state birth defects surveillance programs routinely report on the prevalence of 46 birth defects categories that occur frequently or have important public health significance (Center for Disease Control, 2001). We selected these 46 birth defects categories for reporting, but excluded pulmonary artery anomalies, for which diagnostic echocardiography is currently required (C.A. Moore, Center for Disease Control, unpublished communication, 1998). Further, we included dextrocardia, chromosomal anomalies (other than trisomies 13, 18, and 21), and Goldenhar syndrome (oculoauriculovertebral complex), in response to concerns of GWV families (Araneta et al., 1997; Briggs, 1995; Sylvester and Changers, 1995). Pulmonary valve insufficiency, tricuspid valve insufficiency, and Ebstein anomaly are not reported in California; therefore, California births were excluded when computing prevalence for these birth defects categories. Similarly, data on fetal alcohol syndrome were not available from Arkansas. In 1992, surveillance in Arizona was limited to major structural defects; consequently, data on dextrocardia, other chromosomal anomalies, and Goldenhar syndrome were not available.

The prevalence of these 48 selected birth defects categories was calculated per 10,000 live births, and 95% confidence intervals (CIs) for rates were computed according to Fleiss (1981). Unadjusted prevalence rates are presented because adjustment for maternal age did not significantly alter prevalence rates. Each birth defect of case infants diagnosed with multiple anomalies (two or more of the 48 selected birth defects) was counted separately.

GWVs were defined according to military personnel data, and included those on active duty on February 1991 and were deployed to the Gulf War. NDVs were defined as those on active duty on February 1991, but were not deployed to the Gulf War. For GWV infants, date of birth, gestational age, and the military parent's date of deployment to and return from the Gulf War were used to estimate whether the conception occurred before or after the parent's service in the Gulf War. To estimate conception date, gestational age was subtracted from the infant's birth date. For example, for infants of male GWVs, gestational age was subtracted from infants' birth date to estimate the date of conception; live births conceived after the father returned from the war were defined as an "infant conceived postwar." Gestational age data were missing from the state birth certificate for 0.8% of infants; therefore, a gestational age of 38 weeks was assumed. Any births that occurred after a GWV mother was deployed, including conceptions that occurred or were gestating during de-

ployment, were defined as infants conceived postwar. Because the presence of U.S. military forces in the Persian Gulf was maximal by January 1, 1991, NDV infants conceived after this date were considered infants conceived postwar. Infants conceived prewar were defined as live births to GWV men who were conceived before the father's deployment; GWV infants who were born before their mothers were deployed; or NDV infants conceived before January 1, 1991.

Data were analyzed using Statistical Analysis Software (SAS Institute, Cary, NC). Chi-square, Student's *t*-test and nonparametric tests were used to characterize population differences. Chi-square and Fisher's exact (two-tailed) tests were used to compare the prevalence of birth defects temporally and among subpopulations (Mehta and Patel, 1983). The logit estimator with precision-based CI was used with zero frequencies, where 0.5 was added to each cell stratum (Kleinbaum et al., 1982; SAS Institute, 1990). Logistic regression models were used to adjust for covariates that differed among deployment groups and known risk factors for selected birth defects. Statistical significance was designated at $p < 0.05$ or 95% CI that excluded 1.

RESULTS

Population Characteristics

Linked data from 2,271,747 military personnel and 2,314,908 live births in the six states identified 45,013 infants who were born between 1989–93 to individuals who served in the military in February 1991. One fourth ($n = 11,961$ infants) were born to GWVs. An equal proportion of GWVs (27.4%) and NDVs (25.8%) separated from the military by December 1993.

Approximately 10% ($n = 4416$) of infants were born to women veterans. Of these, 450 (10%) infants had a GWV mother and 3966 infants had a NDV mother. Compared to female NDVs, GWV women were significantly younger, more likely to be black, unmarried, had fewer prenatal visits, served in the Army or Marine Corps, were members of the U.S. Reserves or National Guard and were less likely to be officers (Table 1). No differences were observed between GWV and NDV women with regards to infant's gender, proportion with low birth weight (<2500 gm) or preterm delivery (<37 weeks' gestation by ultrasound or physician's estimate), mean birth weight, paternal age, maternal education, parity, plurality, gestational weight gain, preeclampsia, prenatal smoking and prenatal alcohol.

The majority of infants ($n = 40,597$) were born to male veterans, including 11,511 (28%) infants with GWV fathers and 29,086 infants with NDV fathers. Infant's gender and proportion with low birth weight or preterm delivery did not differ by paternal deployment status. Infants of GWV men had lower mean birth weight, had younger parents, and were more likely to have a mother who was black or Hispanic, had a high school education or less, was unmarried, had fewer prior pregnancies, had a singleton birth (for the current pregnancy), fewer prenatal visits, and lower gestational weight gain (Table 2). The frequency of preeclampsia, and exposure to prenatal smoking and prenatal alcohol did not differ among infants of GWV and NDV men. Infants of male GWVs were more likely to have a father who served in the Marine Corps, were either active-duty military personnel or members of the National Guard during the war, and were enlisted personnel.

Table 1

Demographic and Parental Characteristics of Infants Born in Arizona, Arkansas, California, Georgia, Hawaii, and Iowa to Female Military Personnel, by Gulf War Status

Characteristic	GWV (%)	NDV (%)
Total	450	3,966
State of birth		
Arizona	53 (11.8)	455 (11.5)
Arkansas	19 (4.2)	140 (3.5)
California	82 (18.2)	734 (18.5)
Georgia	69 (15.3)	315 (7.9) ^a
Hawaii	202 (44.9)	2,277 (57.4) ^a
Iowa	25 (5.6)	45 (1.1) ^a
Infant's gender		
Male	221 (48.1)	1,989 (50.1)
Female	229 (50.9)	1,977 (49.9)
Year of Birth		
1989	93 (20.7)	747 (18.8)
1990	48 (10.7)	726 (18.3) ^a
1991	45 (10.0)	815 (20.5) ^a
1992	140 (31.1)	950 (24.0) ^a
1993	124 (27.5)	728 (18.4) ^a
Mean birth weight (gm)	3,351.0	3,341.2
Low birth weight (< 2,500 gm)	28 (6.2)	270 (6.8)
Preterm (< 37 weeks)	39 (8.7)	364 (9.3)
Mean maternal age (years)	25.3	25.9 ^a
Maternal age (years)		
≤ 19	12 (2.7)	135 (3.4)
20–24	215 (47.9)	1,682 (42.4) ^a
25–29	143 (31.8)	1,285 (32.4)
30–34	63 (14.0)	604 (15.2)
≥ 35	16 (3.6)	259 (6.5) ^a
Mean paternal age (years)	27.2	27.5
Maternal Race		
White	228 (50.7)	2,368 (59.7) ^a
Black	173 (38.4)	1,236 (31.2) ^a
Hispanic	25 (5.6)	163 (4.1)
Asian/Pacific Islander	18 (4.0)	163 (4.1)
Other	6 (1.3)	36 (0.9)
Maternal Education		
≤ High school	246 (55.2)	2,102 (53.4)
> High school	200 (44.8)	1,838 (46.6)
Maternal marital status		
Married	305 (71.8)	2,886 (77.2) ^a
Not married	120 (28.2)	853 (22.8)
Parity (mean)	0.58	0.58
Multiple birth (yes)	7 (1.6)	98 (2.5)
Prenatal visits (mean)	11.2	11.7 ^a
Weight gained (lbs)	30.8	31.8
Preeclampsia (yes)	12 (3.1)	129 (3.5)
Smoking (yes)	32 (7.2)	348 (8.9)
Alcohol (yes)	5 (1.4)	47 (1.5)
Branch of Service		
Army	288 (64.0)	1,389 (35.0) ^a
Navy	77 (17.1)	1,501 (37.9)
Marine Corps	50 (11.1)	198 (5.0) ^a
Air Force	35 (7.8)	878 (22.1)
Component		
Active Duty	342 (76.0)	3,476 (87.6) ^a
Reservist	70 (15.6)	455 (11.5) ^a
National Guard	38 (8.4)	35 (0.9) ^a
Paygrade		
E1–E6 Enlisted	401 (90.9)	3,469 (87.5)
E7–E9 Staff Enlisted	5 (1.1)	61 (1.5)
01–010 Officers	35 (7.9)	436 (11.0) ^a

Arizona births from 1989–1992 only.

^a*p* < 0.05 or 95% CI exclude 1.

GWV, Gulf War veteran; NDV, nondeployed veteran.

Table 2

Demographic and Parental Characteristics of Infants Born in Arizona, Arkansas, California, Georgia, Hawaii, and Iowa to Male Gulf War and Nondeployed Veterans

Characteristic	GWV (%)	NDV (%)
Total	11,511	29,086
State of birth		
Arizona	1,917 (16.7)	4,817 (16.5)
Arkansas	905 (7.9)	1,852 (6.4) ^a
California	3,546 (30.8)	8,517 (29.3) ^a
Georgia	1,007 (8.7)	1,747 (6.0) ^a
Hawaii	3,515 (30.5)	11,188 (38.5) ^a
Iowa	621 (5.4)	965 (3.3) ^a
Infant's gender		
Male	5,903 (51.3)	14,819 (50.9)
Female	5,608 (48.7)	14,267 (49.1)
Year of birth		
1989	3,337 (29.0)	8,359 (28.7)
1990	1,968 (17.0)	5,477 (18.8) ^a
1991	1,659 (14.4)	5,765 (19.8) ^a
1992	2,603 (22.6)	5,439 (18.7) ^a
1993	1,944 (16.9)	4,046 (13.9) ^a
Mean birth weight (gm)	3,367.1	3,388.9 ^a
Low birth weight (< 2,500 gm)	680 (5.9)	1,728 (5.9)
Preterm (< 37 weeks)	966 (8.4)	2,454 (8.4)
Mean maternal age (years)	25.3	26.0 ^a
Maternal age (years)		
≤ 19	1,118 (9.7)	2,214 (7.6)
20–24	4,529 (39.4)	9,955 (34.2) ^a
25–29	3,613 (31.4)	9,968 (34.2) ^a
30–34	1,748 (15.2)	5,233 (18.0) ^a
≥ 35	499 (4.3)	1,704 (5.9) ^a
Mean paternal age (years)	26.6	27.5 ^a
Maternal Race		
White	6,764 (58.8)	18,186 (62.5) ^a
Black	1,964 (17.1)	4,293 (14.8) ^a
Hispanic	1,054 (9.1)	2,078 (7.1) ^a
Asian/Pacific Islander	1,631 (14.2)	4,290 (14.8)
Other	98 (0.8)	239 (0.8)
Maternal education		
≤ High school	6,365 (55.7)	14,400 (51.2) ^a
> High school	5,068 (44.3)	13,709 (48.8)
Maternal marital status		
Married	10,245 (89.9)	26,906 (93.2) ^a
Not married	1,150 (10.1)	1,959 (6.8)
Parity (mean)	0.82	0.90 ^a
Multiple birth (yes)	206 (1.8)	692 (2.4) ^a
Prenatal visits (mean)	11.5	11.6 ^a
Weight gained (lbs)	30.1	31.0 ^a
Preeclampsia (yes)	298 (2.6)	748 (2.6)
Prenatal smoking (yes)	842 (7.3)	2,112 (7.3)
Prenatal alcohol (yes)	102 (8.9)	277 (9.5)
Branch of service		
Army	3,440 (29.9)	9,013 (31.0) ^a
Navy	3,524 (30.6)	9,300 (32.0) ^a
Marine Corps	3,220 (28.0)	3,296 (11.3) ^a
Air Force	1,327 (11.5)	7,466 (25.7) ^a
Component		
Active duty	10,324 (89.7)	25,750 (88.5) ^a
Reservist	591 (5.1)	2,781 (9.6) ^a
National Guard	596 (5.2)	555 (1.9) ^a
Paygrade		
E1–E6 Enlisted	9,515 (83.0)	22,587 (77.7) ^a
E7–E9 Staff enlisted	491 (4.3)	1,751 (6.0) ^a
01–010 Officers	1,450 (12.7)	4,746 (16.3) ^a

Arizona births from 1989–1992 only.

^a*p* < 0.05 or 95% CI exclude 1.

GWV, Gulf War veteran; NDV, nondeployed veteran.

Table 3
Birth Defect Prevalence Among Infants Conceived Pre-Gulf War to Gulf War and Nondeployed Female Veterans, Arizona, Arkansas, California, Georgia, Hawaii, Iowa, 1989–1991

Birth defect	GWV (<i>n</i> = 142)		NDV (<i>n</i> = 2,007)		RR (95% CI)
	<i>n</i>	Rate ^a (95% CI)	<i>n</i>	Rate ^a (95% CI)	
Anencephalus	0		0		
Spina bifida without anencephalus	0		0		
Encephalocele	0		1	5.0 (0.3–32.3)	
Microcephalus	0		2	10.0 (1.7–40.1)	
Hydrocephalus without spina bifida	1	70.4 (3.7–445)	2	10.0 (1.7–40.1)	7.1 (0.6–78.9)
Anophthalmia/microphthalmia	0		1	5.0 (0.3–32.3)	
Congenital cataract	0		1	5.0 (0.3–32.3)	
Aniridia	0		0		
Anotia/microtia	0		0		
Common truncus	0		0		
Transposition of great arteries	0		1	5.0 (0.3–32.3)	
Tetralogy of Fallot	0		4	19.9 (6.4–54.7)	
Ventricular septal defect	0		11	54.8 (28.9–101)	
Endocardial cushion defect	0		0		
Pulmonary valve atresia, stenosis	0		3	14.9 (3.9–47.5)	
Pulmonary valve insufficiency	0		0		
Tricuspid atresia and stenosis	0		0		
Tricuspid valve insufficiency	0		0		
Ebstein's anomaly	0		0		
Aortic valve stenosis	0		2	10.0 (1.7–40.1)	
Hypoplastic left heart syndrome	0		0		
Dextrocardia	0		1	5.0 (0.3–32.3)	
Coarctation of aorta	0		0		
Choanal atresia	0		1	5.0 (0.3–32.3)	
Lung agenesis/hypoplasia	0		1	5.0 (0.3–32.3)	
Cleft palate without cleft lip	0		0		
Cleft lip with or without cleft palate	0		3	14.9 (3.9–47.5)	
Esophageal atresia/tracheoesophageal fistula	0		1	5.0 (0.3–32.3)	
Pyloric stenosis	0		5	24.9 (9.2–61.7)	
Rectal/large intestinal atresia/stenosis	0		1	5.0 (0.3–32.3)	
Hirschsprung disease	0		1	5.0 (0.3–32.3)	
Biliary atresia	0		0		
Hypospadias and epispadias	0		5	24.9 (9.2–61.7)	
Renal agenesis/hypoplasia	0		1	5.0 (0.3–32.3)	
Bladder exstrophy	0		0		
Obstructive genitourinary defect	0		6	29.9 (12.2–68.5)	
Reduction deformity, upper limbs	0		1	5.0 (0.3–32.3)	
Reduction deformity, lower limbs	0		1	5.0 (0.3–32.3)	
Goldenhar syndrome	0		0		
Gastroschisis	0		0		
Omphalocele	0		1	5.0 (0.3–32.3)	
Diaphragmatic hernia	0		0		
Down syndrome	0		1	5.0 (0.3–32.3)	
Trisomy 13	0		0		
Trisomy 18	0		0		
Chromosomal anomalies	0		1	5.0 (0.3–32.3)	
Fetal alcohol syndrome	0		0		
Amniotic bands	0		1	5.0 (0.3–32.3)	

^aRate per 10,000 live births.

GWV, Gulf War veteran; NDV, non-deployed veteran.

Infants Conceived Prewar

A total of 26,934 infants were conceived before the war (7005 to GWVs and 19,929 to NDV). Among the infants conceived prewar to GWV women (*n* = 142) and NDV women (*n* = 2007), birth defects prevalence for each of the 48 selected birth defects categories did not differ (Table 3). Similarly, birth defects prevalence for each of the 48 selected birth defects categories did not differ among infants conceived prewar to GWV men (*n* = 6863) and NDV men (*n* = 17,922, Table 4), suggesting no difference in predisposing risk for these birth defects between deployment groups. Further, only one (0.7%) of the infants conceived

prewar to female GWVs had at least one of the selected 48 birth defects; this rate did not differ from that of infants conceived prewar to female NDVs (2.3%, 46/2007; RR, 0.31; 95% CI, 0.04–2.21; *p* = 0.37). A total of 107 (1.56%) infants conceived prewar to male GWVs had at least one of the selected 48 birth defects, which was similar to that of infants conceived prewar to male NDVs (1.76%, 316/17,922; RR, 0.88; 95% CI, 0.71–1.10; *p* = 0.30).

Infants Conceived Postwar

A total of 4956 (41%) GWV infants and 13,123 (40%) NDV infants were conceived during or after the war. As

Table 4
Birth Defect Prevalence Among Infants Conceived Pre-Gulf War to Gulf War and Nondeployed Male Veterans, Arizona, Arkansas, California, Georgia, Hawaii, Iowa, 1989–1991^a

Birth defect	GWV (<i>n</i> = 6,863)		NDV (<i>n</i> = 17,922)		RR (95% CI)
	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)	
Anencephalus	0		1	0.6 (0.03–3.6)	
Spina bifida without anencephalus	3	4.4 (1.1–13.9)	10	5.6 (2.8–10.6)	0.8 (0.2–2.9)
Encephalocele	0		2	1.1 (0.2–4.5)	
Microcephalus	6	8.7 (3.6–20.1)	19	10.6 (6.6–16.9)	0.8 (0.3–2.1)
Hydrocephalus without spina bifida	3	4.4 (1.1–13.9)	14	7.8 (4.4–13.5)	0.6 (0.2–2.0)
Anophthalmia/microphthalmia	1	1.5 (0.1–9.5)	9	5.0 (2.5–9.9)	0.3 (0.04–2.3)
Congenital cataract	2	2.9 (0.5–11.7)	3	1.7 (0.4–5.3)	1.7 (0.3–10.4)
Aniridia	0		0		
Anotia/microtia	1	1.5 (0.1–9.5)	1	0.6 (0.03–3.6)	2.6 (0.2–41.8)
Common truncus	2	2.9 (0.5–11.7)	1	0.6 (0.03–3.6)	5.2 (0.5–57.6)
Transposition of great arteries	3	4.4 (1.1–13.9)	7	3.9 (1.7–8.4)	1.1 (0.3–4.3)
Tetralogy of Fallot	3	4.4 (1.1–13.9)	6	3.3 (1.4–7.7)	1.3 (0.3–5.2)
Ventricular septal defect	13	18.9 (10.5–33.3)	45	25.1 (18.5–33.9)	0.8 (0.4–1.4)
Endocardial cushion defect	0		8	4.5 (2.1–9.2)	
Pulmonary valve atresia, stenosis	6	8.7 (3.6–20.1)	10	5.6 (2.8–10.6)	1.6 (0.6–4.3)
Pulmonary valve insufficiency ^c	0		2	1.6 (0.3–6.6)	
Tricuspid atresia and stenosis	0		3	1.7 (0.4–5.3)	
Tricuspid valve insufficiency ^c	8	17.9 (8.3–36.7)	24	19.7 (12.9–29.8)	0.9 (0.4–2.0)
Ebstein's anomaly	0		0		
Aortic valve stenosis	0		4	2.2 (0.7–6.1)	
Hypoplastic left heart syndrome	1	1.5 (0.1–9.5)	2	1.1 (0.2–4.5)	1.3 (0.1–14.4)
Dextrocardia	0		7	3.9 (1.7–8.4)	
Coarctation of aorta	1	1.5 (0.1–9.5)	7	3.9 (1.7–8.4)	0.4 (0.05–3.0)
Choanal atresia	3	4.4 (1.1–13.9)	5	2.8 (1.0–6.9)	1.6 (0.4–6.6)
Lung agenesis/hypoplasia	3	4.4 (1.1–13.9)	10	5.6 (2.8–10.6)	0.8 (0.2–2.9)
Cleft palate without cleft lip	2	2.9 (0.5–11.7)	17	9.5 (5.7–15.5)	0.3 (0.07–1.3)
Cleft lip with or without cleft palate	7	10.2 (4.5–22.0)	19	10.6 (6.6–16.9)	1.0 (0.4–2.3)
Esophageal atresia/tracheoesophageal fistula	2	2.9 (0.5–11.7)	3	1.7 (0.4–5.3)	1.7 (0.3–10.4)
Pyloric stenosis	14	20.4 (11.6–35.1)	25	13.9 (9.2–20.9)	1.5 (0.8–2.8)
Rectal/large intestinal atresia/stenosis	1	1.5 (0.1–9.5)	8	4.5 (2.1–9.2)	0.3 (0.04–2.6)
Hirschsprung disease	0		3	1.7 (0.4–5.3)	
Biliary atresia	1	1.5 (0.1–9.5)	6	3.3 (1.4–7.7)	0.4 (0.05–3.6)
Hypospadias and epispadias	22	32.1 (20.6–49.4)	51	28.5 (21.4–37.7)	1.1 (0.7–1.9)
Renal agenesis/hypoplasia	0		8	4.5 (2.1–9.2)	
Bladder exstrophy	0		0		
Obstructive genitourinary defect	9	13.1 (6.4–25.9)	29	16.2 (11.0–23.6)	0.8 (0.4–1.7)
Reduction deformity, upper limbs	2	2.9 (0.5–11.7)	6	3.3 (1.4–7.7)	0.9 (0.2–4.3)
Reduction deformity, lower limbs	2	2.9 (0.5–11.7)	4	2.2 (0.7–6.1)	1.3 (0.2–7.1)
Goldenhar syndrome	0		0		
Gastroschisis	1	1.5 (0.1–9.5)	9	5.0 (2.5–9.9)	0.3 (0.04–2.3)
Omphalocele	1	1.5 (0.1–9.5)	0		
Diaphragmatic hernia	0		1	0.6 (0.03–3.6)	
Down syndrome	9	13.1 (6.4–25.9)	21	11.7 (7.4–18.2)	1.1 (0.5–2.5)
Trisomy 13	0		2	1.1 (0.2–4.5)	
Trisomy 18	1	1.5 (0.1–9.5)	7	3.9 (1.7–8.4)	0.4 (0.05–3.0)
Chromosomal anomalies	2	2.9 (0.5–11.7)	13	7.3 (4.0–12.8)	0.4 (0.09–1.8)
Fetal alcohol syndrome ^d	0		4	2.4 (0.8–6.5)	
Amniotic bands	0		4	2.2 (0.7–6.1)	

^aIncludes 113 (0.5%) conceived prior to father's return in 1991.

^bRate per 10,000 live births.

^cCalifornia births excluded.

^dArkansas births excluded.

GWV, Gulf War veteran; NDV, nondeployed veteran.

shown in Table 5, among infants conceived postwar to female GWVs (*n* = 308) and female NDVs (*n* = 1959), the prevalence of hypospadias was significantly higher among sons conceived postwar to female GWVs (4/154 infant boys) compared to female NDVs (4/967 infant boys; RR, 6.3; 95% CI, 1.5–26.3; *p* = 0.015). Although hypospadias and epispadias are jointly reported, none of the infants conceived postwar to female veterans had epispadias. The

proportion of infants who had at least one of the 48 selected defects did not differ among infants conceived postwar to GWV and NDV women (2.92% vs. 1.74%; RR, 1.68; 95% CI, 0.81–3.48; *p* = 0.16).

As shown in Table 6, among infants conceived postwar to male veterans, the prevalence of congenital tricuspid valve insufficiency or regurgitation (RR, 2.7; 95% CI, 1.1–6.6; *p* = 0.039) and aortic valve stenosis (RR, 6.0; 95% CI,

Table 5
Birth Defect Prevalence Among Infants Conceived Post Gulf War to Gulf War and Nondeployed Female Veterans, Arizona, Arkansas, California, Georgia, Hawaii, and Iowa, 1991–1993^a

Birth defect	GWV (<i>n</i> = 308)		NDVs (<i>n</i> = 1,959)		RR (95% CI)
	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)	
Anencephalus	0		0		
Spina bifida without anencephalus	0		1	5.1 (0.3–33.1)	
Encephalocele	0		0		
Microcephalus	0		1	5.1 (0.3–33.1)	
Hydrocephalus without spina bifida	1	32.5 (1.7–209)	1	5.1 (0.3–33.1)	6.4 (0.2–189)
Anophthalmia/microphthalmia	0		0		
Congenital cataract	0		0		
Aniridia	0		0		
Anotia/microtia	0		1	5.1 (0.3–33.1)	
Common truncus	0		0		
Transposition of great arteries	0		0		
Tetralogy of Fallot	0		1	5.1 (0.3–33.1)	
Ventricular septal defect	1	32.5 (1.7–209)	7	35.7 (15.7–76.9)	0.9 (0.05–5.5)
Endocardial cushion defect	0		0		
Pulmonary valve atresia, stenosis	1	32.5 (1.7–209)	1	5.1 (0.3–33.1)	6.4 (0.2–189)
Pulmonary valve insufficiency	0		0		
Tricuspid valve atresia and stenosis	0		0		
Tricuspid valve insufficiency ^c	0		1	6.5 (0.3–42.1)	
Ebstein anomaly	0		0		
Aortic valve stenosis	0		0		
Hypoplastic left heart syndrome	0		0		
Dextrocardia	0		0		
Coarctation of aorta	0		0		
Choanal atresia	0		0		
Lung agenesis/hypoplasia	0		1	5.1 (0.3–33.1)	
Cleft palate without cleft lip	0		1	5.1 (0.3–33.1)	
Cleft lip with or without cleft palate	1	32.5 (1.7–209)	1	5.1 (0.3–33.1)	6.4 (0.2–189)
Esophageal atresia/tracheoesophageal fistula	0		0		
Pyloric stenosis	0		5	25.5 (9.4–63.2)	
Rectal/large intestinal atresia/stenosis	0		0		
Hirschsprung disease	0		0		
Biliary atresia	0		0		
Hypospadias and epispadias	4	129.8 (41.6–352)	4	20.4 (6.5–56.0)	6.4 (1.5–26.8)
Renal agenesis/hypoplasia	1	32.5 (1.7–209)	3	15.3 (3.9–48.7)	2.1 (0.1–17.8)
Bladder exstrophy	0		0		
Obstructive genitourinary defect	1	32.5 (1.7–209)	8	40.8 (19.0–83.7)	0.8 (0.04–4.7)
Reduction deformity, upper limbs	0		0		
Reduction deformity, lower limbs	0		0		
Goldenhar syndrome	0		0		
Gastroschisis	0		1	5.1 (0.3–33.1)	
Omphalocele	0		0		
Diaphragmatic hernia	0		0		
Down syndrome	1	32.5 (1.7–209)	0		
Trisomy 13	0		1	5.1 (0.3–33.1)	
Trisomy 18	0		0		
Chromosomal anomalies ^d	0		2	11.0 (1.9–44.2)	
Fetal alcohol syndrome	0		0		
Amniotic bands	0		0		

^a1993 Arizona births not represented.

^bRate per 10,000 live births.

^cCalifornia births excluded.

^d1992 Arizona births excluded.

GWV, Gulf War veteran; NDV, nondeployed veteran.

1.2–31.0; $p = 0.026$) was significantly higher for GWV infants compared to NDV infants. Coarctation of the aorta was also elevated among infants of GWV men compared to NDV men, but was not statistically significant (RR, 4.0; 95% CI, 0.96–16.8; $p = 0.053$). The proportion of infants conceived postwar with at least 1 of the 48 selected defects was similar by father's deployment status (GWV: 1.55% vs. NDV: 1.61%; RR, 0.96; 95% CI, 0.73–1.26; $p = 0.83$).

Temporal Comparisons Among GWV Infants

No temporal differences in birth defects prevalence were observed between infants conceived prewar and postwar to female GWVs (Table 7), nor among female NDVs (data on Tables 3 and 5). The proportion of infants who had at least one of the 48 selected defects did not differ among infants conceived postwar and prewar to GWV women (2.92% vs.

Table 6
Birth Defect Prevalence Among Infants Conceived Post-Gulf War to Gulf War and Nondeployed Male Veterans, Arizona, Arkansas, California, Georgia, Hawaii, and Iowa, 1991–1993^a

Birth defect	GWV (<i>n</i> = 4,648)		NDV (<i>n</i> = 11,164)		RR (95% CI)
	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)	
Anencephalus	0		1	0.9 (0.05–5.8)	
Spina bifida without anencephalus	2	4.3 (0.7–17.4)	5	4.5 (1.6–11.1)	1.0 (0.2–4.9)
Encephalocele	0		1	0.9 (0.05–5.8)	
Microcephalus	3	6.4 (1.7–20.5)	7	6.3 (2.7–13.5)	1.0 (0.3–4.0)
Hydrocephalus without spina bifida	2	4.3 (0.7–17.4)	7	6.3 (2.7–13.5)	0.7 (0.1–3.0)
Anophthalmia/microphthalmia	0		2	1.8 (0.3–7.2)	
Congenital cataract	0		1	0.9 (0.05–5.8)	
Aniridia	0		0		
Anotia/microtia	2	4.3 (0.7–17.4)	2	1.8 (0.3–7.2)	2.4 (0.3–17.1)
Common truncus	0		1	0.9 (0.05–5.8)	
Transposition of great arteries	1	2.2 (0.1–13.9)	3	2.7 (0.7–8.6)	0.8 (0.08–7.7)
Tetralogy of Fallot	2	4.3 (0.7–17.4)	0		
Ventricular septal defect	10	21.5 (10.9–40.9)	36	32.2 (22.9–45.1)	0.7 (0.3–1.3)
Endocardial cushion defect	0		7	6.3 (2.7–13.5)	
Pulmonary valve atresia, stenosis	3	6.4 (1.7–20.5)	6	5.4 (2.2–12.3)	1.2 (0.3–4.8)
Pulmonary valve insufficiency ^c	0		1	1.2 (0.1–7.7)	
Tricuspid atresia, stenosis	2	4.3 (0.7–17.4)	1	0.9 (0.05–5.8)	4.8 (0.4–53.0)
Tricuspid valve insufficiency ^c	10	28.7 (14.6–54.6)	9	10.7 (5.2–21.1)	2.7 (1.1–6.6)
Ebstein's anomaly ^c	0		2	2.4 (0.4–9.6)	
Aortic valve stenosis	5	10.8 (3.9–26.7)	2	1.8 (0.3–7.2)	6.0 (1.2–31.0)
Hypoplastic left heart syndrome	2	4.3 (0.7–17.4)	2	1.8 (0.3–7.2)	2.4 (0.3–17.1)
Dextrocardia ^d	1	2.4 (0.1–15.9)	4	4.0 (1.3–10.9)	0.6 (0.07–5.5)
Coarctation of aorta	5	10.8 (3.9–26.7)	3	2.7 (0.7–8.6)	4.0 (0.96–16.8)
Choanal atresia	0		0		
Lung agenesis/hypoplasia	4	8.6 (2.8–23.6)	7	6.3 (2.7–13.5)	1.4 (0.4–4.7)
Cleft palate without cleft lip	0		4	3.6 (1.1–9.8)	
Cleft lip with or without cleft palate	4	8.6 (2.8–23.6)	16	14.3 (8.5–23.8)	0.6 (0.2–1.8)
Esophageal atresia/tracheoesophageal fistula	2	4.3 (0.7–17.4)	2	1.8 (0.3–7.2)	2.4 (0.3–17.1)
Pyloric stenosis	7	15.1 (6.6–32.9)	18	16.1 (9.8–26.0)	0.9 (0.4–2.2)
Rectal/large intestinal atresia/stenosis	3	6.4 (1.7–20.5)	5	4.5 (1.6–11.1)	1.4 (0.3–6.0)
Hirschsprung disease	0		2	1.8 (0.3–7.2)	
Biliary atresia	0		1	0.9 (0.05–5.8)	
Hypospadias and epispadias	15	32.3 (18.8–54.5)	35	31.3 (22.2–44.1)	1.0 (0.6–1.9)
Renal agenesis/hypoplasia	5	10.8 (3.9–26.7)	5	4.5 (1.6–11.1)	2.4 (0.7–8.3)
Bladder exstrophy	1	2.2 (0.1–13.9)	1	0.9 (0.05–5.8)	2.4 (0.2–38.4)
Obstructive genitourinary defect	9	19.4 (9.4–38.2)	21	18.8 (11.9–29.3)	1.0 (0.5–2.2)
Reduction deformity, upper limbs	0		1	0.9 (0.05–5.8)	
Reduction deformity, lower limbs	0		4	3.6 (1.1–9.8)	
Goldenhar syndrome	0		0		
Gastroschisis	3	6.4 (1.7–20.5)	3	2.7 (0.7–8.6)	2.4 (0.5–11.9)
Omphalocele	1	2.2 (0.1–13.9)	2	1.8 (0.3–7.2)	1.2 (0.1–13.2)
Diaphragmatic hernia	0		0		
Down syndrome	3	6.4 (1.7–20.5)	13	11.6 (6.5–20.4)	0.6 (0.2–1.9)
Trisomy 13	0		2	1.8 (0.3–7.2)	
Trisomy 18	0		4	3.6 (1.1–9.8)	
Chromosomal anomalies ^d	1	2.4 (0.1–15.9)	12	11.9 (6.5–21.5)	0.2 (0.03–1.6)
Fetal alcohol syndrome	0		0		
Amniotic bands	0		2	1.8 (0.3–7.2)	

^a1993 Arizona births not represented.

^bRate per 10,000 live births.

^cCalifornia births excluded.

^d1992 Arizona births excluded.

GWV, Gulf War veteran; NDV, nondeployed veteran.

0.72%; RR, 4.24; 95% CI, 0.5–33.8; $p = 0.18$) or to NDV women (1.7% vs. 2.3%; RR, 0.8; 95% CI, 0.5–1.2; $p = 0.22$).

Among infants of GWV men, the prevalence of aortic valve stenosis (5/4648, Table 8) was significantly higher among infants conceived postwar than prewar (0/6863; RR, 16.3; 95% CI, 0.9–294; $p = 0.011$). The prevalence of renal agenesis and hypoplasia was also significantly higher among GWV infants conceived postwar than prewar (5/

4648 vs. 0/6863; RR, 16.3; 95% CI, 0.9–294; $p = 0.011$). Comparatively, birth defects prevalence did not increase temporally among NDV infants for any of the 48 birth defects categories (data on Tables 4 and 6). The proportion of infants with at least one of the 48 selected birth defects did not differ temporally among infants of GWV men (1.55% vs. 1.56%; RR, 0.99; 95% CI, 0.74–1.34; $p = 1.0$) or infants of NDV men (1.61% vs. 1.76%; RR, 0.91; 95% CI, 0.76–1.09; $p = 0.35$).

Table 7
Birth Defect Prevalence Among Infants Conceived Pre and Post-Gulf War to Female Gulf War Veterans, Arizona, Arkansas, California, Georgia, Hawaii, and Iowa, 1989–1993^a

Birth defect	Post-war to GWVs (<i>n</i> = 308)		Pre-war to GWVs (<i>n</i> = 142)		RR (95% CI)
	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)	
Anencephalus	0		0		
Spina bifida without anencephalus	0		0		
Encephalocele	0		0		
Microcephalus	0		0		
Hydrocephalus without spina bifida	1	32.5 (1.7–209)	1	70.4 (3.7–445)	0.5 (0.03–7.4)
Anophthalmia/microphthalmia	0		0		
Congenital cataract	0		0		
Aniridia	0		0		
Anotia/microtia	0		0		
Common truncus	0		0		
Transposition of great arteries	0		0		
Tetralogy of Fallot	0		0		
Ventricular septal defect	1	32.5 (1.7–209)	0		
Endocardial cushion defect	0		0		
Pulmonary valve atresia, stenosis	1	32.5 (1.7–209)	0		
Pulmonary valve insufficiency	0		0		
Tricuspid valve atresia and stenosis	0		0		
Tricuspid valve insufficiency	0		0		
Ebstein anomaly	0		0		
Aortic valve stenosis	0		0		
Hypoplastic left heart syndrome	0		0		
Dextrocardia	0		0		
Coarctation of aorta	0		0		
Choanal atresia	0		0		
Lung agenesis/hypoplasia	0		0		
Cleft palate without cleft lip	0		0		
Cleft lip with or without cleft palate	1	32.5 (1.7–209)	0		
Esophageal atresia/tracheoesophageal fistula	0		0		
Pyloric stenosis	0		0		
Rectal/large intestinal atresia/stenosis	0		0		
Hirschsprung disease	0		0		
Biliary atresia	0		0		
Hypospadias and epispadias	4	129.8 (41.6–352)	0		
Renal agenesis/hypoplasia	1	32.5 (1.7–209)	0		
Bladder exstrophy	0		0		
Obstructive genitourinary defect	1	32.5 (1.7–209)	0		
Reduction deformity, upper limbs	0		0		
Reduction deformity, lower limbs	0		0		
Goldenhar syndrome	0		0		
Gastroschisis	0		0		
Omphalocele	0		0		
Diaphragmatic hernia	0		0		
Down syndrome	1	32.5 (1.7–209)	0		
Trisomy 13	0		0		
Trisomy 18	0		0		
Chromosomal anomalies	0		0		
Fetal alcohol syndrome	0		0		
Amniotic bands	0		0		

^a1993 Arizona births not represented.

^bRate per 10,000 live births.

GWV, Gulf War veteran; NDV, nondeployed veteran.

Adjusted Prevalence

The increased prevalence of tricuspid valve insufficiency and aortic valve stenosis among infants conceived postwar to male GWVs did not differ significantly when adjusted by state, maternal age, paternal age, race, marital status, education, plurality, parity, number of prenatal visits, gestational weight gain, branch of military service, or military rank (data not shown). Known risk factors for cardiovascular defects are few and include maternal diabetes mellitus, rubella,

fever, and the absence of periconceptional multivitamin use (Botto et al., 2000). Family history, medication, welding, lead soldering, ionizing radiation and exposure to organic solvents or paint stripping have been associated with selected cardiovascular defects (Correa-Villaseñor et al., 1993), however, such exposure information was not available.

Moderate prenatal alcohol exposure and fetal growth retardation have been associated with renal agenesis or hypoplasia (Moore et al., 1997). Adjusting for prenatal

Table 8
Birth Defect Prevalence Among Infants Conceived Pre- and Post-Gulf War to Male Gulf War Veterans, Arizona, Arkansas, California, Georgia, Hawaii, and Iowa, 1989–1993^a

Birth defect	Post-war to GWVs (<i>n</i> = 4,648)		Pre-war to GWVs (<i>n</i> = 6,863)		RR (95% CI)
	<i>n</i>	Rate ^b (95% CI)	<i>n</i>	Rate ^b (95% CI)	
Anencephalus	0		0		
Spina bifida without anencephalus	2	4.3 (0.7–17.4)	3	4.4 (1.1–13.9)	1.0 (0.2–5.9)
Encephalocele	0		0		
Microcephalus	3	6.4 (1.7–20.5)	6	8.7 (3.6–20.1)	0.7 (0.3–2.9)
Hydrocephalus without spina bifida	2	4.3 (0.7–17.4)	3	4.4 (1.1–13.9)	1.0 (0.2–5.9)
Anophthalmia/microphthalmia	0		1	1.5 (0.1–9.5)	
Congenital cataract	0		2	2.9 (0.5–11.7)	
Aniridia	0		0		
Anotia/microtia	2	4.3 (0.7–17.4)	1	1.5 (0.1–9.5)	2.9 (0.3–32.6)
Common truncus	0		2	2.9 (0.5–11.7)	
Transposition of great arteries	1	2.2 (0.1–13.9)	3	4.4 (1.1–13.9)	0.5 (0.05–4.7)
Tetralogy of Fallot	2	4.3 (0.7–17.4)	3	4.4 (1.1–13.9)	1.0 (0.2–5.9)
Ventricular septal defect	10	21.5 (10.9–40.9)	13	18.9 (10.5–33.3)	1.1 (0.5–2.6)
Endocardial cushion defect	0		0		
Pulmonary valve atresia, stenosis	3	6.4 (1.7–20.5)	6	8.7 (3.6–20.1)	0.7 (0.2–2.9)
Pulmonary valve insufficiency	0		0		
Tricuspid atresia, stenosis	2	4.3 (0.7–17.4)	0		
Tricuspid valve insufficiency ^c	10	28.7 (14.6–54.6)	8	17.9 (8.3–36.7)	1.61 (0.6–4.1)
Ebstein's anomaly	0		0		
Aortic valve stenosis	5	10.8 (3.9–26.7)	0		16.3 (0.9–294) ^d
Hypoplastic left heart syndrome	2	4.3 (0.7–17.4)	1	1.5 (0.1–9.5)	2.9 (0.3–32.6)
Dextrocardia ^e	1	2.4 (0.1–15.9)	0		
Coarctation of aorta	5	10.8 (3.9–26.7)	1	1.5 (0.1–9.5)	7.4 (0.9–63.3)
Choanal atresia	0		3	4.4 (1.1–13.9)	
Lung agenesis/hypoplasia	4	8.6 (2.8–23.6)	3	4.4 (1.1–13.9)	2.0 (0.4–8.8)
Cleft palate without cleft lip	0		2	2.9 (0.5–11.7)	
Cleft lip with or without cleft palate	4	8.6 (2.8–23.6)	7	10.2 (4.5–22.0)	0.8 (0.2–2.9)
Esophageal atresia/tracheoesophageal fistula	2	4.3 (0.7–17.4)	2	2.9 (0.5–11.7)	1.5 (0.2–10.5)
Pyloric stenosis	7	15.1 (6.6–32.9)	14	20.4 (11.6–35.1)	0.7 (0.2–1.8)
Rectal/large intestinal atresia/stenosis	3	6.4 (1.7–20.5)	1	1.5 (0.1–9.5)	4.4 (0.5–42.6)
Hirschsprung disease	0		0		
Biliary atresia	0		1	1.5 (0.1–9.5)	
Hypospadias and epispadias	15	32.3 (18.8–54.5)	22	32.1 (20.6–49.4)	1.0 (0.5–1.9)
Renal agenesis/hypoplasia	5	10.8 (3.9–26.7)	0		16.3 (0.9–294) ^d
Bladder exstrophy	1	2.2 (0.1–13.9)	0		
Obstructive genitourinary defect	9	19.4 (9.4–38.2)	9	13.1 (6.4–25.9)	1.5 (0.6–3.7)
Reduction deformity, upper limbs	0		2	2.9 (0.5–11.7)	
Reduction deformity, lower limbs	0		2	2.9 (0.5–11.7)	
Goldenhar syndrome	0		0		
Gastroschisis	3	6.4 (1.7–20.5)	1	1.5 (0.1–9.5)	4.4 (0.5–42.6)
Omphalocele	1	2.2 (0.1–13.9)	1	1.5 (0.1–9.5)	1.5 (0.09–23.6)
Diaphragmatic hernia	0		0		
Down syndrome	3	6.4 (1.7–20.5)	9	13.1 (6.4–25.9)	0.5 (0.1–1.8)
Trisomy 13	0		0		
Trisomy 18	0		1	1.5 (0.1–9.5)	
Chromosomal anomalies ^e	1	2.4 (0.1–15.9)	2	2.9 (0.5–11.7)	0.8 (0.08–9.3)
Fetal alcohol syndrome	0		0		
Amniotic bands	0		0		

^a1993 Arizona births not represented.

^bRate per 10,000 live births.

^cCalifornia births excluded.

^dLogit estimator method.

^e1992 Arkansas births excluded.

GWV, Gulf War veteran; NDV, nondeployed veteran.

alcohol exposure and intrauterine growth retardation did not account for the higher prevalence of renal agenesis or hypoplasia among infants conceived postwar to GWV men.

The increased prevalence of hypospadias did not differ when adjusted by state, maternal age, race, marital status, education, plurality, smoking, alcohol use, branch of mili-

tary service, or military rank (data not shown). The etiology of hypospadias is multi-factorial and is hypothesized to be associated with endocrine abnormalities, preeclampsia, being small for gestational age, low birth weight, low parity, and paternal age (McIntosh et al., 1995; Fredell et al., 1998; Akre et al., 1999; Moller and Weidner, 1999). Adjusting for low birth weight, small for gestational age,

low parity, paternal age, and preeclampsia, however, did not account for the increased prevalence of hypospadias among infants conceived postwar to GWV women.

Cardiovascular Defects

Cardiovascular defects are complex, occur concomitantly with other cardiac and noncardiac anomalies, and can be caused by many disorders (Waller et al., 1994; Bernstein et al., 1996). All birth defects codes of the postwar infants with congenital tricuspid valve insufficiency or aortic valve stenosis were reviewed in a blinded manner by a pediatric cardiologist (Dr. Lorenzo Botto, CDC) with training in cardiovascular epidemiology, dysmorphology, and genetics. Echocardiographic descriptions, however, were needed but were not available for 10 of these 23 case infants. Without such information, it is unclear if these cardiovascular defects occurred as structural malformations, or appeared as a minor component of other cardiovascular anomalies, or a condition secondary to cardiac congestive failure. Cardiac and noncardiac defects of these 23 case infants appear in Table 9.

DISCUSSION

In the absence of clinical evaluations for all GWV infants, the lack of national active surveillance for birth defects, and the absence of a Department of Defense Birth Defects Registry before 1998, this investigation provided an estimate of the prevalence of birth defects in a sample of GWV infants. The participating states represented *all* the active birth defects surveillance programs operating between 1989–93. Collectively, they are geographically and ethnically diverse and account for 14% of all national births. Such prevalence rates have not been previously determined among GWV progeny where birth defects prevalence are 1) determined through active case ascertainment; include 2) birth defects diagnosed through the first year of life; 3) births among reservists, National Guard, and former military personnel; and 4) surveillance of nonmilitary hospitals and outpatient clinics.

Our observations were similar to those of Kang (2001) where an excess of "isolated anomalies" among infants conceived postwar to GWVs was reported. Cardiovascular and gastrointestinal anomalies comprised 30% of these "isolated anomalies," however, birth defects were based on veteran self-reported data and were not validated against medical records. Kang et al. (2001) and Cowan et al. (1997) combined multiple birth defects into broad categories including "undescribed isolated heart abnormality," "selected chromosomal anomalies," and "selected congenital anomalies of the circulatory system," whereas we reported prevalence for 48 specific birth defects categories. We found no differences in the risk for any of the combined 48 selected defects by deployment status. We observed an elevated risk of 4 birth defects, however, and these differences persisted after adjustment for known risk factors and population differences.

Our results differ from the studies of Cowan et al. (1997) and Penman et al. (1996) and are likely due to this study's more thorough method of ascertaining cases. Data based on active surveillance methods offer a higher level of case ascertainment of birth defects than passive surveillance methods, hospital discharge data, or vital records (Lynberg et al., 1992). For example, half of cardiovascular defects are diagnosed after the neonatal period and would have been missed in a study based solely upon newborn diagnoses.

Our observation of a temporal increase of aortic valve stenosis and renal agenesis or hypoplasia among infants of male GWVs could not have been reported in prior studies that were limited to live births conceived after the Gulf War. The excess of hypospadias among infants conceived postwar to female GWVs was not observed in previous studies because our cohort included admissions to nonmilitary hospitals, where 40% of such case infants were diagnosed.

No temporal differences in birth defects prevalence were observed among NDV infants. This suggests that the increased prevalence of tricuspid valve insufficiency, aortic valve stenosis, and hypospadias among GWV infants was not an artifact of reduced prevalence of these defects among NDV infants.

Etiologic factors and confounders associated with the reported birth defects trends could not be identified because the study was designed to measure birth defects prevalence. Although state birth defects programs collect selected risk factor and prenatal exposure information, this study was not able to identify specific military exposures, adverse events, or teratogenic influences during the periconceptional and prenatal periods. Unlike chemical defoliants like Agent Orange, a teratogen in laboratory animals, and a lipophilic agent where trace levels could be detected among veterans years after the Vietnam War (Stephenson et al., 1996), there is currently no single, recognized teratogen that can be measured precisely among Gulf War veterans.

Although this study had several advantages over previous Gulf War veteran's birth defects studies, some methodological limitations must be acknowledged. Sampling in five of the six states was population based; however, the generalizability of data from our California military cohort might be questioned. The California Birth Defects Monitoring Program does not have access to data in military hospitals, therefore surveillance data were limited to those diagnosed in nonmilitary hospitals. Approximately 40% of births to military personnel occur in nonmilitary hospitals. It is unclear if the prevalence and types of birth defects differ among infants treated in military and nonmilitary hospitals. When data analysis excluded California for three birth defects categories that are not included in California's birth defects surveillance activities, an excess risk of tricuspid valve insufficiency was observed among infants conceived postwar to male GWVs in the remaining five states.

Birth defects surveillance in Iowa from 1991–93 accounted for just two-thirds of the state's births. Surveillance was not limited to selected counties or months; therefore, the denominator of live births could not be restricted to the sampled population. Instead, the denominator included all state births, which would likely underestimate the true prevalence rates. Military births in Iowa, however, accounted for just 3% of our military birth cohort. Further, when data analysis excluded Iowa, the observed trends persisted.

Our ability to identify military infants through linkage of military and birth certificate data depended on the availability of compatible unique personal identifiers. Linkage was likely more precise among states that recorded the social security number, or those with a maximum number of personal identifiers, such as Hawaii, where the sensitivity (87%), specificity (99%), and positive predictive value (97%) of the linkage algorithm was high (Araneta, 2000b). These were tested by comparing the estimated number of

Table 9
 Infants Conceived Postwar with Tricuspid Valve Insufficiency or Aortic Valve Stenosis

Infant	Parental data	Birth defects as abstracted from the birth defects surveillance case report
1	33 yo Army, GWV 25 yo G ₁ P ₀ , white Boy, 3,459 gm, 40 wks	Down syndrome (trisomy 21), tricuspid valve insufficiency or regurgitation (congenital), ostium (septum) secundum defect
2	34 yo Marine, GWV 31 yo G ₁ P ₀ , Asian Girl, 30 wks	Tricuspid valve insufficiency or regurgitation (congenital), ventricular hypertrophy, patent ductus arteriosus, other specified anomalies of brain, other misshapen ear, other specified anomalies of nose, unilateral absence/agenesis/dysplasia/hypoplasia of kidneys (right), polycystic kidneys (left, infantile type), congenital hydronephrosis (left), adrenogenital syndrome
3	24 yo Army, GWV 23 yo G ₃ P ₂ , black Boy, 3,203 gm, 38 wks	Ventricular septal defect, atrial septal defect, tricuspid valve insufficiency or regurgitation (congenital), congenital stenosis of aortic valve, mitral valve insufficiency or regurgitation (congenital), anomalies of myocardium, hypoplastic right, ventricle, ventricular hypertrophy, other defects of the atria, patent ductus arteriosus, unspecified coarctation of aorta, pulmonary artery stenosis, hypospadias (alone)
4	24 yo Navy, GWV 19 yo G ₁ P ₀ , white Girl, 2,013 gm, 34 wks	Atrial septal defect, pulmonary valve insufficiency or regurgitation (congenital), tricuspid valve insufficiency or regurgitation (congenital), aortic valve insufficiency or regurgitation (congenital), mitral valve insufficiency or regurgitation (congenital), persistent left superior vena cava, other specified anomalies of great veins, tongue tie, displacement or transposition of stomach, malrotation of small intestine (alone), unilateral absence, agenesis, dysplasia or hypoplasia of kidneys (right), other and unspecified obstructive defects of renal pelvis and ureter, bowing (femur, right), hypoplasia of lower limb, other anomalies of ribs (right), other specified anomalies of spleen, situs inversus abdominis
5	23 yo Army, GWV 22 yo G ₂ P ₀ , white Preeclampsia Boy, 4,309 gm, 39 wks	Single ventricle, ventricular septal defect, tricuspid valve insufficiency or regurgitation (congenital), congenital stenosis of aortic valve, Lutembacher's syndrome, absence/atresia/hypoplasia of mitral valve, hypoplastic left heart syndrome, dextrocardia without situs inversus, levocardia, other specified anomalies of heart, hypoplastic left ventricle, ventricular hypertrophy, cyanotic congenital heart disease, patent ductus arteriosus, hypoplasia of aorta, other specified anomalies of aorta, aneurysm of pulmonary artery, other specified anomaly of pulmonary artery, total anomalous pulmonary venous return, anomaly of the great veins, single umbilical artery, megalencephaly, pulmonary hypoplasia
6	23 yo Navy, GWV 21 yo G ₂ P ₁ , white Boy, 2,410 gm, 33 wks	Ventricular septal defect, ostium (septum) secundum defect, pulmonary valve insufficiency or regurgitation (congenital), tricuspid valve insufficiency or regurgitation (congenital), congenital stenosis of aortic valve, mitral valve insufficiency or regurgitation (congenital), other specified anomalies of heart, unspecified coarctation of aorta, hypoplasia of aorta
7	38 yo Air Force, GWV 29 yo G ₂ P ₁ , white Boy, 2,797 gm, 29 wks, multiple birth	Tricuspid valve insufficiency or regurgitation (congenital), congenital stenosis of aortic valve, aortic valve insufficiency or regurgitation (congenital), mitral valve insufficiency or regurgitation (congenital)
8	22 yo Navy, GWV 20 yo G ₁ P ₀ , Asian Girl, 652 gm, 25 wks	Nonclosure of foramen ovale, atrial septal defect, tricuspid valve insufficiency or regurgitation (congenital), other anomalies of ribs
9	26 yo Army, GWV 28 yo G ₄ P ₃ , black, + smoking Girl, 1,035 gm, 36 wks	Nonclosure of foramen ovale, tricuspid valve insufficiency or regurgitation (congenital), anomalies of myocardium, patent ductus arteriosus, pulmonary artery stenosis
10	25 yo Marines, GWV 23 yo G ₁ P ₀ , Hispanic Boy, 3,402 gm, 40 wks	Tricuspid valve insufficiency or regurgitation (congenital), hydrocephalus secondary to intraventricular hemorrhage or central nervous system bleed, other specified anomalies of brain, ventricular cysts, hypoglycemia
11	37 yo Army, GWV 32 yo G ₂ P ₁ , black Boy, 1,985 gm, 38 wks	Trisomy 18, microcephaly, posteriorly rotated ears, webbing of neck, congenital anomaly of neck, single ventricle, ventricular septal defect, atrial septal defect, tricuspid atresia, stenosis or hypoplasia, congenital stenosis of aortic valve, proximal coarctation of aorta, cleft lip (unilateral), undescended testicle (bilateral), other deformities of feet (bilateral), anomalies of fingers (bilateral), anomalies of hand (bilateral), other anomalies of lower limb (foot, bilateral), hypertelorism, hypoplastic nails, other specified anomalies of breast (bilateral)
12	25 yo Air Force, NDV 24 yo G ₁ P ₀ , white Girl, 2,550 gm, 37 wks	Spina bifida aperta, meningocele (thoracolumbar, lumbosacral, with hydrocephalus) atrial septal defect, tricuspid valve insufficiency or regurgitation (congenital), other specified anomalies of the aortic valves, absence/atresia/hypoplasia of mitral valve, hypoplastic left heart syndrome, patent ductus arteriosus, unspecified coarctation of aorta, atresia of aorta, hypoplasia of aorta, other specified anomalies of aorta

military infants based on electronic linkage against Hawaii birth certificates, which elicits and records parental military status (Araneta et al., 2000a,b). Hawaii is the only state

that records parental employment in the military on the birth certificate. As such, it was the only state for which we could evaluate the efficiency of our electronic linkage al-

Table 9
 Infants Conceived Postwar with Tricuspid Valve Insufficiency or Aortic Valve Stenosis (Continued)

Infant	Parental data	Birth defects—as abstracted from the birth defects surveillance case report
13	31 yo Air Force, NDV 32 yo G ₁ P ₀ , white Girl, 1474 gm, 37 wks	Microcephalus, plagiocephaly, other specified anomalies of eye, congenital nystagmus, low set ears, congenital anomaly of neck, unspecified anomaly of jaw, other specified anomalies of nose, tongue tie, macroglossia, high arched palate, nonclosure of foramen ovale, tricuspid valve insufficiency or regurgitation (congenital), mitral valve insufficiency or regurgitation (congenital), patent ductus arteriosus, atresia, stricture, or stenosis of ureter, other and unspecified obstructive defects of renal pelvis and ureter, ectopic ureter, variations of vesicoureteral reflux
14	21 yo Navy, NDV 24 yo G ₂ P ₁ , Hispanic Girl, 3,175 gm, 42 wks	Nonclosure of foramen ovale, ostium (septum) secundum defect, tricuspid valve insufficiency or regurgitation (congenital), mitral valve insufficiency or regurgitation (congenital), anomalies of coronary artery or sinus, patent ductus arteriosus, proximal coarctation of aorta, distal coarctation of aorta, supra-aortic stenosis, absence or other anomaly of vulva
15	30 yo Navy, NDV 31 yo G ₁ P ₀ , Asian Boy, 1,845 gm, 34 wk	Blepharophimosis, other misshapen ear, ventricular septal defect, nonclosure of foramen ovale, tricuspid valve insufficiency or regurgitation (congenital), hypoplastic nails, ascites (congenital)
16	21 yo Army, NDV 22 yo G ₁ P ₀ , black Girl, 3,629 gm, 40 wks	Other specified ventricular septal defect, nonclosure of foramen ovale, tricuspid valve insufficiency or regurgitation (congenital), ventricular hypertrophy, patent ductus arteriosus, other specified anomalies of larynx and bronchus
17	20 yo Navy mother, NDV, G ₁ P ₀ , black Boy, 3,567 gm, 39 wks	Tricuspid valve insufficiency or regurgitation (congenital), patent ductus arteriosus
18	25 yo Air Force, NDV 23 yo G ₁ P ₀ , white Boy, 3,665 gm, 37 wks	Ostium (septum) secundum defect, Lutembacher's syndrome, single common atrium, stenosis of pulmonary valve, pulmonary valve insufficiency or regurgitation (congenital), tricuspid valve insufficiency or regurgitation (congenital), Ebstein anomaly, unspecified anomalies of the aortic valves, hypoplastic left ventricle, ventricular hypertrophy, patent ductus arteriosus, other specified anomaly of pulmonary artery, ascites (congenital)
19	37 yo Air Force, NDV 31 yo G ₁ P ₀ , black Boy, 1,530 gm, 31 wks	Other specified anomalies of pulmonary valve, tricuspid valve insufficiency or regurgitation (congenital), aortic valve insufficiency or regurgitation (congenital), mitral valve insufficiency or regurgitation (congenital), other specified anomalies of heart, anomalous bands of heart
20	29 yo Navy, NDV 28 yo G ₃ P ₂ , white + smoking Girl, 4,791 gm, 37 wks	Nonclosure of foramen ovale, tricuspid valve insufficiency or regurgitation (congenital), mitral valve insufficiency or regurgitation (congenital), microcephalus, hypoglycemia
21	22 yo Army, NDV 22 yo G ₁ P ₀ , white Preeclampsia Boy, 2,580 gm, 37 wks	Pulmonary valve insufficiency or regurgitation (congenital), tricuspid valve insufficiency or regurgitation (congenital), hypoplastic right ventricle, patent ductus arteriosus, neuroblastoma
22	35 yo Air Force, NDV 27 yo G ₁ P ₀ , white Boy, 4,196 gm, 39 wks	Common atrioventricular canal, congenital stenosis of aortic valve, hypoplastic left ventricle, patent ductus arteriosus
23	35 yo Air Force, NDV 32 yo G ₃ P ₂ , white Girl, 3,912 gm, 40 wks	Ventricular septal defect, atrial septal defect, congenital stenosis of aortic valve, absence, atresia, or hypoplasia of mitral valve, hypoplastic left heart syndrome, other defects of the atria, patent ductus arteriosus, hypoplasia of aorta, other specified anomalies of aorta, persistent left superior vena cava

GWV, Gulf War veteran; NDV, nondeployed veteran; yo, years old.

gorithm in identifying births to military personnel. States with fewer parental identifiers on birth certificate files, such as California, might have resulted in an underestimate of births to military personnel.

Adequate statistical power is a concern in epidemiological studies of rare diseases, and it is a common methodological problem in studies of birth defects (Bracken, 1984). The sample size was sufficient to compare the combined birth defects prevalence (power = 99%), but it was insufficient for less frequent individual component defects. For example, the statistical power was 67% ($\alpha = 0.10$) in the comparison of hypospadias among infants conceived postwar to GWV and NDV women. A minimum sample of 257 sons conceived postwar to women GWVs were needed to compare the risk of hypospadias with sufficient statistical

power (80% at $\alpha = 0.05$), however, there were only 154 sons conceived postwar to women GWVs. Similarly, a sample of 6373 GWV postwar births were needed to adequately compare the risk of tricuspid valve insufficiency, instead of the 4648 GWV postwar births available.

The birth defects prevalence measured in this investigation was limited to live births. Consequently, the prevalence of birth defects among fetal losses is not represented. This includes stillbirths, pregnancies terminated because of a prenatal diagnosis of a birth defect, and spontaneous abortions. Miscarriages occur in approximately 30% of all conceptions (Wilcox et al., 1988), of which 40–60% have chromosomal aberrations (Kline et al., 1989), and would likely manifest birth defects if these fetuses survived to term. Kang et al. (2001) observed a significantly higher rate

of reported miscarriages among postwar conceptions of male GWVs compared to male NDVs. The availability of prenatal diagnosis of selected birth defects including Down syndrome, other chromosomal defects, and neural tube defects, has resulted in an increase in elective terminations, and a consequent reduction in the birth prevalence of such conditions. Enumerating the prevalence of birth defects among induced abortions is complex, however, because elective terminations are not reportable procedures in all states. A study by Forrester et al. (1998) demonstrated that birth prevalence rates for selected defects can increase by more than 50% if electively terminated cases are included.

Birth defects surveillance was limited to the infant's first birthday; therefore, birth defects diagnosed after infancy are not represented. This is not a major limitation because 95% of birth defects are diagnosed during the initial 12 months of life (Stierman, 1994). Appropriate classification of birth defects, particularly cardiovascular and multiple defects, is an important factor in studies of birth defects prevalence. Prevalence rates of individual component defects may not capture the constellation of complex, multiple defects, or syndromes. Without prospective clinical data, including echocardiographic information, we were not able to implement a hierarchical classification system to assign infants with multiple anomalies to a single diagnostic group, giving the highest priority to structural malformations of the earliest embryonic origin.

Finally, multiple comparisons were carried out to test several independent tests of significance. We did not have any a priori hypotheses about associations between exposure to the Gulf War and risk of particular birth defects. We expected some of the relative risks to be significantly different, and that some associations might be spurious and attributable to chance. For example, among infants conceived postwar to male veterans, we computed relative risks for 26 birth defects categories. Differences were observed in 2 of 26 birth defects categories, but we expected 5%, or 1.3 of 26 birth defects categories to have a statistically significant result by chance. Similarly, when comparing GWV infants conceived postwar versus prewar, we found statistically significant differences in 2 of 24 birth defect categories, and expected 1.2 of 24 birth defects categories to differ due to chance alone. Among infants conceived postwar to women, prevalence was compared for seven birth defects categories; a significant difference was observed in 1 of 7 categories, but 0.35 of 7 categories was expected to differ by chance.

The linkage algorithms in this study are currently used by some of the participating states to routinely link their vital statistics and birth defects surveillance data. These linkage methods have not been previously employed to assemble birth defects data among military progeny. This unique collaboration between the military and state health departments demonstrates the utility of linkage tools for epidemiological research. Moreover, it emphasizes the important role that state birth defects surveillance programs offer in monitoring birth defects trends.

CONCLUSION

Birth defects affect 1 of every 33 live births, with an unknown etiology for two thirds of all congenital anomalies. Evaluating the relationship between wartime environmental exposures and teratogenesis is complex because of methodological challenges including limited statistical

power for rare events, multiple comparisons, problems in measuring and documenting myriad exposures, discerning paternal from maternal exposures, and case ascertainment and classification concerns. We suggest a higher prevalence of tricuspid valve insufficiency, aortic valve stenosis and renal agenesis or hypoplasia among infants conceived postwar to GWV men, as well as hypospadias among infants conceived postwar to female GWVs. We did not, however, have the ability to determine if the excess was caused by inherited, environmental, or synergistic factors, or was due to chance. Future studies should measure the prevalence of birth defects in other population-based samples of GWV progeny and consider etiologic factors that might be associated with specific birth defects.

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