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Covariates of Human Peripheral Nerve Function: I. Nerve Conduction Velocity and Amplitude

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LETZ, R. AND F. GERR. *Covariates of human peripheral nerve function: I. Nerve conduction velocity and amplitude.* NEUROTOXICOL TERATOL **16**(1) 95–104, 1994. – A systematic investigation of covariates of nerve conduction measures was performed on data collected by the U.S. Centers for Disease Control. Nerve conduction velocity and amplitude were obtained for the median motor, median sensory, ulnar sensory, peroneal motor, and sural sensory nerves on 4,462 subjects. The magnitude of effect of skin temperature, height, body mass index, age, race, place of military service, smoking status, alcohol consumption, income, and EMG examiner was estimated for all 10 conduction outcomes. The major covariates were skin temperature, height, and examiner. Covariates with smaller but not unimportant effects on conduction outcomes were age, race, smoking status, and income. Alcohol consumption was associated with only small effects on conduction measures. These results provide an empirical basis for selection of variables to control in studies employing nerve conduction measures.

Nerve conduction Covariates Human Epidemiologic study

NERVE conduction measures are considered the "gold-standard" for noninvasive evaluation of large, myelinated nerve fiber function. They are used for diagnosis of individual patients as well as for measuring the functional status of peripheral nerves in epidemiologic studies of toxic and metabolic neuropathies (23). To improve the diagnostic utility of these measures in the clinical setting, efforts have been made to control systematically or adjust for the effects of measurement factors, such as temperature and host factors, e.g., age. Recently, it has been suggested that adjustments for height also be made to conduction outcomes obtained for diagnostic purposes (30).

In epidemiologic studies, to prevent confounding and biased conclusions and to improve the fit of the statistical models, it is customary to adjust in the data analysis for variables that are associated with the outcomes of interest. Age and alcohol intake have been used as such covariates in epidemiologic analyses of nerve conduction outcomes (33). However, no systematic investigation of which variables should be used as covariates of nerve conduction outcomes using a large study population has been reported.

The Vietnam Experience Study was a large cross-sectional epidemiologic study of a randomly selected group of veterans undertaken by the United States Centers for Disease Control (CDC) "to look for adverse health effects among men who had served in Vietnam" (ref. 8, p. 1). Two groups of men were studied: (a) men who had served in Vietnam; (b) men who had served concurrently but never in Vietnam. An extensive telephone interview was conducted with more than 16,000 subjects of whom over 4000 participated in medical examinations. The medical examinations included evaluation of symptoms, physical examinations, and laboratory tests of multiple organ systems. Included in the examinations were measurements of nerve conduction velocity and amplitude. The data from this study are available for public use.

In this article, estimates are reported of associations between nerve conduction velocities and amplitudes obtained during the Vietnam Experience Study medical examinations

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and a number of potential covariates: skin temperature, age, height, body mass index, race, place of military service, alcohol consumption, income category, and examiner. The availability of data from over 4000 subjects allowed precise estimation of even relatively small associations that might be expected for previously unreported covariates.

METHOD

Subject selection and examination procedures used by the CDC are presented in detail elsewhere (8). A brief description follows.

Subject Eligibility Criteria

The inclusion criteria for the Vietnam Experience Study study were: (a) U.S. Army veteran; (b) male sex; (c) military occupational specialty other than "duty soldier" or "trainee"; (d) single term of enlistment in the Army; (e) minimum of 16 weeks active service; (f) pay grade E-1 to E-5 at discharge; (g) entered military service for first time between January 1, 1965 and December 31, 1971.

Subject Selection

Vietnam-era veterans were randomly selected from a set of computer tapes containing unique identifiers referable to military personnel records on file at the National Personnel Records Center in St. Louis, MO. The identifiers were restricted to those referable to U.S. Army veterans whose records were received between September, 1964 and June, 1977, totalling approximately 5 million records.

To identify the 16,000–17,000 veterans that the CDC required for inclusion in the study, approximately 50,000 veterans were randomly selected, of which 47,258 had locatable records. Sixty-one percent of those with locatable records did not meet all the inclusion criteria and less than 1% were excluded because their records were missing required information. A total of 18,581 men qualified for the study (9558 Vietnam and 9023 non-Vietnam veterans).

A telephone interview was performed with all living veterans who were located and willing to participate. The overall response of Vietnam veterans was 87% and of non-Vietnam veterans was 84%. A random subsample of approximately 42% of those interviewed were invited to undergo medical, psychological, and laboratory examinations. Seventy-five percent (2,490) of the Vietnam veterans and 63% (1972) of the non-Vietnam veterans chose to participate. The measurements analyzed and presented here were obtained during the medical examination phase of the study.

Medical Examination Protocol

All examinations were performed at a single facility (Lovelace Medical Foundation, Albuquerque, NM) between June 3, 1985 and September 30, 1986. All travel-related expenses were paid and a $300 stipend was offered to compensate for pay lost during participation.

The electrophysiologic measurements were performed on the second day of each subject's 4-day examination period. Fasting blood samples were drawn on the morning of the second day. Breath alcohol levels were taken at the beginning of the second and third examination days.

Height and weight were obtained on all subjects by a nurse at the time of physical examination. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared.

A complete neurologic examination was performed on all subjects by a board-certified neurologist. All examining neurologists were trained to conduct a standardized examination. The examination was intended to provide assessment of the cranial nerves, deep tendon reflexes, motor function, and sensory function. Examining clinicians were unaware of participants' exposure or past medical histories (9,10).

Nerve Conduction Examination Procedures

Nerve conduction velocity (NCV) and amplitude for all nerves tested were measured using standard techniques (22) with a TECA TD10-MK2 electromyograph (TECA Corp., Pleasantville, NY) and surface electrodes. Specifically, median motor, median sensory, ulnar sensory, peroneal motor, and sural sensory NCVs and amplitudes were obtained from the dominant limb of each subject. (Although both wrist-to-finger and elbow-to-finger median sensory measurements were performed, to reduce redundancy in the data, the less commonly performed elbow-to-finger sensory measurements were not analyzed for this article.) All sensory conduction velocities were obtained using antidromic stimulation.

For median motor nerve evaluation, the active recording electrode was placed over the abductor pollicis brevis muscle; distal stimulation was performed over the median nerve 2 cm proximal to the distal wrist crease and proximal stimulation was performed at the elbow medial to the biceps tendon. For median sensory nerve evaluation, the active recording ring electrode was placed on the index finger 1 cm distal to the interdigital cleft; proximal and distal stimulation of the nerve was performed at the same sites as for median motor nerve evaluation just described. For ulnar sensory nerve evaluation, the active recording ring electrode was placed on the fifth digit 1 cm distal to the interdigital cleft and stimulation was performed over the flexor carpi ulnaris tendon at the wrist, approximately 14 cm proximal to the active recording electrode. For peroneal motor nerve evaluation the active recording electrode was placed over the extensor digitorum brevis muscle; distal stimulation was performed over the peroneal nerve approximately 8 cm proximal to the active recording electrode and proximal stimulation was performed at the knee, distal and lateral to the head of the fibula. For sural sensory nerve evaluation, the active recording electrode was placed inferior to the lateral malleolus and stimulation was performed approximately 14 cm proximal to the active recording electrode.

Supramaximal stimulation was used to obtain all latencies and amplitudes. Supramaximal stimulation was assured by performing a series of stimulations while increasing the stimulation voltage and observing the evoked response amplitude on the EMG oscilloscope screen. When no increase in evoked response amplitude was observed after two consecutive stimulations, the higher stimulation voltage was considered to be supramaximal. Averaging of 3 to 5 motor responses and 5 to 32 sensory responses was performed to obtain adequate signal-to-noise ratios. Motor and sensory latencies were recorded as the time from stimulation to the onset of the evoked action potential. Amplitudes were obtained by measuring from baseline to the negative (upward) peak of the evoked action potential. Additional details of the electrophysiological testing protocol are provided in CDC documentation (9,10).

Eight technicians were trained to perform the electrophysiological evaluations in a standardized manner. An on-site clinic manager maintained quality control by directly observing each examiner perform an entire nerve conduction test

each week. In addition, 10% of each weeks' nerve conduction data was sent to an outside electrophysiology consultant for review (10).

Skin temperature was recorded at the time of the electrophysiologic testing. Limbs with skin temperatures below 31°C were warmed with a water blanket. Forearm temperature was used as a covariate of median motor outcomes, palm temperature for median and ulnar sensory outcomes, mid-calf temperature for peroneal motor outcomes, and foot temperature for sural sensory outcomes.

Questionnaire Information

Standard questionnaires were administered to all subjects during the telephone interviews as well as during the medical examinations to obtain information about a wide variety of health-related issues. During the telephone interview, among several questions about alcohol consumption, the dates and ages for beginning and ending alcohol consumption, the average number of drinking days per month and the average number of drinks consumed per drinking day were recorded. In addition, subjects were asked if there was a period of time of greater than 6 months duration during which they drank substantially heavier than at other times. Similar information was obtained for this period of time as well. From this information an estimate of each subject's lifetime dose of alcohol was calculated. Two other alcohol consumption summary measures were derived from questions about current drinking practices asked during the medical examinations: average drinking intensity expressed as the current average number of drinks per month and calculated from the average number of drinking days per month multiplied by the average number of drinks per drinking day, and recent heavy drinking, expressed as the number of occasions of drinking 5 or more drinks in 1 day during the past month. Because these three alcohol summary variables (lifetime dose, current average drinking intensity, and recent heavy drinking) were highly skewed to the right and the shapes of the dose response curves were not known, they were stratified into 5–7 easily interpretable ranges that left no fewer than 150 subjects in any group. Subjects who reported during the telephone interview that they never drank more than 1 alcoholic drink per month for a year and who also reported consuming no drinks per month at the time of the medical examination were considered "Never" drinkers.

During the medical examinations, subjects were asked about current and past cigarette smoking. Subjects smoking at least 1 cigarette per day at the time of examination were categorized as current smokers. Race and place of military service were obtained from military service records and verified at the time of the medical examinations. Annual household income was obtained during the telephone interview. Household income categories were: 1 = <$10,000; 2 = $10,000 to $19,999; 3 = $20,000 to $29,999; 4 = $30,000 to $39,999; 5 = > = $39,999.

Data Analysis

Exclusions. Of the 4,462 potential subjects, 406 (9.1%) were excluded from the present analyses. The rationale was to exclude subjects with medical conditions that might affect the nerve conduction outcomes and those with missing or potentially inaccurate covariate measures. The number of subjects meeting each of the exclusion criteria are listed in Table 1. The exclusion criteria met most frequently were missing covariate information from the interview, history of diabetes mellitus, fasting blood glucose level >140 mg/dL, thyroid stimulating hormone level > 8 mIU/L, history of peripheral neuropathy, signs of peripheral neuropathy on examination, unsatisfactory responses during the interview, or use of medications identified by the CDC known to be associated with peripheral neuropathy (9). These medications were chloramphenicol, cisplatin, clioquinol, dapsone, diphenylhydantoin, disulfiram, ethionamide, glutethimide, gold, hydralazine, isoniazid, metronidazole, nitrofurantoin, perhexiline maleate, pyridoxine, sodium cyanate, thalidomide, and vincristine.

TABLE 1

SUBJECT EXCLUSION CRITERIA FOR THE NERVE CONDUCTION ANALYSES

Exclusion Criterion	Number†
Age >46	1
Cancer (except skin)	29
Medications	36
Unsatisfactory interview	40
Covariate information missing (alcohol, income)	114
Breath alcohol >0.1% BAC	1
Blood urea nitrogen >30 mg/dL	1
Thyroid stimulating hormone >8 mIU/L	47
Fasting blood glucose <40 mg/dL	1
History of diabetes mellitus	51
Fasting blood glucose >140 mg/dL	48
History of cirrhosis	12
History of peripheral neuropathy	44
Signs of peripheral neuropathy	40

Total number of subjects undergoing examination = 4462; total number of subjects excluded = 406† (9.1%); total number of subjects NOT excluded = 4056 (90.9%).

†Some subjects met more than one exclusion criterion.

Data voiding. Inspection of initial descriptive statistics revealed a number of impossible values for some parameters. Therefore, a set of quality assurance void criteria were implemented. An individual data point was voided if it exceeded any of the void criteria. These void criteria included: (a) median motor amplitude <400 μV; (b) median sensory amplitude <0.5 μV; (c) ulnar sensory amplitude <0.5 μV; (d) peroneal motor amplitude <400 μV; (e) sural sensory amplitude <0.5 μV; (f) median motor proximal latency < distal latency; (g) median sensory elbow-finger latency < wrist-finger latency; (h) median sensory elbow-wrist distance < wrist-finger distance; (i) peroneal motor proximal latency < distal latency; (j) median motor NCV > 85 m/s; (k) median sensory NCV > 75 m/s; (l) ulnar sensory NCV > 75 m/s; (m) peroneal motor NCV > 85 m/s; (n) sural sensory NCV > 75 m/s. These void criteria were drawn in part from those used by CDC in their analyses of these data to determine the effects of the Vietnam experience (9). If a latency or distance was voided, the corresponding NCV was also voided. In addition, on occasion one or two wild outlier data points identified by visual inspection of plots were voided (e.g., two BMIs > 60.0).

Statistical methods. General linear models (31) were fitted separately for each of the 10 nerve conduction outcomes. In these 10 analyses, 10 variables were included as potential predictors: skin temperature near the nerve segment, height, body mass index, age, an indicator variable for race (nonblack/black), an indicator variable for place of service (non-Viet-

nam/Vietnam), an indicator variable for current smoking status (nonsmoker/smoker), a categorical variable for alcohol drinking intensity level, a categorical variable for annual household income level, and a categorical variable for the eight examiners administering the nerve conduction tests.

RESULTS

Description of Sample Demographics

Demographic characteristics of the 4,056 subjects remaining after application of the exclusion criteria are presented in Table 2. Because one inclusion criterion was first entry into the Army between 1965 and 1971, the sample was relatively young (38.3 years) and the range of ages was restricted (31–46 years). Approximately 11% of the study population was black. Almost half of the subjects were current smokers. Twelve percent of the study population drank 3 or more alcoholic drinks per day and 3.5% drank 6 or more alcoholic drinks per day. Study participants reported a wide range of annual household incomes. Income category 3 ($20,000 to $29,999/year) was the most common. All examiners performed nerve conduction studies on relatively similar proportions of the subjects except for Examiner 6 who performed nerve conduction measures on less than 3% of the total group.

TABLE 2

DEMOGRAPHIC AND OTHER CHARACTERISTICS OF THE STUDY SAMPLE

	Mean	(SD)
Height (cm)	176.3	(6.74)
Body mass index (kg/m^2)	26.8	(4.36)
Age (years)	38.3	(2.50)
Palm temperature (°C)	32.7	(0.86)
Forearm temperature (°C)	33.1	(0.87)
Upper-calf temperature (°C)	32.5	(0.91)
Foot temperature (°C)	32.1	(0.90)
Race (% Black)	11.4	
Place of service (% Ever Vietnam)	55.1	
Current smoking (%)	44.8	
Alcohol drinking category (%)		
Never-drinker	9.9	
0 drinks/month	14.5	
1–29 drinks/month	37.6	
30–89 drinks/month	26.0	
90–179 drinks/month	8.4	
>179 drinks/month	3.6	
Household income category (%)		
1 – <$10,000/yr	9.4	
2 – $10,000–$19,999/yr	18.2	
3 – $20,000–$29,999/yr	27.9	
4 – $30,000–$39,999/yr	22.4	
5 – >$39,999/yr	22.1	
Examiner (%)		
1	15.9	
2	12.4	
3	15.1	
4	14.7	
5	16.3	
6	2.7	
7	11.5	
8	11.5	

n = 4056.

TABLE 3

DESCRIPTIVE STATISTICS OF THE NERVE CONDUCTION VARIABLES

	N	MEAN	SD
Median motor NCV (m/s)	4046	57.44	4.26
Median sensory NCV (m/s)	4008	53.86	6.19
Ulnar sensory NCV (m/s)	4037	55.24	5.90
Peroneal motor NCV (m/s)	4016	46.46	4.13
Sural sensory NCV (m/s)	3923	44.51	5.85
Median motor amplitude (mV)	4054	10.40	3.47
Median sensory amplitude (μV)	4039	23.67	8.64
Ulnar sensory amplitude (μV)	4041	21.79	9.24
Peroneal motor amplitude (mV)	4017	6.91	2.95
Sural sensory amplitude (μV)	3925	16.89	10.72

Description of Velocity and Amplitude Outcomes

The number of valid observations included in the analyses, means, and SDs of the 10 nerve conduction outcomes are presented in Table 3. The number of observations varied slightly among the outcomes. For example, 126 subjects (3.1%) had sural sensory evoked responses recorded as unelicitable or less than 0.5 μV. Slightly fewer observations were valid for the nerve conduction velocity outcomes than the corresponding amplitudes. This occurred because a conduction velocity could be voided if the velocity was in excess of 75 or 85 m/s (depending on the nerve segment; see Method section) or if the distal distance recorded was longer than the proximal distance, while in such cases the associated amplitude was retained.

Results of the General Linear Models

Parameter estimates from fitting the general linear models and their associated standard errors of estimate for covariates of nerve conduction velocity are presented in Table 4. Corresponding results for nerve conduction amplitude are presented in Table 5. With such a large sample size, in general, an effect observed to be significant at the $p < 0.05$ level could account for as little as 0.1% of the total variance in the dependent variable. Therefore, statistical significance alone is not a useful measure of the strength of associations in a sample this large. To provide some indication of the relative importance of each covariate, the estimated magnitude of the change in each electrophysiological outcome over a well-defined range of each covariate is presented in Table 6. For the four continuous covariates (temperature, height, BMI, and age), the ranges provided correspond to the empirical 5th and 95th percentiles of the covariate in this sample. The range of each covariate is provided in parentheses and the estimated change in each outcome over that range is presented in the Table 6. For the three dichotomous variables (race, place of service, and smoking status), the values in Table 6 represent the estimated mean difference in outcome between the dichotomized groups. For the three categorical variables (drinking intensity group, household income and examiner), the results provided are the largest estimated mean differences in outcome between any two categories. The purpose of Table 6 is to provide a guide to the magnitude of change in each outcome measure over the

TABLE 4

PARAMETER ESTIMATES AND THEIR SIGNIFICANCE LEVELS FOR COVARIATES OF NCVs

Parameter	Median Motor	Median Sensory	Ulnar Sensory	Peroneal Motor	Sural Sensory
Skin temperature	0.604§	1.433§	1.539§	0.286§	1.123§
Height	−0.045§	−0.012	−0.068§	−0.208§	−0.171§
Body mass index	0.007	−0.065†	0.278§	0.085§	0.192§
Age	−0.108§	−0.127†	−0.163§	−0.139§	−0.075†
Race	−0.349	−0.572	−2.785§	0.110	−1.334§
Place of service	−0.004	−0.316	−0.350*	−0.113	−0.041
Smoking status	−0.559§	−0.196	−0.130	−0.554§	0.346
Alcohol category					
0	0.211	0.473	0.672	−0.080	0.140
1–29	0.569*	0.887†	0.710*	0.107	0.027
30–89	0.489*	0.855*	0.903†	−0.096	−0.229
90–179	0.411	0.304	0.043	−0.072	0.009
>179	−0.155	0.003	−0.176	−0.811*	−1.042
Never	0.000	0.000	0.000	0.000	0.000
Income category					
1	−1.046§	−1.665§	−1.487§	−0.440	−0.538
2	−0.970§	−1.333§	−0.851†	−0.407*	−0.560
3	−0.930‡	−0.972‡	−0.847‡	−0.862§	−0.795
4	−0.833‡	−0.851†	−0.188*	−0.532†	−0.634*
5	0.000	0.000	0.000	0.000	0.000
Examiner					
1	−0.191	0.213	0.390	0.123	1.444§
2	0.459	1.614§	1.037†	−0.305	0.046
3	−0.104	0.718	0.125	−0.296	0.340
4	−0.718†	1.577§	0.643†	−0.677†	2.084§
5	−0.966§	1.770§	1.804§	0.592*	0.428
6	0.507	2.110†	0.302	0.702	1.451*
7	−1.467§	−0.659	−1.174‡	0.001	0.894*
8	0.000	0.000	0.000	0.000	0.000

*Signifies $p < 0.05$; †$p < 0.01$; ‡$p < 0.001$; §$p < 0.0001$.

range of covariate values likely to be encountered in general practice (with the exception of age, which was restricted in range in this cohort).

Temperature. Decreased limb temperature was associated with slower conduction velocity for all five nerves. The effect of temperature was greater for sensory than for motor conduction velocity. Over the 2.5°C range presented in Table 6, ulnar sensory conduction velocity varied by almost 4 m/s and median sensory conduction velocity varied by 3.6 m/s. For all five outcomes, velocity varied from 0.29 to 1.5 m/s/°C (Table 4). The relationship between temperature and sural sensory conduction velocity is illustrated in Fig. 1. Temperature was negatively related to all three sensory amplitudes (Table 5). Over the 2.5°C range presented in Table 6, median sensory amplitude varied by 2.4 μV, ulnar sensory amplitude by 1.8 μV, and sural sensory amplitude by 1.9 μV.

Height. Increased height was associated with slower conduction velocity and smaller amplitude for most nerves studied. For the five conduction velocity outcomes, velocity varied from 0.0 to 0.21 m/s/cm (Table 4). The effect of height was substantially greater on conduction velocity measures in the lower extremity than on those in the upper extremity. Over the 5th to 95th percentile range of height observed in the current study, peroneal motor and sural sensory velocities varied by 4.6 and 3.8 m/s, respectively (Table 6). The relationship between height and sural sensory conduction velocity is illustrated in Fig. 2. The effect of height on amplitude was similar for nerves in the upper and lower extremities. Only for median sensory velocity and median motor amplitude was the effect of height not statistically significant.

Body Mass Index. BMI was inconsistently associated with conduction velocities, having a small negative effect on median sensory velocity, and positive effects on ulnar sensory, sural sensory, and peroneal motor conduction velocity. BMI had essentially no effect on median motor conduction velocity. The relationship between BMI and sural sensory conduction velocity is illustrated in Fig. 3. BMI was negatively associated with all amplitudes except peroneal motor amplitude. Over the 5th to 95th percentile range of BMI observed in the current study, ulnar sensory and sural sensory conduction velocity varied by 3.7 and 2.6 m/s, respectively (Table 6). Over the same range, median sensory and ulnar sensory amplitude varied by 5.5 and 3.9 μV, respectively (Table 6).

Age. A relatively uniform negative association between age and conduction velocity was observed for all five conduction velocity measures. Even over the relatively restricted range of 9 years, velocities showed slowing that ranged from 0.7 to 1.5 m/s (Table 6). Median sensory, ulnar sensory, and peroneal motor amplitudes were reduced with increasing age. Over the restricted range in this study, age was not significantly related to median motor or sural sensory amplitude.

Race. Black race was associated with slower conduction velocity for all nerves except the peroneal motor nerve. As shown in Table 4, the effect was especially strong for ulnar

TABLE 5

PARAMETER ESTIMATES AND THEIR SIGNIFICANCE LEVELS FOR COVARIATES OF AMPLITUDES

Parameter	Median Motor	Median Sensory	Ulnar Sensory	Peroneal Motor	Sural Sensory
Skin Temperature	−0.050	−0.938§	−0.738§	−0.062	−0.754§
Height	−0.004	−0.201§	−0.236§	−0.055§	−0.360§
Body mass index	−0.144§	−0.408§	−0.294§	0.015	−0.197§
Age	0.003	−0.235§	−0.264§	−0.074§	0.052
Race	1.015§	0.656	−1.450‡	1.344§	−1.258*
Place of service	−0.175	−0.363	−0.215	−0.145	−0.480
Smoking status	−0.341†	−1.179§	−1.248§	−0.245*	−0.774*
Alcohol category					
0	−0.029	0.304	0.807	−0.028	−0.526
1–29	0.109	1.240†	1.380†	0.015	−0.194
30–89	0.022	1.256†	1.104*	−0.047	0.415
90–179	0.123	0.575	0.709	0.048	0.789
>179	−0.227	0.182	−0.070	−0.027	0.136
Never	0.000	0.000	0.000	0.000	0.000
Income category					
1	−0.654†	−2.049§	−2.394§	−0.396*	−1.398*
2	−0.561‡	−2.226§	−1.992*	−0.418†	−0.814
3	−0.452†	−2.086§	−1.635‡	−0.383*	−0.106
4	−0.372*	−1.330‡	−0.784†	−0.258	−0.005
5	0.000	0.000	0.000	0.000	0.000
Examiner					
1	−1.204§	−1.275*	1.195*	−0.732§	0.390
2	0.690†	−1.803‡	−1.314*	−0.159	−3.343§
3	−0.236	−1.012*	0.277	−0.220	−1.559*
4	−0.373	−1.540†	−0.538	0.362*	−4.782§
5	0.407*	−0.160	0.287	0.046	−4.530§
6	1.022†	−0.554	−1.365	0.161	1.646
7	−0.752‡	−1.811†	−3.122§	−0.546†	−6.586§
8	0.000	0.000	0.000	0.000	0.000

*Signifies $p < 0.05$; †$p < 0.01$; ‡$p < 0.001$; §$p < 0.0001$.

sensory (-2.8 m/s) and sural sensory (-1.3 m/s) conduction velocity. The effect of race was not significant on median motor, median sensory, or peroneal motor velocities. Black race was positively associated with median motor and peroneal motor amplitude and negatively associated with ulnar sensory and sural sensory amplitude.

Place of military service. A small negative effect of service in Vietnam when compared to never serving in Vietnam was observed only for ulnar sensory nerve conduction velocity (Table 4). No significant effect of place of military service was observed for the remaining 9 outcome measures.

Smoking status. A negative effect of smoking was ob-

TABLE 6

MAGNITUDE OF CHANGE OVER RANGE OF COVARIATE

	Conduction Velocity					Amplitude				
Source	Median Motor	Median Sensory	Ulnar Sensory	Peroneal Motor	Sural Sensory	Median Motor	Median Sensory	Ulnar Sensory	Peroneal Motor	Sural Sensory
Skin temperature (32° to 34.5°C)	1.51	3.58	3.85	0.72	2.81	−0.13	−2.35	−1.84	−0.16	−1.88
Height (165 to 187 cm)	−0.99	−0.26	−1.50	−4.57	−3.77	−0.09	−4.41	−5.20	−1.21	−7.92
Body mass index (20.9 to 34.3)	0.09	−0.88	3.73	1.15	2.57	−1.93	−5.46	−3.93	0.20	−2.64
Age (34 to 43 yr)	−0.97	−1.14	−1.47	−1.25	−0.68	0.03	−2.11	−2.38	−0.67	0.47
Race (nonblack–black)	−0.35	−0.58	−2.79	0.11	−1.33	1.02	0.66	−1.45	1.34	−1.26
Place of service (Never–Ever Vietnam)	−0.01	−0.32	−0.35	−0.13	−0.04	−0.18	−0.36	−0.22	−0.15	−0.48
Smoking status (nonsmoker–smoker)	−0.56	−0.20	−0.13	−0.55	0.35	−0.34	−1.18	−1.25	−0.25	−0.77
Drinking category (range)	0.72	0.89	1.08	0.92	1.18	0.35	1.26	1.45	0.10	1.31
Income category (range)	1.05	1.67	1.49	0.86	0.80	0.65	2.23	2.39	0.42	1.40
Examiner (range)	1.97	2.76	2.98	1.38	3.43	2.22	1.81	4.32	1.94	8.22

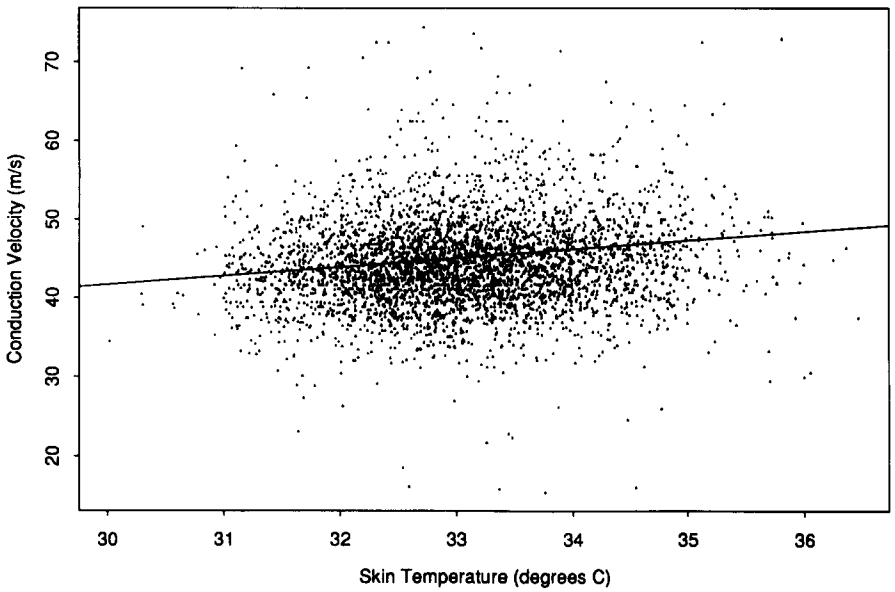

FIG. 1. Sural sensory conduction velocity as a function of skin temperature.

served for all amplitudes and both motor conduction velocities. A small nonsignificant positive effect of smoking was observed for sural sensory conduction velocity. The effect of smoking was largest for the motor velocities, for which smokers had about 0.5 m/s slower conduction than nonsmokers (Table 4).

Alcohol consumption. The parameter estimates in Table 4 and Table 5 for alcohol consumption category are presented relative to the Never-drinker group. Over a wide range of alcohol consumption, little change in either conduction velocity or amplitude was observed. Consumers of up to 179 drinks per month tended to have slightly faster conduction than both "Never" drinkers and those consuming more than 179 drinks per month (Table 4). Of all the nerve conduction velocity outcomes studied, the largest difference between any two drinking categories was 1.2 m/s (Table 6). Similarly small positive effects of light to moderate alcohol consumption were observed on median and ulnar sensory amplitude (Table 5). The largest differences in amplitude observed between any two drinking categories were 0.4 μV for motor outcomes and 1.5 μV for sensory outcomes (Table 6).

Income. The parameter estimates for income are presented relative to the highest income category. For all nerves tested, conduction velocity and amplitude were poorer in the lower

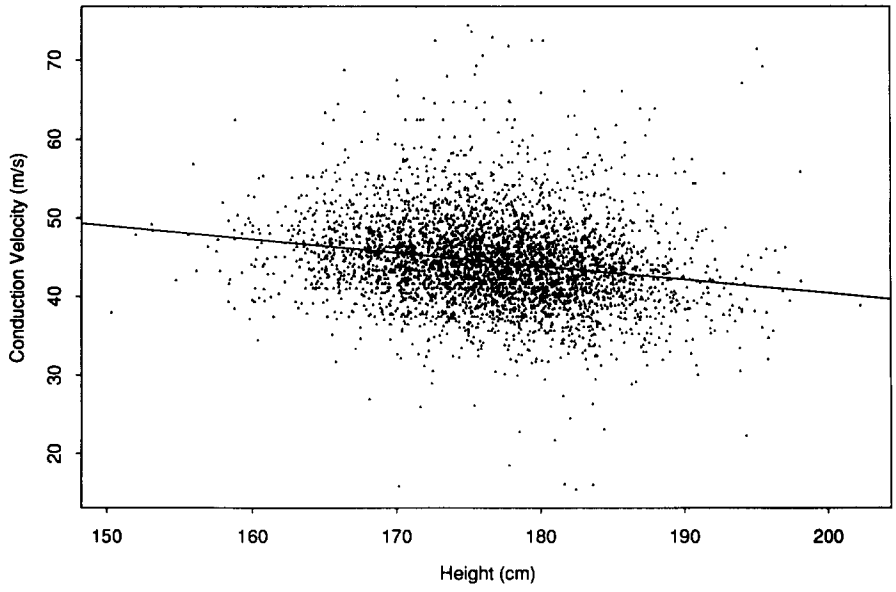

FIG. 2. Sural sensory conduction velocity as a function of height.

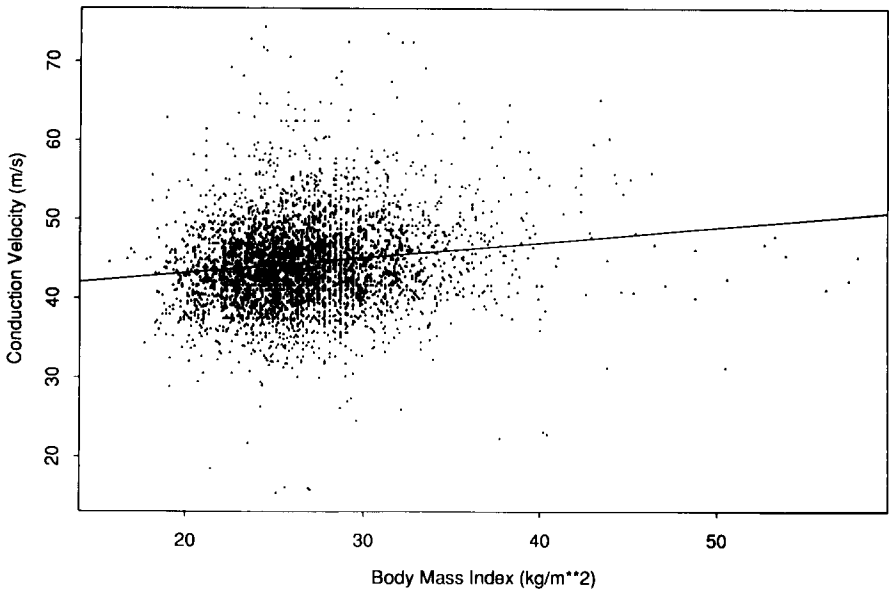

FIG. 3. Sural sensory conduction velocity as a function of body mass index.

income categories. In general, velocity and amplitude diminished monotonically with decreasing income group. This relationship was stronger for conduction measures performed in the upper extremity than for those performed in the lower extremity and for sensory conduction measures than for motor conduction measures. The maximum difference between any two income groups among the sensory conduction velocities was about 1.7 m/s and the maximum difference between any two income groups among the sensory amplitudes was 2.4 μV (Table 6).

Examiner. Considerable systematic variability due to which of eight examiners performed the measurements was observed in most of the nerve conduction outcomes. The parameter estimates in Table 4 and Table 5 are presented relative to one examiner, chosen arbitrarily. The largest difference in any conduction velocity outcome observed between any two examiners was 3.4 m/s (Table 6). Mean sural sensory amplitude varied by more than 8 μV over the range of eight examiners performing the measures. Although modestly large and highly statistically significant variability was observed between examiners, no examiner produced consistently higher or lower conduction velocity or amplitude values across all nerves than did the other examiners.

DISCUSSION

The medical examinations of the Vietnam Experience Study generated the largest set of nerve conduction measurements collected according to a common protocol ever reported. In this population-based study of relatively healthy, young males, the major covariates of nerve conduction outcomes were skin temperature, height, body mass index, and examiner. Other covariates with lesser but nontrivial effects on conduction outcomes were age, race, smoking status, and income. Alcohol consumption had only small effects on conduction measures, and place of military service was essentially unrelated to all conduction outcomes.

Skin temperature was positively associated with all NCVs. The association was greater for sensory than for motor NCVs. A small negative association was observed between temperature and amplitudes. The magnitudes and direction of the effects of temperature on conduction velocity and amplitude observed in the current study are within the ranges reported previously in the literature (1,6,13,16,17,19,35,37,38).

Age had a nontrivial negative association with outcome, even in this relatively young, restricted age range. Estimates of the magnitude of the effect of age on conduction measures from this study were remarkably similar to those from studies with substantially larger ranges of age (3,12,14,29,30,36). The consistency of the results of the current study for the effects of age and temperature with those reported by previous studies suggests that the data quality and analysis methods were capable of generating valid estimates of subtle effects of covariates of peripheral nerve conduction measurements.

Height was negatively related to the nerve conduction measures. It was more strongly associated with lower extremity conduction measures than upper extremity measures. These results are consistent with two reports in which estimates of the effect of height on nerve conduction velocity were provided (30,36). They are not consistent with a recent study of sural conduction velocity among 92 subjects in which no association with height was observed (39). The significant negative associations between height and all amplitudes studied except median motor amplitude appear to be the first reported in the literature.

The effect of examiner was large and inconsistent across nerve conduction outcomes. No study systematically evaluating differences in conduction measures among equivalently trained examiners has been reported previously. These results suggest that stringent quality control measures as well as rigorous training are required in studies using multiple examiners. These results also confirm the widely held belief that conduction values are examiner-dependent and that comparison of results between laboratories may result in systematic error.

The association between BMI and conduction outcomes was inconsistent, though frequently highly significant. Review

of the literature revealed one study where BMI was associated with a conduction measure, the maximum latency difference of the median nerve at the wrist, a measure used for detection of carpal tunnel syndrome (28). Specifically, in that study increasing BMI was associated with poorer median sensory conduction across the wrist. A similar effect was observed for median sensory conduction velocity in the present study, although increasing BMI was associated with better nerve conduction in other nerve segments. These findings are currently without explanation.

Black race was strongly negatively associated with ulnar sensory NCV and inconsistently associated with other measures, even while controlling for socioeconomic status. Extensive review of the literature failed to reveal any other comparative studies of the effect of race on conduction parameters.

Smoking had small and mostly negative associations with velocity and amplitude measures. No other studies of this effect have been reported.

Consistent with the conclusion of the CDC regarding the effect of the Vietnam experience (8), place of service had virtually no association with nerve conduction outcomes.

Income had a relatively large positive association with median motor and median sensory nerve conduction velocity and amplitude. Similarly, although less consistent, associations were observed for ulnar sensory conduction velocity and amplitude. Essentially no association was observed between income category and lower extremity conduction parameters. These results may reflect associations between income and occupational use of the upper extremities, a possible risk-factor for entrapment neuropathy. These results need to be explored further with analyses that include information about occupational exposure to ergonomic stressors. No other studies have been published that report associations between income and conduction velocity.

Only small effects of alcohol consumption were observed in this study. Much literature has developed regarding the effect of alcohol consumption on the peripheral nervous system (2,4,5,7,11,18,20,21,24,25,26,27,32,34,40,41,42). However, virtually all published studies of the effects of alcohol on nerve conduction velocity have been performed on chronic alcoholic subjects or patients with alcohol-related diseases. The results of the current study are the only ones available in which associations between alcohol consumption and conduction parameters were estimated in a population not chosen on the basis of either a diagnosis of alcoholism or the presence of a known alcohol-related health effect. Contrary to the conclusions of some investigators (4,27), these results suggest that moderate alcohol consumption, per se, is not directly toxic to those elements of the peripheral nervous system tested with conduction measures. Additional analyses and discussion of these data with respect to reported alcohol consumption are provided in a companion paper (15).

One potential concern is that the data voiding criteria used may have resulted in distortion of the effect of various covariates on nerve conduction measures. Despite rigorous quality control measures, some recording and coding errors are inevitable in epidemiologic studies of thousands of subjects. Void criteria were chosen to maximize removal of erroneous data while minimizing removal of abnormal but correct values. Most of the void criteria used in the current study were adopted from those developed by CDC investigators and their consultants. To some extent, these choices are arbitrary. The number of data points voided was small and the magnitude of any potential bias in the analyses resulting from voiding is likely to have been small as well. The strong consistency of results of the current study with other studies of specific covariates suggests that substantial bias did not occur in our analyses.

These results have important implications for both epidemiologic research as well as clinical practice. They suggest that skin temperature, height, and examiner should be controlled for in analyses of nerve conduction data in epidemiologic studies of relatively healthy adult males. Age, race, smoking status, and income also have the potential to bias study results, although to a lesser degree, if not adequately controlled. Failure to control for alcohol consumption is not likely to produce substantial confounding of results.

In clinical practice, limb temperature, patient height and age, and examiner must be considered when reviewing results of conduction velocities. Furthermore, extreme caution is recommended when comparing conduction results obtained by different examiners. Finally, alcohol consumption alone is an unlikely explanation for slowed conduction velocity and diminished amplitude in all but extremely heavy drinkers among males less than 50 years of age.

Caution is advised when generalizing results from this study to other populations. The subjects of the current study were relatively young males who had been screened for health at the time of entry into military service. The results obtained from this group may not apply to subjects with other demographic characteristics outside the range of these subjects.

Additional research is needed to confirm the previously unreported associations between race, cigarette smoking, and income and conduction parameters. Investigation to further clarify the associations between alcohol consumption, height, and BMI and conduction parameters is required. In addition, research to elucidate the mechanism of the effects of several covariates is needed.

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REFERENCES

1. Alfonsi, E.; Merlini, G. P.; Gioretti, A.; Ceroni, M.; Piccolo, G.; Agostinis, C.; Savoldi, F. Temperature-related changes in sensory nerve conduction: Studies in normal subjects and in patients with paraproteinemia. Electromyogr. Clin. Neurophysiol. 27:277–282; 1987.
2. Ballantyne, J. P.; Hansen, S.; Weir, A.; Whitehead, J. R. G.; Mullin, P. J. Quantitative electrophysiological study of alcoholic neuropathy. J. Neurol. Neurosurg. Psychiat. 43:427–432; 1980.
3. Behse, F.; Buchthal, F. Normal sensory conduction in the nerves of the leg in man. J. Neurol. Neurosurg. Psychiat. 34:404–414; 1971.
4. Behse, F.; Buchthal, F. Alcoholic neuropathy: Clinical, electrophysiological and biopsy findings. Ann. Neurol. 2:95–110; 1977.
5. Blackstock, E.; Rushworth, G.; Gath, D. Electrophysiological studies in alcoholism. J. Neurol. Neurosurg. Psychiat. 35:326–334; 1972.

6. Bolton, C. F.; Sawa, G. M.; Carter, K. The effects of temperature on human compound action potentials. J. Neurol. Neurosurg. Psychiat. 44:407–413; 1981.
7. Casey, E. B.; Le Quesne, P. M. Electrophysiological evidence for a distal lesion in alcoholic neuropathy. J. Neurol. Neurosurg. Psychiat. 35:624–630; 1972.
8. Centers for Disease Control. Health status of Vietnam veterans. Vol. I, Synopsis. Atlanta, GA: U.S. Department of Health and Human Services; 1989.
9. Centers for Disease Control. Health status of Vietnam veterans, Vol. III: Medical examinations. Atlanta, GA: U.S. Department of Health and Human Services; 1989.
10. Centers for Disease Control. Health status of Vietnam veterans. Supplement C: Medical and psychological procedure manuals and forms. Atlanta, GA: U.S. Department of Health and Human Services; 1989.
11. Claus, D.; Eggers, R.; Engelhardt, A.; Neundorfer, B.; Warecka, K. Ethanol and polyneuropathy. Acta Neurol. Scand. 72:312–316; 1985.
12. Cruz Martinez, A.; Barrio, M.; Perez Conde, M. C.; Ferrer, M. T. Electrophysiological aspects of sensory conduction velocity in healthy adults. 1. Conduction from digit to palm, from palm to wrist, and across the elbow, as a function of age. J. Neurol. Neurosurg. Psychiat. 41:1092–1096; 1978.
13. de Jesus, P. V.; Hausmanowa-Petrusewicz, I.; Barchi, R. L. The effect of cold on nerve conduction of human slow and fast nerve fibers. Neurology 23:1182–1189; 1973.
14. Dorfman, L. J.; Bosley, T. M. Age-related changes in peripheral and central nerve conduction in man. Neurology 29:38–44; 1979.
15. Gerr, F.; Letz, R. Covariates of human peripheral nerve function: III. Effects of reported drinking. Neurotoxicol. Teratol. 16:113–122; 1994.
16. Halar, E. M.; DeLisa, J. A.; Brozovich, F. V. Nerve conduction velocity: Relationship of skin, SC and intramuscular temperatures. Arch. Phys. Med. Rehabil. 61:199–203; 1980.
17. Halar, E. M.; DeLisa, J. A.; Brozovich, F. V. Peroneal nerve conduction velocity: The importance of temperature correction. Arch. Phys. Med. Rehabil. 62:439–443; 1981.
18. Hawley, R. J.; Kurtzke, J. F.; Armbrustmacher, V. W.; Saini, N.; Manz, H. The course of alcoholic-nutritional peripheral neuropathy. Acta. Neurol. Scand. 66:582–589; 1982.
19. Hlavova, A.; Abramson, D. I.; Rickert, B. L.; Talso, J. F. Temperature effects on duration and amplitude of distal median nerve action potential. J. Appl. Physiol. 28:808–812; 1970.
20. Jurko, M. F.; Currier, R. D.; Foshee, D. P. Peripheral nerve changes in chronic alcoholics: A study of conduction velocity in motor nerves. J. Nerve Ment. Dis. 139:488–490; 1964.
21. Kempainen, R.; Juntunen, J.; Hillbom, M. Drinking habits and peripheral alcoholic neuropathy. Acta Neurol. Scand. 65:11–18; 1982.
22. Kimura, J. Electrodiagnosis in diseases of nerve and muscle: Principles and practice. Philadelphia: F. A. Davis; 1983.
23. Kimura, J. Electrodiagnosis in diseases of nerve and muscle: Principles and practice, 2nd ed. Philadelphia: F. A. Davis; 1989.
24. Lefebvre D'Amour, M.; Shahani, B. T.; Young, R. R.; Bird, K. T. The importance of studying sural nerve conduction and late responses in the evaluation of alcoholic subjects. Neurology 29: 1600–1604; 1979.
25. Mayer, R. Peripheral nerve conduction in alcoholics. Psychosom. Med. 28:475–483; 1966.
26. Mawdsley, C.; Mayer, R. F. Nerve conduction in alcoholic polyneuropathy. Brain 88:335–356; 1965.
27. Meldgaard, B.; Andersen, K.; Ahlgren, P.; Danielsen, U. T.; Sorensen, H. Peripheral neuropathy, cerebral atrophy, and intellectual impairment in chronic alcoholics. Acta Neurol. Scand. 70: 336–344; 1984.
28. Nathan, P. A.; Keniston, R. C.; Myers, L. D.; Meadows, K. D. Obesity as a risk factor for slowing of sensory conduction of the median nerve in industry. J. Occ. Med. 34:379–383; 1992.
29. Norris, A. H.; Shock, N. W.; Wagman, I. H. Age changes in the maximum conduction velocity of motor fibers of human ulnar nerves. J. Appl. Physiol. 5:589–593; 1953.
30. Rivner, M. H.; Swift, T. R.; Crout, B. O.; Rhodes, K. P. Toward more rational nerve conduction interpretations: The effect of height. Muscle & Nerve 13:232–239; 1990.
31. SAS Users Guide: Statistics (Version 5) Cary, NC, 1985.
32. Scholz, E.; Diener, H. C.; Dichgans, J.; Langohr H. D.; Schied, W.; Schupmann, A. Incidence of peripheral neuropathy and cerebellar ataxia in chronic alcoholics. J. Neurol. 233:212–217; 1986.
33. Seppalainen, A. M.; Hernberg, S.; Vesanto, R.; Kock, B. Early neurotoxic effects of occupational lead exposure: A prospective study. Neurotoxicol. 4:181–192; 1983.
34. Shields, R. W. Alcoholic polyneuropathy. Muscle & Nerve. 8: 183–187; 1985.
35. Stegman, D. F.; De Weerd, J. P. C. Modelling compound action potentials of peripheral nerves in situ. II. A study of the influence of temperature. Electroenceph. Clin. Neurophys. 54:516–529; 1982.
36. Soudman, R.; Ward, L. C.; Swift, T. R. Effect of height on nerve conduction velocity. Neurology 32:407–410; 1982.
37. Tashjian, E. A.; Ellenberg, M. R.; Gross, N.; Chodoroff, G.; Honet, J. C. Temperature effect on antidromic and orthodromic sensory nerve action potential latency and amplitude. Arch. Phys. Med. Rehabil. 68:549–552; 1987.
38. Todnem, K.; Knudsen, G. K.; Riise, T.; Nyland, H.; Aarli, J. A. The nonlinear relationship between nerve conduction velocity and skin temperature. J. Neurol. Neurosurg. Psychiat. 52:497–501; 1989.
39. Trojaborg, W. T.; Moon, A.; Anderson, B. B.; Trojaborg, N. S. Sural nerve conduction parameters in normal subjects related to age, gender, temperature, and height: A reappraisal. Muscle & Nerve. 15:666–671; 1992.
40. Victor, M.; Adams, R. D. On the etiology of the alcoholic neurologic diseases. Am. J. Clin. Nutr. 9:379–397; 1961.
41. Walsh, J. C.; McLeod, J. G. Alcoholic neuropathy: An electrophysiological and histological study. J. Neurol. Sci. 10:457–469; 1970.
42. Willer, J. C.; Dehen, H. Respective importance of different electrophysiological parameters in alcoholic neuropathy. J. Neurol. Sci. 33:387–396; 1977.