CHAPTER 15

CARDIOVASCULAR EVALUATION

INTRODUCTION

Cardiac disease and peripheral vascular disease are not classically recognized sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin.

Most observational and experimental animal studies using 2,4-D, 2,4,5-T, or TCDD have not extensively commented on resulting cardiac abnormalities or dysfunction. The studies described below viewed the cardiac abnormalities as expected consequences of a moribund state, and not as an indicator of primary cardiac toxicity to the putative chemical. Following oral administration of 2,4-D and 2,4,5-T, sheep and cattle developed cardiac hemorrhages.[1] A lethal oral dose of TCDD in young Rhesus monkeys produced increased heart weights in another experiment.[2] Horses and cats showed generalized vascular degeneration following exposure to soil contaminated with TCDD,[3] and mice and guinea pigs fed high amounts of TCDD manifested low heart weights.[4] A teratogenic experiment using 2,4,5-T in developing fish eggs showed graduated lethality and cardiovascular anomalies, which included enlarged veins and heart chambers.[5] Another study using ventricular muscle strips from chick embryos exposed to PCB's (including TCDD) showed a marked decrease in contractility.[6] This primary cardiotoxic response was presumably mediated by the Ah receptor, and was associated with increased prostaglandin synthesis.

Human case reports, case series of individuals with chloracne, and epidemiological studies also confirmed that cardiac function is not a sensitive indicator of exposure to herbicides or TCDD. In three case reports of acute 2,4-D poisoning, cardiac dilation and cardiac arrest were observed in the one fatal case,[7] while only transient nodal tachycardia was observed in one of the two nonfatal cases.[8,9] Three laboratory technicians with chloracne, neurological symptoms, and hypercholesterolemia following significant direct exposure to TCDD did not manifest any cardiac dysfunction,[10] however, of 10 industrial workers with chloracne, 4 complained of heart palpitations and shortness of breath.[11] In another two studies totaling 128 industrial workers, no excesses of cardiac complaints or findings were noted.[12-14]

Furthermore, in two contemporary epidemiological studies using similar cohorts from the Nitro, West Virginia, plant, no significant cardiac impairments were detected in exposed workers.[15,16] However, one study found significantly lower levels of high density lipoprotein (HDL) cholesterol in individuals with chloracne as contrasted to individuals without chloracne.[16] Two recent clinical-epidemiological pilot studies of residential areas in Missouri contaminated by TCDD did not disclose any significant cardiac disease in exposed residents,[17,18] although the Times Beach study noted a borderline association of diminished peripheral pulses in the exposed group (as did the AFHS Baseline study).

Because the herbicide literature has not identified consistent cardiovascular findings that merited a specific clinical focus, this study has collected generalized data on past cardiac events by questionnaire and medical record reviews. Current cardiac and peripheral vascular status were measured by physical examination and laboratory procedures. Coronary heart disease (CHD) has been of general concern in this study because both male cohorts are largely within the high risk ages of 40 to 65.

Since TCDD probably does not directly and permanently affect cardiovascular function, a theoretical question that arises is whether TCDD might have altered a cardiovascular disease risk factor that will exert a future adverse impact. There may be indirect evidence for such a possibility.

Risk factors for CHD include age, sex, race, family history, past personal history, diabetes (all types), smoking, cholesterol (and cholesterol-HDL ratio), diet, blood pressure, body weight, exercise pattern, stress (personality type), and alcohol.[19-22] Of these risk factors, hypertension and cholesterol have received consistent attention in clinical and epidemiological evaluations. Hypertension, either at routine examination or via specific study,[23] has not been related to phenoxy herbicide or TCDD exposure. However, hypercholesterolemia has been repeatedly associated with acute exposure to chlorophenols and dioxin.[10,12,13,16,24,25]

Baseline Summary Results

The 1982 Baseline examination found no statistically significant differences between the Ranch Hand and Comparison groups in systolic or diastolic blood pressure, the frequency of abnormal electrocardiographs (ECG's), heart sound abnormalities, abnormal funduscopic findings, or carotid bruits. However, a statistically significant difference emerged in the frequency of abnormal peripheral pulses: 12.8 percent of the nonblack Ranch Hands exhibited absent or diminished peripheral pulses compared to 9.4 percent of the nonblack Original Comparisons ($p=0.05$). This difference was consistent across various pulse combinations and remained statistically significant when all Ranch Hands were contrasted with all Comparisons, adjusting for age, past smoking history, and cholesterol level.

No statistically significant differences were found between the two groups in the occurrence of reported or verified heart disease or heart attacks, although a significant group-by-heart disease-by-smoking interaction was noted in the older (40 or more years of age) subgroup, i.e., older Ranch Hands smoking more than 10 pack-years developed more heart disease than their Comparisons, whereas older Ranch Hands smoking less than 10 pack-years exhibited less heart disease. No significant dose-response relationships of any of the cardiovascular response variables with the exposure index were noted.

Over 80 percent of reported cardiac conditions obtained from the study questionnaire were verified by a detailed review of medical records. There was also strong correlation between the past medical history of cardiac disease and the Baseline cardiovascular examination findings. However, the differences in peripheral pulse abnormalities primarily occurred in older individuals **without** a history of cardiovascular disease. These abnormalities, therefore, may be a precursor to more serious arterial disease or central dysfunction.

Finally, the well-known risk factors of age, smoking, and cholesterol were found to be highly correlated with each other and with several of the cardiovascular response variables.

Parameters of the 1985 Cardiovascular Examination

The 1985 cardiovascular examination was very similar to the 1982 Baseline examination. Data collection was divided into three major categories: heart disease history, central cardiac function, and peripheral vascular function.

Historical data were collected by a questionnaire administered at the examination site, covering the interval from 1982 through 1985. In addition, the review-of-systems portion of the physical examination recorded the overall history of heart trouble and other serious illnesses. Medical records were sought on all individuals to verify the reported conditions and to determine the time of occurrence of major cardiac events. Each participant was classified as to whether or not he developed essential hypertension, and whether he developed heart disease or had an acute myocardial infarction since his tour of duty in Southeast Asia (SEA). These endpoints were analyzed along with all other dependent variables to assess the degree of correlation between the history of cardiovascular disease and present medical findings. In addition, mortality findings were combined with the cardiovascular disease histories to form additional endpoints.

Central cardiac function was assessed by the measurements of systolic blood pressure, heart sounds (by auscultation), and an ECG. Blood pressure was determined in a standardized manner (see section on Physical Examination Data), and all examiners and diagnosticians were retrained on the detection of fourth heart sounds and the notation of innocent murmurs without recording them as abnormal heart sounds. ECG's were obtained after adherence to a 4-hour fast and abstinence from tobacco. Twelve-lead ECG's were recorded with a rhythm strip, and the following items were considered to be abnormal: right bundle branch block (RBBB), left bundle branch block (LBBB), nonspecific T-wave changes, bradycardia, tachycardia, arrhythmia, and other diagnoses (e.g., A-V block, evidence of a prior myocardial infarction).

Evaluation of the peripheral vascular system was based on diastolic blood pressure, funduscopic examination, auscultation of the carotid arteries, and determination of the quality of five peripheral pulses. The presence of carotid bruits was recorded in both carotid arteries. The femoral, popliteal, dorsalis pedis, posterior tibial, and radial pulses were assessed both by manual palpation and Doppler techniques because of the significant group differences discovered at the Baseline examination. Doppler results were considered the "gold standard" for the pulse measurements, although sensitivity correlations were established with palpation results. Rate changes of abnormal pulses occurring since the Baseline examination were also examined.

In addition to the above dependent variables, considerable analytical attention was directed to the cardiovascular risk factors of age, race, occupation (OCC), and updated values for smoking history (pack-years [PACKYR], and current smoking level [CSMOK]), alcohol history (drink-years [DRKYR], and current drinking level [ALC]), cholesterol (CHOL), HDL, cholesterol-HDL ratio (CHOL/HDL), percent body fat (%BFAT), personality score (PS), and differential cortisol response (DIFCORT).

Individuals with a verified history of diabetes (or those with an elevated 2-hour postprandial glucose level) were excluded from all analyses except the morbidity-mortality analysis. In addition, individuals with peripheral edema were excluded from analyses of the manual peripheral pulses because of the difficulty of measuring the pulse in the presence of edema.

Logistic regression models were used for dichotomous variables, and general linear models for continuous variables. All covariates except race and occupation were treated as continuous variables. Due to the large number of covariates, analyses were carried out as follows. Models adjusting only for age, race, and occupation were examined first, followed by models incorporating group (GRP)-by-age, group-by-race, and group-by-occupation interactions. Analyses were then performed, adjusting for (1) all covariates and (2) all covariates, but with only one variable selected from among each of the sets: pack-years of smoking, current smoking; cholesterol, HDL, cholesterol-HDL ratio; and drink-years of alcohol, current alcohol intensity. Selection of the covariate from each set was based on examination of the pairwise covariate-by-dependent variable associations and the coefficient from the fully adjusted model.

Stepwise modeling was then conducted using all covariates, but with only one variable selected from each of the sets described above. Only group-by-covariate interactions were examined, as were the three-factor interactions of group-by-age-by-race, group-by-age-by-occupation, and group-by-race-by-occupation. "Best models" refer to the models including only the statistically significant covariate and interaction terms. Minor numeric disparities in the tables that follow reflect missing dependent variable or covariate data. Parallel analyses using Original Comparisons can be found in Tables M-12 through M-20 of Appendix M.

Morbidity and mortality data on the full Ranch Hand cohort and an appropriate Comparison cohort were tabulated for four endpoints: (1) death (any cause) or verified nonfatal heart disease, (2) death (any cause) or verified nonfatal myocardial infarction, (3) fatal or nonfatal verified heart disease, and (4) fatal or nonfatal verified myocardial infarction or fatal heart disease. This analysis involved a number of assumptions, particularly with respect to missing histories in the noncompliant study subjects.

RESULTS AND DISCUSSION

Questionnaire Data: Reported and Verified Heart Disease

For each participant, a cardiovascular disease history was obtained from both the questionnaire and physical examination review of systems history. The baseline and third-year followup data were merged to determine, for each participant completing the third-year followup examination, whether there was ever a reported history of cardiovascular disease following service in Vietnam. Reported conditions were verified by medical record reviews and classified according to the ICD-9-CM. The following three variables were analyzed in terms of both reported and verified events:

Variables	ICD-9CM Codes
Essential Hypertension	401
Heart Disease (Excluding Essential Hypertension)	391, 393-398, 402, 404 410-414, 415-417, 420-429
Acute Myocardial Infarction	410

Table 15-1 gives the unadjusted analysis of reported and verified cardiovascular disease in the Ranch Hand and Comparison groups and the results of unadjusted group contrasts. Essential hypertension was reported in slightly over 25 percent of the participants, with rates not significantly different in the two groups (p=0.596). About 80 percent of these cases were verified, leaving similar rates of 20.7 and 20.2 percent in the Ranch Hand and Comparison groups, respectively, for verified essential hypertension. Reported heart disease was a little higher in the Ranch Hand group (28.1% vs. 26.1%) but the difference in the percentage of verified heart disease was of borderline significance (23.8% vs. 20.3%, p=0.054). The rates of reported and verified myocardial infarctions were about 2 percent and 1 percent, respectively, and not significantly different in the two groups.

The associations between each of the covariates and the three verified cardiovascular endpoints are presented in Tables 15-2, 15-3, and 15-4. The tables containing the covariate associations with the reported cardiovascular diseases are included in Tables M-1 through M-3 of Appendix M. All reported cardiac illnesses (verified and unverified) are included in these tables. Many of the classic risk factors were identified. Age, smoking, cholesterol and/or cholesterol-HDL ratio, percent body fat, differential cortisol, and alcohol use were significantly associated with reported and verified essential hypertension, although the smoking effect was in the opposite direction of that expected. Age, occupation, and the cholesterol-HDL ratio were significantly associated with reported and verified heart disease, with more disease found in officers than in enlisted personnel. Age, pack-years of smoking, cholesterol-HDL ratio, and drink-years of alcohol were significantly associated with reported and/or verified myocardial infarction (the smoking effect being in the expected direction).

The results of logistic regression analyses adjusting for these variables are presented in Table 15-5. The results were similar to the unadjusted results, but the adjusted relative risk for verified heart disease reached statistical significance (p=0.036). No significant group-by-covariate interactions were noted. Nearly identical results were obtained in the analysis of the Ranch Hands and Original Comparisons (see Tables M-12 and M-13 of Appendix M).

Morbidity-Mortality Analysis

Differential mortality in the two groups could introduce bias in the analysis of morbidity data. For the cardiovascular evaluation, morbidity and mortality data on all Ranch Hands (diabetics included) and the first Comparison of the randomly ordered set matched to the Ranch Hands were combined to estimate the frequency of four hierarchical cardiovascular endpoints. Because of competing mortality and possible misclassification of the cause of death, the endpoints of death (any cause) or verified nonfatal heart disease, and death (any cause) or verified nonfatal myocardial infarction were examined to assess group differences in the most extreme case (i.e., all deaths being associated with cardiovascular disease). The other two endpoints were limited to fatal or nonfatal verified heart disease, and fatal or nonfatal verified myocardial infarction or fatal heart disease.

The analysis was based on 1,257 Ranch Hands and 1,253 Comparisons. The history of each individual from the end of his tour of duty in SEA to the present was reviewed. Histories of verified heart disease and myocardial

TABLE 15-1.

Unadjusted Analyses for Reported and Verified Heart Disease by Group

		Group					
		Ranch Hand		Comparison			
Variable	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Reported Essential Hypertension	n	942		1,206			
	Yes	247	26.2	304	25.2	1.05 (0.87,1.28)	0.596
	No	695	73.8	902	74.8		
Verified Essential Hypertension	n	942		1,206			
	Yes	195	20.7	244	20.2	1.03 (0.83,1.27)	0.787
	No	747	79.3	962	79.8		
Reported Heart Disease (Excluding Hypertension)	n	942		1,206			
	Yes	265	28.1	315	26.1	1.11 (0.91,1.34)	0.298
	No	677	71.9	891	73.9		
Verified Heart Disease (Excluding Hypertension)	n	942		1,206			
	Yes	224	23.8	245	20.3	1.22 (1.00,1.50)	0.054
	No	718	76.2	961	79.7		
Reported Myocardial Infarction	n	942		1,206			
	Yes	20	2.1	22	1.8	1.17 (0.63,2.15)	0.617
	No	922	97.9	1,184	98.2		
Verified Myocardial Infarction	n	942		1,206			
	Yes	9	1.0	13	1.1	0.88 (0.38,2.08)	0.779
	No	933	99.0	1,193	98.9		

TABLE 15-2.

Association Between Verified Essential Hypertension and the Covariates in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Percent Abnormal	p-Value
Age	Born ≥1942	934	17.2	0.001
	Born <1942	1,214	22.9	
Race	Black	126	25.4	0.191
	Nonblack	2,022	20.1	
Occupation	Officer	807	21.2	
	Enlisted Flyer	354	20.1	0.798
	Enlisted Groundcrew	987	20.0	
Current Smoking	0	1,262	22.8	
	>0 - 20	463	16.6	0.005
	>20	422	17.5	
Pack-Years Smoking	0	512	24.8	
	>0 - 10	760	17.9	0.010
	>10	869	20.0	
Cholesterol	≤200	766	15.5	
	>200 - 230	650	21.1	<0.001
	>230	732	25.0	
HDL	≤40	719	21.6	
	>40 - 50	754	20.6	0.524
	>50	675	19.1	
Cholesterol-HDL Ratio	≤4.2	717	16.2	
	>4.2 - <5.5	743	21.3	0.001
	≥5.5	688	24.0	
Percent Body Fat	<10	10	0.0	
	10 - 25	1,758	16.7	<0.001
	>25	379	38.5	
Personality Score	<-5	829	22.3	
	-5 - 5	731	20.5	0.113
	>5	580	17.8	
Differential Cortisol	≤0.6	704	23.6	
	>0.6 - 4.0	745	19.1	0.033
	>4.0	683	18.4	
Current Alcohol Use (Drinks/Day)	0	592	21.4	
	>0 - 1	809	17.2	0.011
	>1	738	23.2	
Drink-Years Alcohol	≤1.25	691	21.1	
	>1.25 - 25	719	18.4	0.116
	>25	666	22.8	

TABLE 15-3.

Association Between Verified Heart Disease and the Covariates in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Percent Abnormal	p-Value
Age	Born ≥1942	934	17.9	<0.001
	Born <1942	1,214	24.9	
Race	Black	126	23.0	0.826
	Nonblack	2,022	21.8	
Occupation	Officer	807	24.8	
	Enlisted Flyer	354	20.9	0.034
	Enlisted Groundcrew	987	19.8	
Current Smoking	0	1,262	22.7	
	>0 - 20	463	21.2	0.461
	>20	422	19.9	
Pack-Years Smoking	0	512	23.2	
	>0 - 10	760	20.9	0.617
	>10	869	21.9	
Cholesterol	≤200	766	21.2	
	>200 - 230	650	21.1	0.533
	>230	732	23.2	
HDL	≤40	719	21.7	
	>40 - 50	754	20.4	0.357
	>50	675	23.6	
Cholesterol-HDL Ratio	≤4.2	717	24.1	
	>4.2 - <5.5	743	18.8	0.041
	≥5.5	688	22.7	
Percent Body Fat	<10	10	30.0	
	10 - 25	1,758	22.1	0.619
	>25	379	20.3	
Personality Score	<-5	829	21.4	
	-5 - 5	731	20.9	0.369
	>5	580	24.0	
Differential Cortisol	≤0.6	704	19.2	
	>0.6 - 4.0	745	22.4	0.084
	>4.0	683	24.0	
Current Alcohol Use Drinks/Day	0	592	23.0	
	≤1	809	22.5	0.441
	>0 - 1	738	20.3	
Drink-Years Alcohol	≤1.25	691	21.4	
	>1.25 - 25	719	22.0	0.968
	>25	666	21.8	

TABLE 15-4.

Association Between Verified Myocardial Infarction and the Covariates in the Combined Ranch Hand and Comparison Groups

Covariate	Covariate Category	Total	Percent Abnormal	p-Value
Age	Born ≥1942	934	0.2	0.002
	Born <1942	1,214	1.6	
Race	Black	126	0.0	0.471
	Nonblack	2,022	1.1	
Occupation	Officer	807	0.9	
	Enlisted Flyer	354	1.4	0.697
	Enlisted Groundcrew	987	1.0	
Current Smoking	0	1,262	0.8	
	>0 - 20	463	1.7	0.228
	>20	422	1.0	
Pack-years Smoking	0	512	0.2	
	>0 - 10	760	0.8	0.018
	>10	869	1.7	
Cholesterol	≤200	766	0.5	
	>200 - 230	650	0.9	0.095
	>230	732	1.6	
HDL	≤40	719	1.5	
	>40 - 50	754	0.9	0.210
	>50	675	0.6	
Cholesterol-HDL Ratio	≤4.2	717	0.4	
	>4.2 - <5.5	743	0.9	0.046
	≥5.5	688	1.7	
Percent Body Fat	<10	10	0.0	
	10 - 25	1,758	1.0	0.872
	>25	379	0.8	
Personality Score	<-5	829	0.8	
	-5 - 5	731	1.5	0.278
	>5	580	0.7	
Differential Cortisol	≤0.6	704	1.0	
	>0.6 - 4.0	745	1.1	0.989
	>4.0	683	1.0	
Current Alcohol Use (Drinks/Day)	0	592	1.5	
	>0 - 1	809	0.9	0.376
	>1	738	0.8	
Drink-Years Alcohol	≤1.25	691	1.3	
	>1.25 - 25	719	0.4	0.143
	>25	666	1.4	

TABLE 15-5.

Adjusted Analyses for Reported and Verified Heart Disease

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Reported Essential Hypertension	1.14 (0.93,1.41)	0.211	AGE (p<0.001), CSMOK (p=0.001),CHOL (p<0.001), %BFAT (p<0.001), ALC (p<0.001)
Verified Essential Hypertension	1.11 (0.89,1.39)	0.347	AGE (p=0.021), CSMOK (p=0.021), CHOL (p<0.001), %BFAT (p<0.001), PS (p=0.039)
Reported Heart Disease	1.12 (0.92,1.36)	0.258	AGE (p<0.001)
Verified Heart Disease	1.25 (1.02,1.54)	0.036	AGE (p<0.001)
Reported Myocardial Infarction	1.16 (0.60,2.23)	0.667	AGE (p<0.001),OCC (p=0.014), CHOL/HDL (p=0.016)
Verified Myocardial Infarction	0.93 (0.38,2.23)	0.865	AGE (p<0.001), CHOL/HDL (p=0.025)

*Abbreviations:

CSMOK: Current smoking
CHOL: Cholesterol
%BFAT: Percent body fat
ALC: Current alcohol use (drinks/day)
PS: Personality score
OCC: Occupation
CHOL/HDL: Cholesterol-HDL ratio

infarction for living individuals who were noncompliant at Baseline and at the followup were missing. For the living noncompliant individuals, the observed rate in the compliant individuals was used to estimate the number of nonfatal events among the noncompliant individuals for each cohort. It was assumed that there were no nonfatal cardiovascular events in the noncompliant individuals who died due to a cause other than cardiovascular system failure. The results are shown in Table M-4 of Appendix M.

There was a total of 66 deaths in the Ranch Hand group and 77 in the group of Comparisons. The estimated percentage of Ranch Hands who died (any cause) or had a verified nonfatal history of heart disease was 27.4 as contrasted to 24.5 in the Comparisons.

The rate of verified nonfatal myocardial infarctions was approximately 1 percent in each group. The estimated percentage of deaths (any cause) or verified nonfatal myocardial infarction was 6.4 percent in the Ranch Hands and 7.0 percent in the Comparisons.

Only 5 of the 66 deaths in the Ranch Hands and 3 of the 77 deaths in the Comparisons either were from heart disease, or were individuals who had verified heart disease histories. The estimated percentage of fatal and nonfatal verified heart disease was 22.5 percent in the Ranch Hands and 18.6 percent in the Comparisons.

Of the 66 deaths in the Ranch Hands only 1 individual died from cardiovascular disease or had a verified history of myocardial infarction as compared to 2 of the 77 deaths in the Comparisons. The estimated percentage of fatal or nonfatal verified myocardial infarction or fatal heart disease was 1.2 percent in the Ranch Hands and 1.0 percent in the Comparisons.

These contrasts must be interpreted guardedly since they involve some unverifiable assumptions. Nevertheless, they are consistent with the morbidity findings presented in the chapter, and tend to show that the clinical cardiovascular disease spectrum is approximately equal in both groups.

Physical Examination Data

Central Cardiac Function

Central cardiac function was assessed by the measurement of systolic blood pressure, heart sounds, and an ECG. Systolic blood pressure was determined by a standardized sphygmometer, at the appearance of the first sound with the nondominant arm placed at heart level; the lowest value of three readings was recorded. Detection of abnormal heart sounds was conducted by standard auscultation with the participant placed in sitting, supine, and left lateral supine positions. Fourth heart sounds were assessed; murmurs were graded in intensity and location and were judged to be functional (normal) or organic (abnormal) in nature. Fourth heart sounds were scored as abnormal. ECG data were collected by a standardized 12-lead machine; approximately 95 percent of the clinical interpretations were performed by one cardiologist. All participants were asked to abstain from smoking for at least 4 hours prior to their ECG.

Systolic Blood Pressure

Systolic blood pressure was analyzed both as continuous and dichotomized variables (normal, 140 or less mm Hg; abnormal, more than 140 mm Hg). Combined distributional data from both groups revealed significant digit preference for values ending in zero ($p<0.0001$ for both systolic and diastolic readings), but standard statistical analyses were performed since the zero-digit peaks (e.g., 130, 140, 150 mm Hg) were relatively uniform and did not visually differ between the Ranch Hand and Comparison groups. Zero digit readings were recorded for 59.4 percent of the systolic blood pressures and 55.0 percent of the diastolic blood pressures.

Table 15-6 gives the percentage of participants with abnormally high systolic values. The percent of abnormals was not significantly different from each other (p=0.529). Systolic blood pressure, analyzed as a continuous variable, had a mean of 118.96 mm Hg (95% C.I.: [118.06,119.86]) for the Ranch Hand group and a mean of 119.55 mm Hg (95% C.I.: [118.71,120.39]) for the Comparison group. These means were not significantly different (p=0.349). The means were also not significantly different when Original Comparisons were used (p=0.182).

The association between each of the covariates (categorized into either two or three levels) and dichotomized systolic blood pressure in the combined Ranch Hand and Comparison groups is shown in Table 15-7. Age, cholesterol, percent body fat, personality score, and alcohol use (both current use and drink-years) were significantly associated with increased systolic pressure. These covariate effects were in the direction typically found in other studies,[26,27] except for personality score where those participants with low scores (in the Type B direction) had the highest percentage of abnormal values.

Adjustment of the categorical systolic blood pressure by the above covariates was performed by logistic regression analysis, and these results are presented in Table 15-8. As shown, there were no significant differences between the Ranch Hand and Comparison groups (p=0.920). Age, cholesterol, percent body fat, personality score, and current alcohol use all had statistically significant effects. An adjusted analysis of systolic blood pressure in the continuous form revealed a significant group (GRP)-by-age-by-race interaction (p=0.012) along with the significant main effects of current smoking ($p<0.001$), cholesterol ($p<0.001$), percent body fat ($p<0.001$), personality score ($p<0.001$), and current alcohol use (p=0.002). Exploration of the interaction revealed that among Blacks there was a group-by-age interaction (p=0.007), with a mean systolic pressure greater in the Ranch Hand group than in the Comparison group at the younger age levels, but lower at the older age levels. The estimated Ranch Hand-Comparison difference was 4.56 (± 3.30) mm Hg at the Baseline age of 35 and -16.01 (± 5.87) mm Hg at the Baseline age of 53 (see Table M-5 of Appendix M). In the nonblack cohort the group-by-age interaction was not significant (p=0.338), nor was there evidence of any overall group effect (p=0.356). In the analysis of the Ranch Hands and Original Comparisons, there were no statistically significant group differences, either unadjusted or adjusted for covariate effects (see Tables M-14 and M-15 of Appendix M).

TABLE 15-6.

Unadjusted Analyses for Central Cardiac Function By Group (Diabetics Excluded)

		Group					
		Ranch Hand		Comparison			
Variable	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Systolic Blood Pressure	n	942		1,205			
	Abnormal	60	6.4	85	7.1	0.90 (0.64, 1.26)	0.529
	Normal	882	93.6	1,120	92.9		
Heart Sounds	n	941		1,206			
	Abnormal	31	3.3	32	2.7	1.25 (0.76,2.06)	0.384
	Normal	910	96.7	1174	97.3		
ECG (Overall)	n	947		1,206			
	Abnormal	121	12.8	169	14.0	0.90 (0.70,1.16)	0.430
	Normal	821	87.2	1,037	86.0		
ECG: RBBB	n	942		1,206			
	Abnormal	5	0.5	9	0.7	0.71 (0.24,2.13)	0.542
	Normal	937	99.5	1,197	99.3		
ECG: LBBB	n	942		1,206			
	Abnormal	0	0.0	0	0.0	--	--
	Normal	942	100.0	1,206	100.0		
ECG: Nonspecific T-Wave Changes	n	942		1,206			
	Abnormal	85	9.0	107	8.9	1.02 (0.76,1.37)	0.904
	Normal	857	91.0	1,099	91.1		

TABLE 15-6. (continued)

Unadjusted Analyses for Central Cardiac Function By Group (Diabetics Excluded)

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
ECG: Bradycardia	n	942		1,206			
	Abnormal	45	4.8	56	4.6	1.03 (0.69,1.54)	0.889
	Normal	897	95.2	1,150	95.4		
ECG: Tachycardia	n	942		1,206			
	Abnormal	0	0.0	0	0.0	--	--
	Normal	942	100.0	1,206	100.0		
ECG: Arrhythmia	n	942		1,206			
	Abnormal	31	3.3	41	3.4	0.97 (0.60,1.55)	0.889
	Normal	911	96.7	1,165	96.6		
ECG: Other Diagnoses	n	942		1,206			
	Abnormal	97	10.3	132	11.0	0.93 (0.71,1.23)	0.631
	Normal	845	89.7	1,074	89.0		

--No relative risk given, since no abnormals are present.

TABLE 15-7.

Association Between Central Cardiac Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol	HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Systolic Blood Pressure	<0.001	NS	NS	NS	NS	<0.001	NS	NS	0.001	0.002	NS	0.018	<0.001
Heart Sounds	0.005	NS	NS*	NS	NS	NS	NS*	0.003	NS	NS	NS	NS	NS
ECG (Overall)	<0.001	NS	NS*	NS	0.010	NS*	NS*	0.016	<0.001	NS	NS	NS	NS
ECG: RBBB	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ECG: Nonspecific T-Wave Changes	<0.001	NS	NS	NS	0.038	0.002	NS	<0.001	<0.001	NS	NS	NS	0.006
ECG: Bradycardia	NS*	NS	0.010	NS	0.007	NS*	0.002	<0.001	NS	NS	NS	NS	NS
ECG: Arrhythmia	NS	NS	0.023	NS	0.028	NS	NS	NS	NS	NS	NS	NS	NS
ECG: Other Diagnoses	<0.001	NS	0.011	NS*	0.023	NS	NS	NS	NS	NS	NS	0.019	NS

NS: Not significant ($p>0.10$).

NS*: Borderline significant ($0.05 < p \leq 0.10$).

TABLE 15-8.

Adjusted Analyses for Central Cardiac Function
(Diabetics Excluded)*

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Systolic Blood Pressure (Discrete)	0.98 (0.69,1.40)	0.920	AGE (p<0.001) CHOL (p=0.004) %BFAT (p<0.001) PS (p=0.002) ALC (p=0.020)
Systolic Blood Pressure (Continuous)	****	****	GRP*RACE*AGE (p=0.012) CSMOK (p<0.001) CHOL (p<0.001) %BFAT (p<0.001) PS (p<0.001) ALC (p=0.002)
Heart Sounds	1.33 (0.80,2.24)	0.276	AGE (p<0.001) RACE (p=0.003) CHOL/HDL (p=0.002)
ECG (Overall)	****	****	AGE (p<0.001) RACE (p=0.005) %BFAT (p<0.001) GRP*PACKYR (p=0.008)
ECG: RBBB	0.72 (0.24,2.15)	0.555	AGE (p=0.008)
ECG: Nonspecific ST-T-Wave Changes	1.12 (0.81,1.53)	0.497	AGE (p<0.001) RACE (p=0.005) CHOL (p=0.007) %BFAT (p<0.001)

TABLE 15-8. (continued)

Adjusted Analyses for Central Cardiac Function (Diabetics Excluded)*

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
ECG: Bradycardia	1.08 (0.72,1.62)	0.726	OCC (p=0.047) CHOL/HDL (p<0.001)
ECG: Arrhythmia	****	****	AGE (p=0.001) OCC (p<0.001) GRP*PACKYR (p=0.018) GRP*%BFAT (p=0.038)
ECG: Other Diagnoses	0.92 (0.69,1.23)	0.575	AGE (p<0.001) RACE (p=0.015) CSMOK (p=0.039)

*Some adjusted analyses did not explore effects of all covariates due to sparse number of abnormalities (see text).

**Additional Abbreviations:

GRP: group
PACKYR: pack-years smoking

****Group-by-covariate interaction, relative risk/difference in group means, 95% confidence interval, and p-value not presented (see Table M-5 of Appendix M).

Heart Sounds

As shown in Table 15-6, the unadjusted frequency of abnormal heart sounds in the two groups was not significantly different (p=0.384).

The covariate tests of association (Table 15-7) showed significant effects for age (p=0.005), cholesterol-HDL ratio (p=0.003), and a borderline association with occupation (p=0.069). Increased age (born before 1942) had a frequency of 3.9 percent heart sound abnormalities as contrasted to 1.6 percent abnormalities in the younger age group (born in or after 1942). The cholesterol-HDL ratio (less than or equal to 4.2, between 4.2 and 5.5, and greater than or equal to 5.5) was positively associated with increasing frequencies of abnormal heart sounds (1.7, 2.6, and 4.7 percent, respectively). The observed frequencies of abnormal heart sounds were 3.8, 1.4, and 2.7 percent in the officers, enlisted flyers, and the enlisted groundcrew, respectively.

The adjusted analysis (Table 15-8) did not detect any significant group differences (p=0.276). Age, race, and the cholesterol-HDL ratio were significant covariates (p<0.001, p=0.003, and p=0.002, respectively). No two- or three-way group interactions were noted. Similarly, nonsignificant results were found in the analyses of the Original Comparisons versus the Ranch Hands (see Table M-15 of Appendix M).

Electrocardiograph Findings

All ECG tracings were scored as normal or abnormal; specific abnormalities included RBBB, LBBB, nonspecific T-wave changes, bradycardia, tachycardia, arrhythmia, and other diagnoses.

The unadjusted analysis of these variables (Table 15-6) showed no statistically significant differences in the overall ECG results, or any of the specific subcategories, between the Ranch Hand and Comparison groups. Two additional findings in the analysis were of interest: (1) the Ranch Hands had a uniformly lower number of ECG abnormalities than the Comparisons (though not statistically significant), and (2) the sum of the specific ECG findings exceeds the proportion of abnormalities scored on the overall ECG because some individuals accounted for two or more abnormalities.

The associations between the covariates and the various ECG findings are presented in Table 15-7. Age was significantly associated with the overall ECG findings (p<0.001), nonspecific T-wave changes (p<0.001), and other ECG diagnoses (p<0.001), with more abnormalities found in the older age group. Occupation was significantly associated with bradycardia (p=0.010), arrhythmia (p=0.023), and other ECG findings (p=0.011). A higher percentage of officers than enlisted flyers or groundcrew had bradycardia, whereas enlisted flyers had the lowest proportion of arrhythmias, and enlisted groundcrew had the highest percentage. Officers and enlisted flyers had a higher percentage than the enlisted groundcrew cohort of other ECG findings.

Pack-years of smoking was significantly associated with the overall ECG findings (p=0.010), T-wave changes (p=0.038), bradycardia (p=0.007), arrhythmia (p=0.028), and other ECG diagnoses (p=0.023). For the overall ECG findings, nonspecific T-wave changes, and arrhythmias, the moderate smoking group (greater than 0 to 10 pack-years) had the fewest abnormalities.

Bradycardia was negatively associated with pack-years of smoking, with the highest frequency of abnormalities (7.2%) found in the 0 pack-years category versus the lowest proportion (3.6%) of abnormalities in the greater than 10 pack-years category. Cholesterol levels and/or the cholesterol-HDL ratio were positively associated with abnormalities in the overall ECG (p=0.016) and T-wave findings (p<0.001), but were negatively associated with bradycardia (p<0.001).

Increased percent body fat was significantly associated with overall ECG abnormalities (p<0.001) and nonspecific T-wave changes (p<0.001). Drink-years of alcohol was only associated with T-wave changes (p=0.006), with more abnormalities in the greater than 25 drink-years category than in the less than or equal to 1.25 drink-years category, but relatively fewer abnormalities in the more than 1.25 to 25 drink-years category. The covariate of current alcohol use was associated only with the category of other ECG diagnoses (p=0.019), but not in a consistent manner (individuals averaging less than one drink per day had more abnormalities than nondrinkers, but those averaging more than one drink per day had the lowest percentage of abnormalities). The covariates of race, current smoking, personality score, and differential cortisol level, however, did not significantly affect the variables of central cardiac function.

Results from the adjusted logistic regression analyses are shown in Table 15-8. No significant group differences were detected for categorical RBBB, T-wave changes, bradycardia, and other ECG diagnoses. The covariates of age, race, percent body fat, pack-years of smoking, current smoking, cholesterol, and cholesterol-HDL ratio were significantly associated with one or more of the ECG variables. RBBB was adjusted only for age due to the small number of abnormalities.

The adjusted analysis of the overall ECG findings revealed a significant group-by-pack-year interaction (p=0.008), and the analysis of the arrhythmia variable disclosed two significant interactions: a group-by-pack-year association (p=0.018) and a group-by-percent body fat association (p=0.038). All of these interactions are displayed in Table M-5 of Appendix M. In the case of the overall ECG findings, the adjusted relative risk among nonsmokers was significantly less than one (p=0.038), i.e., a lower risk for Ranch Hands than Comparisons. For heavy smokers (30 pack-years), the adjusted relative risk was 1.25 (95% C.I.: [0.89,1.76], p=0.197). For cardiac arrhythmias, exploration of the group-by-pack-year interaction at the approximate mean percent body fat of 21 percent showed a borderline significant relationship favoring the nonsmoking Ranch Hands (Adj. RR: 0.58, 95% C.I.: [0.30,1.10], p=0.093); heavy smoking Ranch Hands had a higher proportion of arrhythmias than heavy smoking Comparisons, but this association was not statistically significant (p=0.162). For the group-by-percent body fat interaction, 10 percent and 30 percent body fat levels were analyzed at the approximate median of 7 pack-years of smoking. The adjusted relative risk of 0.23 (95% C.I.: [0.07,0.78]) was statistically significant for the 10 percent body fat category (p=0.018), indicating a lower adjusted frequency of cardiac arrhythmias for nonobese Ranch Hands than for nonobese Comparisons. This situation was reversed for obese Ranch Hands, but the association was not statistically significant (RR: 1.88, 95% C.I.: [0.66,5.34], p=0.234).

The adjusted analyses using the Original Comparisons were nearly identical to the analyses of the total Comparison group, including the three group interactions for overall ECG findings and cardiac arrhythmias described above. The analyses of the Original Comparison group are found in Tables M-15 and M-16 of Appendix M.

Peripheral Vascular Function

Peripheral vascular function was assessed by the diastolic blood pressure, funduscopic examination of small vessels, the presence or absence of carotid bruits, and both manual palpation and Doppler bilateral measurements of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Individual peripheral pulses were combined to form overall indices of peripheral vascular status. Diastolic blood pressure was measured by the standard auscultatory technique, and was recorded at the pressure level corresponding to the disappearance of sound. The funduscopic examination was conducted with undilated pupils in a standard manner, with emphasis placed upon the detection of arterio-venous nicking, hemorrhages, exudate, and papilledema. Carotid bruits were assessed by standard bilateral auscultation; confirmation of bruits was not attempted by the Doppler technique. Manual pulse determinations were performed by the examining physician, independent of the Doppler measurements performed by qualified technicians. Tobacco abstinence for at least four hours was required for the Doppler examination, but not for the manual palpation. Only the physician diagnostician had access to both sets of pulse data.

Diastolic Blood Pressure

Diastolic blood pressure was analyzed as a continuous variable and as a dichotomized variable (normal value less than or equal to 90 mm Hg; abnormal value greater than 90 mm Hg). As with the systolic readings, a significant zero digit preference was noted for the diastolic blood pressure values.

Table 15-9 arrays the results of the unadjusted categorical analyses. As shown, there are no statistically significant group differences for the proportions of diastolic abnormalities (p=0.999). Diastolic blood pressure, analyzed as a continuous variable, had a mean of 79.76 mm Hg (95% C.I.: [71.97, 80.35]) for the Ranch Hand group and a mean of 79.77 mm Hg (95% C.I.: [79.24, 80.30]) for the Comparison Group. These means were not significantly different (p=0.986). The means were also not significantly different when Original Comparisons were used (p=0.555).

The tests of covariate association with diastolic blood pressure are given in Table 15-10. Cholesterol, cholesterol-HDL ratio, percent body fat, differential cortisol, and current alcohol use were significantly related to diastolic blood pressure (p<0.001, p=0.006, p<0.001, p=0.041, and p=0.014, respectively). For increasing cholesterol, cholesterol-HDL ratio, and percent body fat, increases in proportions of abnormal diastolic blood pressure were obtained, whereas for increasing differential cortisol values, a decline in blood pressure abnormalities was found. Current alcohol use (drinks per day) revealed an inconsistent association with diastolic blood pressure abnormalities, with nondrinkers having a higher proportion of abnormalities than low-level drinkers, but a lower proportion of abnormalities than moderate drinkers (8.3, 6.4, and 10.6 percent abnormalities, respectively). The covariates of age, race, occupation, current smoking, pack-years of smoking, HDL, personality score, and drink-years of alcohol were not associated with diastolic blood pressure abnormalities.

TABLE 15-9.

Unadjusted Analyses for Peripheral Vascular Function by Group (Diabetics Excluded)

		Group					
		Ranch Hand		Comparison			
Variable	Statistic	Number	Percent	Number	Percent	Est. Relative Risk (95% C.I.)	p-Value
Diastolic Blood Pressure	n	942		1,204			
	Abnormal	79	8.4	101	8.4	1.00 (0.74,1.36)	0.999
	Normal	863	91.6	1,103	91.6		
Funduscopic Examination	n	941		1,206			
	Abnormal	7	0.7	6	0.5	1.50 (0.50,4.47)	0.472
	Normal	934	99.3	1,200	99.5		
Carotid Bruits	n	941		1,205			
	Abnormal	7	0.7	7	0.6	1.28 (0.45,3.66)	0.646
	Normal	934	99.3	1,198	99.4		
Radial Pulses (Manual)	n	929		1,191			
	Abnormal	4	0.4	8	0.7	0.64 (0.19,2.13)	0.465
	Normal	925	99.6	1,183	99.3		
Radial Pulses (Doppler)	n	942		1,203			
	Abnormal	3	0.3	4	0.3	0.96 (0.21,4.30)	0.952
	Normal	939	99.7	1,199	99.7		
Femoral Pulses (Manual)	n	929		1,191			
	Abnormal	20	2.2	25	2.1	1.03 (0.57,1.86)	0.932
	Normal	909	97.8	1,166	97.9		

TABLE 15-9. (continued)

Unadjusted Analyses for Peripheral Vascular Function by Group (Diabetics Excluded)

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Femoral Pulses (Doppler)	n	942		1,205			
	Abnormal	6	0.6	4	0.3	1.92 (0.54,6.82)	0.312
	Normal	936	99.4	1,201	99.7		
Popliteal Pulses (Manual)	n	929		1,191			
	Abnormal	16	1.7	28	2.4	0.73 (0.39,1.35)	0.317
	Normal	913	98.3	1,163	97.6		
Popliteal Pulses (Doppler)	n	942		1,204			
	Abnormal	10	1.1	8	0.7	1.60 (0.63,4.08)	0.322
	Normal	932	98.9	1,196	99.3		
Dorsalis Pedis Pulses (Manual)	n	929		1,191			
	Abnormal	102	11.0	127	10.7	1.03 (0.78,1.36)	0.818
	Normal	827	89.0	1,064	89.3		
Dorsalis Pedis Pulses (Doppler)	n	938		1,202			
	Abnormal	228	24.3	274	22.8	1.09 (0.89,1.33)	0.412
	Normal	710	75.7	928	77.2		
Posterior Tibial Pulses (Manual)	n	929		1,191			
	Abnormal	27	2.9	31	2.6	1.12 (0.66,1.89)	0.674
	Normal	902	97.1	1,160	97.4		
Posterior Tibial Pulses (Doppler)	n	939		1,202			
	Abnormal	19	2.0	25	2.1	0.97 (0.53,1.78)	0.928
	Normal	920	98.0	1,177	97.9		

TABLE 15-9. (continued)

Unadjusted Analyses for Peripheral Vascular Function by Group, (Diabetics Excluded)

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Leg Pulses (Manual)	n	929		1,191			
	Abnormal	131	14.1	177	14.9	0.94 (0.74,1.20)	0.624
	Normal	798	85.9	1,014	85.1		
Leg Pulses (Doppler)	n	938		1,202			
	Abnormal	237	25.3	288	24.0	1.07 (0.88,1.31)	0.490
	Normal	701	74.7	914	76.0		
Peripheral Pulses (Manual)	n	929		1,191			
	Abnormal	133	14.3	181	15.2	0.93 (0.73,1.18)	0.575
	Normal	796	85.7	1,010	84.8		
Peripheral Pulses (Doppler)	n	938		1,202			
	Abnormal	239	25.5	290	24.1	1.08 (0.88,1.31)	0.472
	Normal	699	74.5	912	75.9		
All Pulses (Manual)	n	929		1,191			
	Abnormal	133	14.3	182	15.3	0.93 (0.73,1.18)	0.535
	Normal	796	85.7	1,009	84.7		
All Pulses (Doppler)	n	938		1,201			
	Abnormal	239	25.5	291	24.2	1.07 (0.88,1.30)	0.509
	Normal	699	74.5	910	75.8		

TABLE 15-10.

Association Between Peripheral Vascular Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol	HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Diastolic Blood Pressure	NS	NS	NS	NS	NS	<0.001	NS	0.006	<0.001	NS	0.041	0.014	NS
Funduscopic Examination	0.004	0.040	NS	NS	NS	NS	NS	0.016	0.026	NS	NS	0.004	NS
Carotid Bruits	NS*	NS	NS	NS*	NS	NS*	NS	NS	NS	NS	NS	NS	0.021
Radial Pulses (Manual)	NS	NS	NS	NS	NS	NS	NS	0.033	NS	NS	NS	NS	NS
Radial Pulses (Doppler)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Femoral Pulses (Manual)	<0.001	NS	NS	NS	NS	NS*	0.002	<0.001	0.001	NS	NS	NS	<0.001
Femoral Pulses (Doppler)	NS*	NS	NS	0.001	0.006	NS*	NS	0.019	NS	NS	NS	NS	0.013
Popliteal Pulses (Manual)	NS*	NS	NS	NS	0.001	NS	NS	0.002	NS	NS	NS	NS	NS*
Popliteal Pulses (Doppler)	0.002	NS	NS	<0.001	0.010	NS	NS	NS*	NS	NS	NS	NS	NS

TABLE 15-10. (continued)

Association Between Peripheral Vascular Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol	HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Dorsalis Pedis Pulses (Manual)	0.018	NS	NS*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Dorsalis Pedis Pulses (Doppler)	NS*	0.001	0.007	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Posterior Tibial Pulses (Manual)	0.034	<0.001	NS	<0.001	<0.001	NS*	NS	NS*	NS	NS	NS	NS	NS
Posterior Tibial Pulses (Doppler)	0.003	NS*	NS	0.021	NS	NS	NS	0.035	NS	0.028	NS*	NS	NS*
Leg Pulses (Manual)	0.001	NS	NS	NS	0.031	NS	0.013	0.013	NS	NS	NS	NS	NS
Leg Pulses (Doppler)	0.020	0.009	0.012	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Peripheral Pulses (Manual)	<0.001	NS	NS	NS	0.028	NS	0.013	0.010	NS	NS	NS	NS	NS

TABLE 15-10. (continued)

Association Between Peripheral Vascular Function Variables and the Covariates in the Combined Ranch Hand and Comparison Groups (Diabetics Excluded)

Variable	Age	Race	Occupation	Current Smoking	Pack-Years Smoking	Cholesterol	HDL	Cholesterol-HDL Ratio	Percent Body Fat	Personality Score	Differential Cortisol	Current Alcohol Use (Drinks per Day)	Drink-Years Alcohol
Peripheral Pulses (Doppler)	0.037	0.015	0.019	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
All Pulses (Manual)	<0.001	NS	NS	NS	0.023	NS	0.013	0.012	NS	NS	NS	NS	NS
All Pulses (Doppler)	0.032	0.014	0.023	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

NS: Not significant (p>0.10).

NS*: Borderline significant (0.05<p≤0.10).

The adjusted categorical and continuous analyses are shown in Table 15-11. No significant group differences were found in the proportions of diastolic abnormalities (p=0.653), or in the difference of group mean values (p=0.299). The covariates of current smoking, cholesterol, percent body fat, and current alcohol use were statistically significant in both the categorical and continuous analyses; age was significant only in the analysis of group mean differences (p=0.005). No significant group-by-covariate interactions were found in either the logistic regression or general linear models. The adjusted analyses for the Original Comparisons were very similar to those described on the total Comparison group (see Table M-18 of Appendix M).

Funduscopic Examination

The funduscopic examination detected only 13 individuals with arterio-venous nicking (a sign of chronic blood pressure elevation) or vessel hemorrhages, 7 from the Ranch Hands and 6 from the Comparisons (p=0.472, Table 15-9).

The covariate tests of association are given in Table 15-10. Age, race, cholesterol/HDL ratio, percent body fat, and current drinking were statistically significant (p=0.004, 0.040, 0.016, 0.026, and 0.004, respectively). All funduscopic abnormalities were found in the older age group (born in or before 1942). Blacks had a higher proportion of abnormalities than nonblacks (2.4 percent versus 0.5 percent, respectively). The highest cholesterol-HDL category contained the highest proportion of funduscopic abnormalities; and increasing levels of percent body fat were associated with increases in proportions of abnormalities. Current alcohol consumption showed that nondrinkers had the highest proportion of abnormalities. The covariates of occupation, current smoking, pack-years of smoking, cholesterol, HDL, personality score, differential cortisol and drink-years of alcohol did not show significant effects.

In the adjusted analysis by logistic regression (Table 15-11), there were no significant differences in funduscopic abnormalities between the Ranch Hand and Comparison groups (Adj. RR: 1.78; 95% C.I.: [0.56,5.62], p=0.322). Due to sparse data the model was adjusted only for the covariates of age, race, cholesterol-HDL ratio, percent body fat, and current alcohol consumption; and all were significant in the model. No group interactions were detected, and the results of the contrast of the Ranch Hand with the Original Comparison group were also nonsignificant (Table M-18 of Appendix M).

Carotid Bruits

The unadjusted group contrast of carotid bruits is displayed in Table 15-9. The proportions of bruits in both groups were similar (Est. RR: 1.28, 95% C.I.: [0.45,3.66], p=0.646). Overall, only 14 bruits were detected, 7 from each group, limiting the scope of the adjusted analyses.

The covariate effects are given in Table 15-10. Age, current smoking, and cholesterol were of borderline statistical significance, whereas drink-years of alcohol was significantly correlated with carotid bruits (p=0.021), with the greater than 25 drink-years category having the highest proportion.

TABLE 15-11.

Adjusted Analysis for Peripheral Vascular Function by Group (Diabetics Excluded)*

Variable	Statistical/ Clinical Analysis	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
Diastolic Blood Pressure	Discrete	1.08 (0.78,1.48)	0.653	CSMOK (p=0.040) CHOL (p<0.001) %BFAT (p<0.001) ALC (p=0.008)
	Continuous	0.38 (-0.34, 1.11)[a]	0.299[a]	AGE (p=0.005) CSMOK (p<0.001) CHOL (p<0.001) %BFAT (p<0.001) ALC (p=0.002)
Funduscopic Examination		1.78 (0.56,5.62)	0.322	AGE (p<0.001) RACE (p<0.001) CHOL/HDL (p=0.017) %BFAT (p=0.037) ALC (p=0.038)
Carotid Bruits		1.05 (0.35,3.16)	0.928	AGE (p=0.024) DRKYR (p<0.001)
Radial Pulses	Manual	0.64 (0.19,2.14)[b]	0.472[b]	AGE (p=0.040)
	Doppler	0.96 (0.21,4.30)[b]	0.952[b]	--
Femoral Pulses	Manual	1.21 (0.63,2.31)	0.562	AGE (p<0.001) CHOL/HDL (p=0.010) %BFAT (p<0.001) DIFCORT (p=0.002)
	Doppler	1.74 (0.48,6.31)	0.401	AGE (p=0.001) CSMOK (p=0.001) CHOL/HDL (p=0.042)
Popliteal Pulses	Manual	****	****	AGE (p=0.003) PACKYR (p=0.005) CHOL/HDL (p=0.011) GRP*RACE (p=0.038)
	Doppler	1.50 (0.58,3.91)	0.401	AGE (p<0.001) RACE (p=0.023) CSMOK (p<0.001)
Dorsalis Pedis Pulses	Manual	****	****	AGE (p=0.004) DRKYR (p=0.038) GRP*OCC (p=0.046)
	Doppler	1.07 (0.87,1.31)	0.535	AGE (p=0.004) RACE (p=0.006) %BFAT (p=0.003)

TABLE 15-11. (continued)

Adjusted Analysis for Peripheral Vascular Function by Group (Diabetics Excluded)*

Variable	Statistical/ Clinical Analysis	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
Posterior Tibial Pulses	Manual	****	****	AGE (p<0.001) RACE (p<0.001) PACKYR (p=0.007) GRP*OCC (p=0.017)
	Doppler	0.94 (0.50,1.77)	0.849	AGE (p<0.001) RACE (p=0.002) CSMOK (p=0.007) CHOL/HDL (p=0.015)
Leg Pulses	Manual	****	****	AGE (p<0.001) GRP*OCC (p=0.016) GRP*%BFAT (p=0.034)
	Doppler	1.06 (0.87,1.30)	0.549	AGE (p=0.001) RACE (p=0.029) %BFAT (p=0.006)
Peripheral Pulses	Manual	****	****	AGE (p<0.001) %BFAT (p=0.018) GRP*OCC (p=0.033)
	Doppler	1.06 (0.87,1.30)	0.562	AGE (p=0.001) %BFAT (p=0.006)
All Pulses	Manual	****	****	AGE (p<0.001) %BFAT (p=0.022) GRP*OCC (p=0.036)
	Doppler	1.06 (0.86,1.29)	0.603	AGE (p=0.001) %BFAT (p=0.006)

*Some adjusted analyses did not explore effects of all covariates due to sparse number of abnormalities (see text).

**Additional Abbreviations:

DRKYR: drink-years of alcohol

DIFCORT: differential cortisol.

[a]Difference in group means (Ranch Hand-Comparison) and associated p-value given, rather than relative risk, for continuous analysis of dependent variables.

[b]Unadjusted for any covariates--same results as for unadjusted analysis.

****Group-by-covariate interaction--relative risk, confidence interval, and p-value not presented (see Table M-6 of Appendix M).

The adjusted analysis was performed with only the covariates of age and drink-years of alcohol due to the small number of detected bruits. The results (Table 15-11) demonstrate a lack of significant group differences (Adj. RR: 1.05, 95% C.I.: 0.35, 3.16], p=0.928). Both age and drink-years of alcohol were significant adjusting variables, but no significant group interactions were noted. The results of the Ranch Hand, Original Comparison group contrast was also nonsignificant (see Table M-18 of Appendix M).

Peripheral Pulses

Five peripheral pulses (radial, femoral, popliteal, dorsalis pedis, and posterior tibial) were analyzed using data assessments from both manual palpation and Doppler recordings. Palpation data from the examining physician were judged abnormal if the pulse was diminished or absent on either side. Assessment of the Doppler data was more complex and involved visual examination of the waveform morphology (pulsatility, systolic forward flow, and diastolic reverse flow) on analog strips and Polaroid® photographs, with careful comparison of the laterality of results. Confirmatory functional data (e.g., treadmill, segmental pressure readings) of abnormal pulses were not performed. The interpretation of each pulse was scored as normal, mild impairment, moderate impairment, severe impairment, or total occlusion (for the purpose of this analysis, all interpretations other than normal were considered abnormal). All Doppler measurements were conducted with a minimum of a 4-hour abstinence from smoking; compliance to the nonsmoking requirement was recorded by the Doppler technician.

Besides analysis of each pulse as a distinct dependent variable, three pulse aggregates were prescribed for analysis in order to maintain continuity with the Baseline analysis. The rationale of the pulse aggregates was to localize pulse abnormalities in broad anatomic categories. The aggregates were: leg pulses (femoral, popliteal, dorsalis pedis, and posterior tibial); peripheral pulses (radial, femoral, popliteal, dorsalis pedis, and posterio tibial); and all pulses (peripheral pulses plus carotid pulses, the latter assessed by only manual techniques). Any one abnormal pulse in an aggregate constituted an abnormality for the overall category.

The agreement of manual and Doppler assessments was tested by McNemar's chi-square test using paired data when an individual was compliant to both examination procedures. The paired analyses for the radial, femoral, popliteal, dorsalis pedis, posterior tibial, leg, peripheral, and all pulses are displayed in Table 15-12. As shown, the two methods of pulse assessment differed profoundly (p<0.001) for the femoral, popliteal, dorsalis pedis, leg pulses, peripheral pulses, and all pulses, but only mildly (p=0.044) for the posterior tibial pulse; the methodology differences for the radial pulse were not significantly discordant (p=0.149). Further, as shown by the off-diagonal elements in the specific pulse tables, the manual palpation method classified more cases as abnormal for the femoral, popliteal, and posterior tibial pulses, whereas the Doppler technique detected more abnormalities for the dorsalis pedis pulse, and consequently, the three pulse aggregates. Overall, more credence is given to the Doppler results due to the more "objective" means of determining a pulse abnormality.

The unadjusted analyses of all the pulses and pulse aggregates by manual and Doppler techniques (Table 15-9) showed that no statistically significant

TABLE 15-12.

Agreement Between Manual and Doppler Pulse Assessments
(McNemar's χ^2 Test)

Radial

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	2,102	3
Abnormal	9	3

$\chi^2 = 2.08$ $p=0.149$

Femoral

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	2,072	3
Abnormal	38	6

$\chi^2 = 28.2$ $p<0.001$

Popliteal

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	2,067	8
Abnormal	35	8

$\chi^2 = 15.7$ $p<0.001$

Dorsalis Pedis

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	1,546	341
Abnormal	71	155

$\chi^2 = 175.6$ $p<0.001$

Posterior Tibial

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	2,035	23
Abnormal	40	16

$\chi^2 = 4.1$ $p=0.044$

Leg

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	1,462	346
Abnormal	135	170

$\chi^2 = 91.7$ $p<0.001$

Peripheral

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	1,455	347
Abnormal	139	172

$\chi^2 = 88.2$ $p<0.001$

All

MANUAL	DOPPLER Normal	DOPPLER Abnormal
Normal	1,454	347
Abnormal	138	173

$\chi^2 = 89.2$ $p<0.001$

group differences were detected for any pulse or pulse combination by either technique.

The covariate tests of association for each pulse and pulse combination by technique are listed in Table 15-10. The following paragraphs describe the results shown in this table.

Increased age (born before 1942) was significantly associated with a higher proportion of pulse abnormalities for the femoral pulses (manual; $p<0.001$), popliteal pulses (Doppler; $p=0.002$), dorsalis pedis pulses (manual; $p=0.018$), posterior tibial pulses (manual, $p=0.034$; Doppler, $p=0.003$), leg pulses (manual, $p=0.001$; Doppler, $p=0.020$), peripheral pulses (manual, $p<0.001$; Doppler, $p=0.037$), and all pulses (manual, $p<0.001$, Doppler, $p=0.032$). Age was of borderline significance ($0.050<p\leq0.100$) for femoral pulses (Doppler), and for popliteal pulses (manual) and dorsalis pedis pulses (Doppler).

Race was associated with dorsalis pedis pulses (Doppler, $p=0.001$), posterior tibial pulses (manual, $p<0.001$), leg pulses (Doppler, $p=0.009$), peripheral pulses (Doppler, $p=0.015$), and all pulses (Doppler, $p=0.014$), with Blacks having a lower proportion of abnormalities for the dorsalis pedis, leg, peripheral, and all pulses than nonblacks, but a higher proportion of abnormalities for the posterior tibial pulse. Race was of borderline significance for the Doppler-determined posterior tibial pulses. Occupation was significantly associated with abnormalities of the dorsalis pedis pulses (Doppler, $p=0.007$), leg pulses (Doppler, $p=0.012$), peripheral pulses (Doppler, $p=0.019$), and all pulses (Doppler, $p=0.023$), with officers uniformly having more abnormalities than enlisted flyers, who had more abnormalities than enlisted groundcrew.

Current smoking (cigarettes per day) was significantly associated with increased abnormalities for the posterior tibial pulses (manual, $p<0.001$; Doppler, $p=0.021$), femoral pulses (Doppler, $p=0.001$), and the popliteal pulses (Doppler, $p<0.001$), despite the 4-hour abstinence prior to the Doppler examination. A relationship of increased smoking and increased abnormalities was only observed for the Doppler determination of the femoral and popliteal pulses. Pack-years of smoking was significantly related to increased abnormalities with popliteal pulses (manual, $p=0.001$; Doppler, $p=0.010$), posterior tibial pulses (manual, $p<0.001$), femoral pulses (Doppler, $p=0.006$), leg pulses (manual, $p=0.031$), peripheral pulses (manual, $p=0.028$), and all pulses (manual, $p=0.023$). Classical increasing associations were noted for the popliteal pulses (manual and Doppler), the posterior tibial pulses (manual), and the femoral pulses (Doppler).

For the related variables involving cholesterol, the cholesterol-HDL ratio showed the most numerous and strongest associations with pulse abnormalities. The cholesterol-HDL ratio was significantly and positively associated with increases in manually determined radial, femoral, and popliteal pulse abnormalities ($p=0.033$, $p<0.001$, and $p=0.002$, respectively); however, other significant associations with all pulses and the leg and peripheral pulse indices revealed an inconsistent pattern ($p=0.012$, $p=0.013$, and $p=0.010$, respectively). In addition, the ratio was significantly related to femoral and posterior tibial pulse abnormalities, as detected by the Doppler technique ($p=0.019$, $p=0.035$, respectively), but the relationships were not uniform from low to high values of the ratio. HDL was significantly associated with manually determined pulse abnormalities for femoral, leg, peripheral, and all pulses (p=0.002, p=0.013, p=0.013, p=0.013, respectively), but in all four cases, the mid-level category of HDL (greater than 40 to 50) was associated with the lowest proportion of abnormalities. Cholesterol showed only marginally significant associations with increased abnormalities of femoral pulse (manual and Doppler) and posterior tibial pulses (manual).

Percent body fat was significantly associated with increases of femoral pulse abnormalities (manual, p=0.001); personality score was associated with posterior tibial deficits (Doppler; p=0.028; nonlinear pattern); and drink-years of alcohol was related to femoral pulse abnormalities detected by both methods (manual, p<0.001; Doppler, p=0.013). Finally, in addition to numerous other marginally significant associations (e.g., drink-years and posterior tibial abnormalities, Doppler, p=0.083; drink-years and popliteal abnormalities, manual, p=0.085), differential cortisol showed a nonlinear association with posterior tibial pulse abnormalities (Doppler, p=0.074).

The distribution of each of the covariates in the Ranch Hand and Comparison groups is presented in Table 15-13. As noted, the distributions of the three matching variables, age, race, and occupation, are nearly identical (p=0.987, p=0.745, and p=0.661, respectively). For current smoking, however, Ranch Hands smoke significantly more cigarettes per day (higher mean level) than the Comparisons (p=0.043) a finding also observed at Baseline. Additionally, the difference in mean percent body fat was of borderline significance (p=0.074), with a slightly higher average level in the Comparison group.

The results of the adjusted analyses for the manual and Doppler pulse determinations are presented in Table 15-11. Due to the small number of abnormalities, manual radial pulses were adjusted only for age and the cholesterol-HDL ratio, and Doppler radial pulses were not adjusted for any covariates. Similarly, femoral Doppler pulses were adjusted only for age, current smoking, and the cholesterol-HDL ratio. Doppler popliteal pulses were adjusted only for main covariate effects, i.e., interactions were not examined.

The adjusted analyses of all Doppler-determined pulse and pulse aggregate abnormalities did not disclose any significant differences between the Ranch Hand and Comparison groups. Age showed a consistent and profound effect in all of the adjusted Doppler analyses, whereas race, percent body fat, and smoking were significantly influential in about half of the analyses, and the cholesterol-HDL ratio was significant for only two of the pulse variables. The effects of these four covariates were all in the expected (classical) direction.

For the manual pulse readings, the adjusted results (Table 15-11) were decidedly different from the Doppler analyses, with all but the radial and femoral pulses involved in significant group-by-covariate interactions. There were no significant group differences for the radial and femoral pulses (p=0.472, p=0.562, respectively). For manually determined popliteal pulses, there was a significant group-by-race interaction (p=0.038), with Blacks having an adjusted relative risk of 6.74 (95% C.I.: [0.72,63.40], p=0.095) in contrast to nonblacks, who had an adjusted relative risk of 0.55 (95% C.I.: 0.28,1.12] p=0.099]). All significant group-by-covariate interactions are shown in Table M-6 of Appendix M.

TABLE 15-13.

Summary Statistics for Cardiovascular Covariates by Group

Covariate	Covariate Category	Group: Ranch Hand	Group: Comparison	p-Value
		Percent	Percent	
Race	Black	5.6	6.0	
	Nonblack	94.4	94.0	0.745
Occupation	Officer	37.2	37.9	
	Enlisted Flyer	17.3	15.8	
	Enlisted Groundcrew	45.5	46.3	0.661
		Mean ± SE	Mean ± SE	
Age (At Baseline)	--	43.57±0.25	43.57±0.22	0.987
Current Smoking[a]	--	10.50±0.50	9.19±0.42	0.043
Pack-years Smoking	--	12.62±0.52	12.51±0.48	0.883
Cholesterol	--	216.8±1.3	218.1±1.2	0.463
HDL	--	46.32±0.42	46.90±0.35	0.288
Cholesterol-HDL Ratio	--	4.99±0.05	4.92±0.04	0.303
Percent Body Fat	--	20.85±0.16	21.23±0.14	0.074
Personality Score	--	-1.11±0.30	-1.50±0.26	0.322
Differential Cortisol	--	2.31±0.13	2.46±0.12	0.398
Current Alcohol Use (Drinks per Day)	--	1.23±0.07	1.28±0.07	0.611
Drink-years Alcohol	--	25.62±1.44	22.91±0.96	0.117

[a]Equivalent cigarettes/day.

--Covariate not categorized for these results.

For the dorsalis pedis, posterior tibial, leg, peripheral, and all pulses, significant group interactions with occupation were detected (p=0.046, p=0.017, p=0.016, p=0.033, and p=0.036, respectively). In all cases, the adjusted relative risk was less than one for the officers and greater than one for the enlisted flyers and groundcrew. In addition, the adjusted relative risk for enlisted flyers was consistently greater than the risk for the enlisted groundcrew. Statistically significant associations by pulse, by occupational category, were as follows: Posterior tibial pulses in enlisted flyer, p=0.032; leg pulses in officers (21% body fat level), p=0.026; peripheral pulses in officers, p=0.030; all pulses in officers, p=0.030. All other pulse-occupational strata contrasts were not statistically significant. As there was also a significant group by percent body fat interaction for leg pulses (p=0.034), each occupational category was analyzed by level of obesity (obese, percent body fat greater than 25 percent; nonobese, percent body fat equal to or less than 25 percent). For officers, the adjusted relative risks were less than one for both the obese (Adj. RR: 0.44, 95% C.I.: [0.17, 1.12], p=0.084) and the nonobese (Adj. RR: 0.66, 95% C.I.: [0.42,1.04], p=0.072). For enlisted flyer personnel, the adjusted relative risks were greater than one for both body fat categories, but were not statistically significant. The enlisted groundcrew manifested an adjusted relative risk of less than 1 for obese individuals (Adj. RR: 0.91, 95% C.I.: [0.39,2.10], p=0.818), and greater than 1 for nonobese individuals (Adj. RR: 1.20, 95% C.I.: [0.79,1.83], p=0.390), but also not statistically significant.

The unadjusted analyses of the manual and Doppler pulse assessments (shown in Table M-17 of Appendix M), using the Original Comparisons, did not disclose any significant group differences. For the Doppler adjusted analyses, the results for the Ranch Hand versus Original Comparison contrasts were similar to those found in the Ranch Hand versus total Comparison group, i.e., no statistically significant group differences or group-by-covariate interactions.

For the adjusted manual pulse determinations, however, the results differed somewhat from the contrast of the Ranch Hand versus total Comparison group in terms of the significant group-by-covariate interactions detected (see Tables M-18 and M-19 of Appendix M). As before, there were no statistically significant group differences for radial and femoral pulses. For popliteal pulses, however, there was a significant (p=0.048) group-by-occupation interaction, with an adjusted relative risk of less than one for the officers (p=0.219) and greater than one for the enlisted flyers, although not significantly so (p=0.165). For dorsalis pedis pulses, there were no significant group effects or interactions, but for posterior tibial pulses the results were similar to those found in the contrast of the Ranch Hands versus the total Comparison group analysis, i.e., a significant group-by-occupation interaction. For the three pulse aggregates, there were significant group-by-occupation and group-by-percent body fat interactions for the leg pulses (officers having a risk less than one; enlisted flyers and enlisted groundcrew having risks greater than one) and significant group-by-percent body fat interactions for peripheral pulses and all pulses (individuals with low percent body fat having adjusted relative risks greater than one, and obese individuals having an adjusted risk less than one).

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted for the Ranch Hand officer, enlisted flyer, and enlisted groundcrew cohorts separately to determine if any dose-response relationships could be identified. In many cases, the data were too sparse to permit statistical comparisons. Adjusted analyses included the exposure level and only the main effects of age, race, pack-years of smoking, cholesterol-HDL ratio, percent body fat, personality score, differential cortisol, and current drinks per day, whenever appropriate. (In several instances, the stepwise logistic modeling did not detect any statistically significant covariate effects. However, adjusted best model results may differ slightly from the unadjusted results due to the omission of individuals with missing covariate information from the adjusted analysis.)

Reported and Verified Heart Disease

Tabular results of adjusted exposure index analyses for reported and verified heart disease are presented in Table 15-14 (unadjusted exposure index analyses are in Table M-7 of Appendix M). There were no statistically significant differences for reported or verified essential hypertension or reported or verified myocardial infarction by exposure level. (The data on myocardial infarctions were quite sparse.) Results were also negative for reported and verified heart disease, except for the enlisted groundcrew cohort, where the percentage of individuals with reported or verified disease was lowest in the medium exposure category.

Central Cardiac Function

Table 15-15 gives the adjusted exposure results for systolic blood pressure (dichotomized), heart sounds, and ECG findings. The unadjusted exposure analyses are given in Table M-8 of Appendix M. The only exposure level effect reaching statistical significance was the medium versus low contrast for bradycardia in the enlisted groundcrew ($p=0.048$), where the adjusted relative risk was significantly less than one.

There were borderline significant effects, with adjusted relative risks greater than one for systolic blood pressure (enlisted groundcrew, medium versus low exposure) and T-wave findings (enlisted flyers, medium versus low contrast). There were borderline significant effects, with relative risks less than one for T-wave findings in the enlisted groundcrew cohort, medium versus low exposure (unadjusted only), and high versus low contrast (adjusted only).

The results for systolic blood pressure analyzed as a continuous variable showed no statistically significant exposure level effects, either unadjusted or adjusted for covariates. The adjusted medium versus low exposure level contrast was of borderline significance in the enlisted groundcrew ($p=0.069$). Age, percent body fat, and personality score were significant covariates in one or more occupational strata.

TABLE 15-14.

Adjusted Exposure Index Analyses for Reported and Verified Heart Disease by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Reported Essential Hypertension	Officer	Medium vs. Low	0.92 (0.50,1.70)	0.795	AGE (p=0.016)
		High vs. Low	1.08 (0.58, 2.01)	0.810	%BFAT (p<0.001)
	Enlisted Flyer	Medium vs. Low	0.84 (0.34,2.05)	0.704	%BFAT (p=0.002)
		High vs. Low	1.34 (0.57,3.16)	0.509	
	Enlisted Groundcrew	Medium vs. Low	1.37 (0.79,2.43)	0.289	%BFAT (p<0.001)
		High vs. Low	1.26 (0.68,2.33)	0.459	
Verified Essential Hypertension	Officer	Medium vs. Low	0.94 (0.48,1.84)	0.849	%BFAT (p<0.001)
		High vs. Low	1.36 (0.70,2.65)	0.363	
	Enlisted Flyer	Medium vs. Low	0.45 (0.15,1.33)	0.150	DIFCORT (p=0.026)
		High vs. Low	0.92 (0.35,2.40)	0.865	
	Enlisted Groundcrew	Medium vs. Low	1.47 (0.82,2.66)	0.201	%BFAT (p<0.001)
		High vs. Low	1.33 (0.71,2.49)	0.379	
Reported Heart Disease	Officer	Medium vs. Low	0.79 (0.45,1.38)	0.407	AGE (p=0.011)
		High vs. Low	0.69 (0.39,1.23)	0.204	
	Enlisted Flyer	Medium vs. Low	1.30 (0.58,2.94)	0.529	NONE
		High vs. Low	0.66 (0.27,1.62)	0.368	
	Enlisted Groundcrew	Medium vs. Low	0.51 (0.29,0.90)	0.020	AGE (p=0.046)
		High vs. Low	1.10 (0.65,1.86)	0.711	

TABLE 15-14. (continued)

Adjusted Exposure Index Analyses for Reported and Verified Heart Disease by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Verified Heart Disease	Officer	Medium vs. Low	0.75 (0.42,1.34)	0.332	AGE (p=0.007)
		High vs. Low	0.73 (0.40,1.32)	0.298	
	Enlisted Flyer	Medium vs. Low	1.11 (0.48,2.59)	0.803	NONE
		High vs. Low	0.57 (0.22,1.46)	0.242	
	Enlisted Groundcrew	Medium vs. Low	0.38 (0.20,0.73)	0.004	AGE (p=0.024)
		High vs. Low	0.95 (0.55,1.66)	0.865	
Reported Myocardial Infarction	Officer	Medium vs. Low	4.01 (0.43,37.2)	0.222	ALC (p=0.044)
		High vs. Low	1.20 (0.07, 19.9)	0.897	
	Enlisted Flyer	Medium vs. Low High vs. Low	--	--	--
	Enlisted Groundcrew	Medium vs. Low	0.86 (0.13,5.47)	0.873	AGE (p<0.001)
		High vs. Low	0.79 (0.14,4.35)	0.787	
Verified Myocardial Infarction	Officer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Groundcrew	Medium vs. Low	--	--	--
		High vs. Low	--	--	--

--Analysis not performed due to sparse cells.

TABLE 15-15.

Adjusted Exposure Index Analyses for Central Cardiac Function Variables by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Systolic Blood Pressure	Officer	Medium vs. Low	0.78 (0.27,2.26)	0.638	AGE (p=0.004)
		High vs. Low	1.03 (0.35,3.08)	0.952	PS (p=0.010)
	Enlisted Flyer	Medium vs. Low	0.94 (0.22,3.98)	0.936	NONE
		High vs. Low	0.74 (0.16,3.46)	0.697	
	Enlisted Groundcrew	Medium vs. Low	2.76 (0.93,8.24)	0.069	AGE (p=0.041)
		High vs. Low	1.97 (0.61,6.32)	0.254	%BFAT (p=0.006)
Heart Sounds	Officer	Medium vs. Low	0.71 (0.16,3.16)	0.660	AGE (p=0.004)
		High vs. Low	1.33 (0.33,5.40)	0.689	DIFCORT (p=0.009)
	Enlisted Flyer	--	--		--
	Enlisted Groundcrew	Medium vs. Low	0.25 (0.05,1.41)	0.116	CHOL/HDL (p<0.001)
		High vs. Low	1.26 (0.40,4.00)	0.689	
ECG	Officer	Medium vs. Low	1.36 (0.63,2.97)	0.435	AGE (p=0.007)
		High vs. Low	1.15 (0.50,2.62)	0.741	%BFAT (p=0.009)
	Enlisted Flyer	Medium vs. Low	1.54 (0.53,4.32)	0.412	AGE (p=0.007)
		High vs. Low	0.86 (0.29,2.49)	0.779	%BFAT (p<0.001)
	Enlisted Groundcrew	Medium vs. Low	0.66 (0.29,1.54)	0.342	AGE (p=0.001)
		High vs. Low	0.76 (0.34,1.71)	0.516	PACKYR (p=0.036)
					DIFCORT (p=0.038)

TABLE 15-15. (continued)

Adjusted Exposure Index Analyses for Central Cardiac Function Variables by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Nonspecific T-Wave Changes	Officer	Medium vs. Low	1.65 (0.65,4.20)	0.289	AGE (p=0.027)
		High vs. Low	1.47 (0.55,3.92)	0.441	RACE (p=0.027)
					%BFAT (p=0.002)
	Enlisted Flyer	Medium vs. Low	3.10 (0.85,11.28)	0.085	AGE (p=0.032)
		High vs. Low	1.64 (0.43,6.28)	0.472	%BFAT (p<0.001)
	Enlisted Groundcrew	Medium vs. Low	0.50 (0.19,1.28)	0.150	AGE (p=0.003)
		High vs. Low	0.37 (0.14,1.02)	0.055	
Bradycardia	Officer	Medium vs. Low	1.06 (0.37,3.06)	0.912	RACE (p=0.035)
		High vs. Low	1.10 (0.37,3.27)	0.865	
	Enlisted Flyer	Medium vs. Low	5.09 (0.57,45.1)	0.144	NONE
		High vs. Low	2.04 (0.18,23.1)	0.569	
	Enlisted Groundcrew	Medium vs. Low	0.21 (0.04,0.98)	0.048	NONE
		High vs. Low	0.50 (0.15,1.65)	0.254	
Arrhythmia	Officer	Medium vs. Low	0.21 (0.04,1.14)	0.070	AGE (p=0.011)
		High vs. Low	0.17 (0.02,1.44)	0.105	
	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low			
	Enlisted Groundcrew	Medium vs. Low	0.63 (0.18,2.26)	0.484	PACKYR (p<0.001)
		High vs. Low	0.99 (0.32,3.02)	0.984	

TABLE 15-15. (continued)

Adjusted Exposure Index Analyses for Central Cardiac Function Variables by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
	Officer	Medium vs. Low	1.29 (0.61,2.72)	0.704	AGE (p=0.003)
		High vs. Low	0.86 (0.37,1.96)	0.711	
Other Diagnoses	Enlisted Flyer	Medium vs. Low	0.54 (0.17,1.78)	0.312	AGE (p=0.034)
		High vs. Low	0.37 (0.11,1.32)	0.522	
	Enlisted Groundcrew	Medium vs. Low	0.91 (0.36,2.29)	0.841	AGE (p<0.001)
		High vs. Low	0.76 (0.30,1.92)	0.562	RACE (p=0.030)

--Analysis not performed due to sparse cells.

Peripheral Vascular System

There were no significant dose-response effects for diastolic blood pressure (dichotomized), funduscopic abnormalities, or carotid bruits (Table 15-16). Analysis of diastolic blood pressure as a continuous variable also did not reveal any statistically significant exposure level effects. Significant covariates were percent body fat, personality type, cholesterol-HDL ratio, and current alcohol use.

Exposure index analyses of the peripheral pulses did not detect any statistically significant exposure effects, either unadjusted (Tables M-9 and M-10 of Appendix M for the manual and Doppler pulse readings) or adjusted (Tables 15-17 and 15-18).

Main-effect exposure analyses of 6 historical and verified heart disease variables, 10 central cardiac function variables, and 11 peripheral cardiac function variables (with both manual and Doppler results), showed no evidence of a dose-response relationship at the followup examination. Two statistically significant and several borderline significant exposure associations lacked a pattern of dose-response consistency, and appeared to be random in nature.

Association of Cardiovascular Examination Findings With Verified Heart Disease

The central and peripheral cardiovascular examination findings were analyzed together with the verified cardiovascular disease endpoints to determine the degree of correlation between the third-year followup examination and the past medical history. The results are shown in Table M-11 of Appendix M. There were highly significant associations between verified essential hypertension and systolic and diastolic blood pressures, ECG abnormalities, and abnormal fundi ($p<0.001$, <0.001, <0.001, 0.008, respectively). There was also a significant association between essential hypertension and abnormal heart sounds ($p=0.036$), as well as a borderline significant association between hypertension and carotid bruits ($p=0.080$). The frequency of verified essential hypertension, however, was not significantly different in those with and without peripheral pulse abnormalities (as determined by either the manual or Doppler technique).

For verified heart disease, there was a negative association with diastolic blood pressure ($p=0.043$) and positive associations with ECG abnormalities, heart sounds, abnormal fundi, and abnormal peripheral pulses as determined by the Doppler technique ($p<0.001$, $p=0.017$, $p=0.014$, and $p=0.007$, respectively). Finally, there were significant positive associations between ECG and heart sound abnormalities ($p<0.001$ for both) and the occurrence of a verified myocardial infarction. The consistency between the examination findings and the past medical history provides support for the overall validity of the cardiovascular measurement systems, whether by self-report, medical records, physician assessments, or objective determinations (e.g., ECG).

TABLE 15-16.

Adjusted Exposure Index Analyses for Diastolic Blood Pressure Funduscopic Abnormalities and Carotid Bruits by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Diastolic Blood Pressure	Officer	Medium vs. Low	0.79 (0.27,2.30)	0.667	%BFAT (p=0.002)
		High vs. Low	1.44 (0.54,3.86)	0.465	
	Enlisted Flyer	Medium vs. Low	0.76 (0.19,2.98)	0.697	%BFAT (p=0.006)
		High vs. Low	1.06 (0.29,3.84)	0.928	
	Enlisted Groundcrew	Medium vs. Low	1.50 (0.63,3.59)	0.363	CHOL/HDL (p=0.037)
		High vs. Low	1.24 (0.53,2.86)	0.667	%BFAT (p<0.001)
Funduscopic Abnormalities	Officer	--	--	0.337[a]	--
	Enlisted Flyer	--	--	--	--
			--	--	--
	Enlisted Groundcrew	--	--	--	--
Carotid Bruits	Officer	--	--	0.388[a]	--
	Enlisted Flyer	--	--	--	--
	Enlisted Groundcrew	--	--	--	--

[a]Overall analysis; sparse cells, chi-square test may not be valid.

--Analysis not performed due to sparse cells.

TABLE 15-17.

Adjusted Exposure Index Analyses for Peripheral Vascular System Manual Pulse Readings by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Radial Pulses	Officer	Medium vs. Low High vs. Low	--	--	--
	Enlisted Flyer	Medium vs. Low High vs. Low	--	--	--
	Enlisted Groundcrew	Medium vs. Low High vs. Low	-- --	-- --	-- --
Femoral Pulses	Officer	Medium vs. Low High vs. Low	-- --	-- --	-- --
	Enlisted Flyer	Medium vs. Low High vs. Low	0.36 (0.02,7.42) 3.20 (0.31,32.6)	0.509 0.238	RACE (p=0.006) %BFAT (p=0.032) PS (p=0.041)
	Enlisted Groundcrew	Medium vs. Low High vs. Low	-- --	-- --	-- --
Popliteal Pulses	Officer	Medium vs. Low High vs. Low	-- --	-- --	-- --
	Enlisted Flyer	Medium vs. Low High vs. Low	-- --	-- --	-- --
	Enlisted Groundcrew	Medium vs. Low High vs. Low	0.91 (0.14,5.90) 1.05 (0.20,5.52)	0.928 0.952	AGE (p=0.030) RACE (p=0.048) DIFCORT (p=0.048)

TABLE 15-17. (continued)

Adjusted Exposure Index Analyses for Peripheral Vascular System Manual Pulse Readings by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Dorsalis Pedis Pulses	Officer	Medium vs. Low	0.88 (0.40,1.97)	0.764	NONE
		High vs. Low	0.52 (0.20,1.33)	0.171	
	Enlisted Flyer	Medium vs. Low	1.53 (0.51,4.65)	0.447	NONE
		High vs. Low	1.39 (0.45,4.33)	0.569	
	Enlisted Groundcrew	Medium vs. Low	0.61 (0.27,1.35)	0.222	NONE
		High vs. Low	0.95 (0.45,2.02)	0.897	
Posterior Tibial Pulses	Officer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Flyer	Medium vs. Low	0.75 (0.13,4.20)	0.741	RACE (p=0.027)
		High vs. Low	1.26 (0.26,6.10)	0.772	
	Enlisted Groundcrew	Medium vs. Low	2.00 (0.48,8.33)	0.337	AGE (p=0.003)
		High vs. Low	1.51 (0.37,6.17)	0.569	RACE (p<0.001)
Leg Pulses	Officer	Medium vs. Low	0.96 (0.44,2.12)	0.920	NONE
		High vs. Low	0.84 (0.37,1.95)	0.697	
	Enlisted Flyer	Medium vs. Low	1.01 (0.37,2.75)	0.984	PS (p=0.034)
		High vs. Low	1.21 (0.45,3.27)	0.711	
	Enlisted Groundcrew	Medium vs. Low	0.69 (0.35,1.36)	0.285	NONE
		High vs. Low	0.89 (0.46,1.75)	0.741	

TABLE 15-17. (continued)

Adjusted Exposure Index Analyses for Peripheral Vascular System Manual Pulse Readings by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Peripheral Pulses	Officer	Medium vs. Low	0.89 (0.41,1.94)	0.764	NONE
		High vs. Low	0.86 (0.42,1.75)	0.719	
	Enlisted Flyer	Medium vs. Low	1.01 (0.37,2.75)	0.984	PS (p=0.034)
		High vs. Low	1.21 (0.45,3.27)	0.711	
	Enlisted Groundcrew	Medium vs. Low	0.69 (0.35,1.36)	0.285	NONE
		High vs. Low	0.89 (0.46,1.75)	0.741	
All Pulses	Officer	Medium vs. Low	0.89 (0.41,1.94)	0.764	NONE
		High vs. Low	0.86 (0.42,1.75)	0.719	
	Enlisted Flyer	Medium vs. Low	1.01 (0.37,2.75)	0.984	PS (p=0.034)
		High vs. Low	1.21 (0.45,3.27)	0.711	
	Enlisted Groundcrew	Medium vs. Low	0.69 (0.35,1.36)	0.285	NONE
		High vs. Low	0.89 (0.46,1.75)	0.741	

--Analysis not performed due to sparse cells.

TABLE 15-18.

Adjusted Exposure Index Analyses for Peripheral Vascular System Doppler Pulse Reading by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Dorsalis Pedis Pulses	Officer	Medium vs. Low	1.12 (0.63,1.97)	0.704	NONE
		High vs. Low	1.08 (0.60,1.96)	0.787	
	Enlisted Flyer	Medium vs. Low	1.30 (0.51,3.28)	0.575	NONE
		High vs. Low	1.43 (0.56,3.64)	0.447	
	Enlisted Groundcrew	Medium vs. Low	0.94 (0.53,1.65)	0.772	RACE (p=0.034)
		High vs. Low	1.04 (0.58,1.87)	0.764	
Posterior Tibial Pulses	Officer	Medium vs. Low	2.09 (0.38,11.6)	0.401	AGE (p=0.025)
		High vs. Low	1.01 (0.13,7.58)	0.992	DIFCORT (p=0.026)
	Enlisted Flyer	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
	Enlisted Groundcrew	Medium vs. Low	--	--	--
		High vs. Low	--	--	--
Leg Pulses	Officer	Medium vs. Low	1.26 (0.71,2.21)	0.430	NONE
		High vs. Low	1.19 (0.66,2.13)	0.562	
	Enlisted Flyer	Medium vs. Low	1.57 (0.63,3.90)	0.327	NONE
		High vs. Low	1.58 (0.63,3.98)	0.327	
	Enlisted Groundcrew	Medium vs. Low	0.94 (0.54,1.87)	0.818	NONE
		High vs. Low	1.01 (0.57,1.80)	0.772	

TABLE 15-18. (continued)

Adjusted Exposure Index Analyses for Peripheral Vascular System Doppler Pulse Reading by Occupation

Variable	Occupation	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Significant Covariates
Peripheral Pulses	Officer	Medium vs. Low	1.26 (0.71,2.21)	0.430	NONE
		High vs. Low	1.19 (0.66,2.13)	0.562	
	Enlisted Flyer	Medium vs. Low	1.57 (0.63,3.90)	0.327	NONE
		High vs. Low	1.58 (0.63,3.98)	0.327	
	Enlisted Groundcrew	Medium vs. Low	0.90 (0.52,1.57)	0.704	NONE
		High vs. Low	1.02 (0.58,1.79)	0.960	
All Pulses	Officer	Medium vs. Low	1.26 (0.71,2.21)	0.430	NONE
		High vs. Low	1.19 (0.66,2.13)	0.562	
	Enlisted Flyer	Medium vs. Low	1.57 (0.63,3.90)	0.327	NONE
		High vs. Low	1.58 (0.63,3.98)	0.327	
	Enlisted Groundcrew	Medium vs. Low	0.90 (0.52,1.57)	0.704	NONE
		High vs. Low	1.02 (0.58,1.79)	0.960	

--Analysis not performed due to sparse cells.

LONGITUDINAL ANALYSES

Two cardiovascular variables, the index of all pulses (by palpation) and the overall ECG interpretation, were investigated to assess the longitudinal differences between the 1982 Baseline examination and the 1985 followup examination. Both variables are classified as abnormal or normal. As shown in Table 15-19, 2x2 tables were constructed for each group for each variable. These tables show the number of participants who were abnormal at Baseline and abnormal at followup, abnormal at Baseline and normal at followup, normal at Baseline and abnormal at followup, and normal at both Baseline and followup examinations. The odds ratio given is the ratio of the number of participants who were normal at the Baseline and abnormal at the followup to the number of participants who were abnormal at the Baseline and normal at the followup (the "off-diagonal" elements). The changes in normal/abnormal status within each group are contrasted between the Ranch Hand and Comparison groups, and the p-value is derived from Pearson's chi-square test of the hypothesis that the pattern of change in the two groups is the same.

TABLE 15-19.

Longitudinal Analyses of All Pulses Index and Overall ECG's: A Contrast of Baseline and First Followup Examination Abnormalities

Variable	Group	1982 Baseline Exam	1985 Followup Exam		Odds* Ratio (OR)	p-Value (OR_{RH} vs. OR_C)
			Abnormal	Normal		
All Pulses (Manual)	Ranch Hand	Abnormal	50	72	1.44	0.01
		Normal	104	743		
	Comparison	Abnormal	40	63	2.43	
		Normal	153	880		
ECG (Overall)	Ranch Hand	Abnormal	86	192	0.22	0.42
		Normal	43	650		
	Comparison	Abnormal	112	208	0.27	
		Normal	56	763		

$$\text{*Odds Ratio: } \frac{\text{Number Normal Baseline, Abnormal Followup}}{\text{Number Abnormal Baseline, Normal Followup}}$$

The data showed a significant difference (p=0.01) in the pulse index in the two groups between examinations. The percentage of Ranch Hands and Comparisons with abnormalities for the pulse index increased from the Baseline examination to the followup examination; however, the Comparison group showed a larger increase in the proportion of pulse index abnormalities. The greater relative increase in the Comparisons caused the significant result. No significant group differences were detected between examinations for overall ECG abnormalities (p=0.42).

DISCUSSION

In general, the foregoing analyses on a wide range of cardiovascular variables, have shown a lack of significant differences between the Ranch Hands and the Comparisons. The sole exception was the finding of increased verified heart disease in the Ranch Hands versus the Comparisons (24% and 20%, respectively, p=0.054, unadjusted; p=0.036, adjusted). These results were not noted in the Baseline examination (p=0.982, unadjusted). A review of the relative risk patterns, whether or not statistically significant, for all of the other cardiovascular variables showed general equality, with about half of the risks below unity and half above. This rough equivalence suggests that, although the Ranch Hands have slightly more reported heart disease, the finding is not mirrored by substantial and consistent clinical cardiovascular defects at this time. This observation should not be lightly dismissed, and is cause for continued close surveillance.

The most notable cardiovascular finding at the followup examination was the lack of significant peripheral pulse abnormalities, which were unexpectedly found at the 1982 Baseline examination (p=0.05). The primary contributory cause of the change in pulse significance from Baseline to followup was probably the rigid 4-hour tobacco abstinence required prior to Doppler testing (due to the known vasoconstriction effects of nicotine). Tobacco abstinence, however, was not a requirement for the Baseline manual pulse readings. Although tobacco abstinence was not a requirement prior to manual readings at the followup examination, there was general compliance to the smoking prohibition, particularly if a participant's general physical examination preceded the Doppler testing. Therefore it might be expected that the manual readings would show more pulse abnormalities than Doppler testing; in fact, this was the case (see section on Peripheral Pulses).

Whatever the true cause(s), the prevailing fact is that there are no longer significant group differences in pulse abnormalities, as noted by both manual and Doppler techniques, regardless of the poor agreement between the two methods.

The close approximation of the estimated relative risks to unity for practically all of the cardiovascular variables is clearly indicative of equivalent cardiovascular health between the two groups. Furthermore, the general similarity of the unadjusted and adjusted results was suggestive of near equivalence of the important cardiovascular risk factors in the Ranch Hands and Comparisons (see Table 15-13), as well as a balance for unanalyzed or hidden covariates of importance.

These health assessments of the two groups are considerably strengthened by the almost consistent, classical effects of the covariates in this chapter. In particular, the age effect was uniformly profound, affecting almost all of the dependent variables in the functional categories of reported-verified heart diseases, and central and peripheral vascular function. The covariates of race, percent body fat, and cholesterol (particularly the cholesterol-HDL ratio), and smoking were also generally strong and consistent in their effects. Statistically significant, positive associations were seen between the current level of smoking and posterior tibial, popliteal, and femoral pulses, as well as borderline significant associations between current smoking and other ECG diagnoses, carotid bruits, and reported myocardial infarctions. However, significant negative associations were observed between current smoking and reported and verified essential hypertension. Pack-years of smoking was significantly positively associated with several ECG variables and pulse assessments, although not always in a consistently increasing manner. There was a statistically significant and consistently increasing effect of pack-years of smoking on reported and verified myocardial infarctions, but there was a negative association between pack-years of smoking and verified essential hypertension, with the greatest number of abnormalities in the zero pack-year category. Alcohol was infrequently interactive with the dependent variables, but covariate tests of association generally revealed the classical pattern of more cardiovascular abnormalities in the nondrinking category than in the low drinking category.

Personality score, however, usually failed to demonstrate the "expected" aggregation of cardiovascular abnormalities in the Type A direction. In fact, most associations were in the Type B direction. Generally, only cardiovascular studies ascertaining personality type by the Structured Interview technique have shown an association of Type A personality (Type A-1, in particular) to heart disease endpoints, and conversely, studies using questionnaire techniques to measure personality type have not demonstrated the association. Lastly, the strong association between historical-verified cardiovascular events and the specific dependent variables provides assurance that the overall cardiovascular measurements have been accurate and valid.

SUMMARY AND CONCLUSIONS

The cardiovascular health of both cohorts was assessed by collection of reported and record-verified heart disease events; measurement of central cardiac function by systolic blood pressure, abnormal heart sounds, and electrocardiograph (ECG) findings; and evaluation of peripheral vascular function by diastolic blood pressure, funduscopic examination, presence of carotid bruits, and detailed manual and Doppler measurements of five peripheral pulses. Table 15-20 presents the overall summary of the unadjusted and adjusted results. Where possible, the analyses used the covariates of age, race, occupation, percent body fat, cholesterol, high density lipoprotein (HDL) cholesterol, cholesterol-HDL ratio, smoking history (pack-years and current smoking level), alcohol history (drink-years and current drinking level), personality score, and differential cortisol.

The cardiovascular variables did not reveal significant group differences, with the exception of verified heart disease, for which the proportions of recorded cardiac events were 24 and 20 percent in the Ranch Hand and Comparison groups, respectively, (p=0.054 unadjusted, p=0.036 adjusted). This finding was not reinforced by results of individual questionnaire or examination variables showing impairment in the Ranch Hands. There was a remarkable balance in relative risks above and below unity between the groups.

TABLE 15-20.

Overall Summary Results of Unadjusted and Adjusted Analyses Cardiovascular Variables

Variable	Statistical/ Clinical Analysis	Unadjusted	Adjusted
Historical and Verified Heart Disease			
Reported Hypertension		NS	NS
Verified Hypertension		NS	NS
Reported Heart Disease[a]		NS	NS
Verified Heart Disease[a]		NS*	S[b]
Reported Heart Attack		NS	NS
Verified Heart Attack		NS	NS
Central Cardiac Function			
Systolic Blood Pressure	Discrete	NS	NS
	Continuous	NS	****
Heart Sounds		NS	NS
Electrocardiogram (Overall)		NS	****
ECG: RBBB		NS	NS
ECG: LBBB		---	N/A
ECG: Nonspecific T-Wave Changes		NS	NS
ECG: Bradycardia		NS	NS
ECG: Tachycardia		---	N/A
ECG: Arrhythmia		NS	****
ECG: Other Diagnoses		NS	NS

TABLE 15-20. (continued)

Overall Summary Results of Unadjusted and Adjusted Analyses
Cardiovascular Variables

Variable	Statistical/ Clinical Analysis	Unadjusted	Adjusted
Peripheral Vascular Function			
Diastolic Blood Pressure	Discrete	NS	NS
	Continuous	NS	NS
Funduscopic Examination		NS	NS
Carotid Bruits		NS	NS
Radial Pulses	Manual	NS	NS
	Doppler	NS	NS
Femoral Pulses	Manual	NS	NS
	Doppler	NS	NS
Popliteal Pulses	Manual	NS	****
	Doppler	NS	NS
Dorsalis Pedis Pulses	Manual	NS	****
	Doppler	NS	NS
Posterior Tibial Pulses	Manual	NS	****
	Doppler	NS	NS
Leg Pulses	Manual	NS	****
	Doppler	NS	NS
Peripheral Pulses	Manual	NS	****
	Doppler	NS	NS
All Pulses	Manual	NS	****
	Doppler	NS	NS

NS:Not significant (p>0.10).

NS*:Borderline significant (0.05<p≤0.10).

****Group-by-covariate interaction.

[a]Excluding hypertension.

[b]RH>C (Adj. RR: 1.25; 95% C.I.: [1.02, 1.54], p=0.036).

Other related analyses showed an absence of significant group differences in reported or verified hypertension, reported or verified heart attacks, and reported heart disease. There was good correlation between the verified cardiovascular history and the central and peripheral cardiovascular abnormalities detected at the physical examination, supporting accuracy and validity of the cardiovascular measurements.

The adjusted analyses of central cardiac function disclosed a significant group-by-age interaction involving systolic blood pressure in the Black cohort, with a mean systolic blood pressure greater in the Ranch Hands than the Comparisons at younger age levels, but a lower mean pressure at the older ages; the group-by-age interaction was not significant in the nonblack cohort. Additionally, there was a significant group-by-pack-years of smoking interaction for the overall ECG findings, and significant group-by-pack-years of smoking and group-by-percent body fat interactions for arrhythmia, but they all generally pointed to lower adjusted relative risks in the Ranch Hands.

In the analysis of peripheral vascular function, no significant group differences were observed for abnormalities involving radial, femoral, popliteal, posterior tibial, dorsalis pedis, or three anatomic aggregates of these pulses, either by manual palpation or Doppler techniques. This overall finding was in distinct contrast to the 1982 Baseline examination, which by the manual palpation method, showed significant peripheral pulse deficits in the Ranch Hands. This favorable pulse reversal over the two examinations is primarily attributed to the rigid 4-hour tobacco abstinence applied prior to Doppler testing, although other factors may be related. The lack of group differences for pulse abnormalities was noted even though the manual and Doppler techniques differed significantly ($p<0.05$, $p<0.001$ for most) in the detection of abnormalities for all but one of the pulses or pulse combinations.

For manually-determined pulse abnormalities, there was a significant group-by-race interaction for the popliteal pulses, a significant group-by-percent body fat interaction for the leg pulses, and significant group-by-occupation interactions for the posterior tibial, dosalis pedis, and the three pulse aggregates (leg, peripheral, and all pulses). No interactions were encountered in the adjusted analyses of the Doppler results, and none showed significant group differences.

Statistical analyses involving the Original Comparisons also showed no significant differences in the cardiovascular measurements between groups, although slightly different interactions were detected in some of the adjusted analyses.

For the exposure analyses, the only statistically significant effects were those pointing to less bradycardia and less reported and verified heart disease in the medium exposure level category, as contrasted to the low exposure category, among the enlisted groundcrew. In many cases there were too few abnormalities within the occupational categories to permit formal statistical tests. Overall, the exposure analyses were deemed as unsupportive of any meaningful dose-response relationships.

The longitudinal analysis of the pulse index confirmed the significant difference in the change in the pattern of results from the Baseline examination to the followup examination, largely due to a relatively greater increase of pulse abnormalities in the Comparison group than in the Ranch Hand group. There was no significant change in pattern between the two groups in overall ECG findings between examinations.

There was a similar distribution of the covariates between groups, except for a slightly higher level of current Ranch Hand smoking (also observed at Baseline), and a corresponding slightly lower mean percent body fat. The general covariate effects were strong and showed expected, classical associations with the cardiovascular measurements. However, unexpected effects were consistently noted for personality score, with higher proportions of various cardiovascular abnormalities associated with scores in the Type B direction, a finding possibly attributable to the method of personality determination. Nonetheless, the repeated demonstration of classical covariate associations with cardiovascular pathology lends considerable credence to the quality of the data. Although smoking was positively associated with many of the cardiovascular measurements, negative associations were seen between current smoking and reported and verified essential hypertension and between pack-years of smoking and verified hypertension.

In conclusion, of 27 cardiovascular variables, only one, verified heart disease, showed a significant excess in the Ranch Hands, but this finding was largely unsupported by other cardiac measurements. Both manual palpation and Doppler recordings of five peripheral pulses were similar in both groups, in marked contrast to the 1982 Baseline examination which found significant pulse deficits in the Ranch Hand group. This change at the followup examination was most likely due to required tobacco abstinence prior to the pulse measurements. Exposure index analyses did not support a consistent dose-response relationship for any variable. Overall, there was remarkable similarity in the cardiovascular health between the Ranch Hand and Comparison groups.

CHAPTER 15

REFERENCES

1. Palmer, J.S., and R.D. Radeleff. 1964. The toxicologic effects of certain fungicides and herbicides on sheep and cattle. Ann. N.Y. Acad. Sci. 111:729-736.

2. McConnell, E.E., J.A. Moore, and D.W. Dalgard. 1978. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Rhesus monkeys (Macaca mulatta) following a single oral dose. Toxicol. Appl. Pharmacol. 43(1):175-187.

3. Kimbrough, R.D., C.D. Carter, J.A. Liddle, R.E. Cline, and P.E. Phillips. 1977. Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. Arch. Environ. Health 32(2):77-86.

4. McConnell, E.E., J.A. Moore, J.K. Haseman, and M.W. Harris. 1978. The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol. Appl. Pharmacol. 44(2):335-356.

5. Schreiweis, D.O., and G.J. Murray. 1976. Cardiovascular malformations in Oryzias latipes embryos treated with 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Teratology 14(3):287-290.

6. Rifkind, A.B., Y. Hattori, R. Levi, M.J. Hughes, C. Quilley, and D.R. Alonso. The chick embryo as a model for PCB and dioxin toxicity: Evidence of cardiotoxicity and increased prostaglandin synthesis. In Banbury report 18: Biological mechanisms of dioxin action ed. A. Poland and R.D. Kimbrough, pp. 255-266. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory.

7. Dudley, A.W., and N.T. Thapar. 1972. Fatal human ingestion of 2,4-D, a common herbicide. Arch. Path. 94:270-275.

8. Paggiaro, P.L., E. Martino, and S. Mariotti. 1974. A case of 2,4-dichlorophenoxyacetic acid (2,4-D) poisoning. Med. Lavoro 65(3-4):128-135.

9. Berwick, P. 1970. 2,4-Dichlorophenoxyacetic acid poisoning in man. JAMA 214(6):1114-1117.

10. Oliver, R.M. 1975. Toxic effects of 2,3,7,8-tetrachloro-dibenzo-1, 4-dioxin in laboratory workers. Br. J. Ind. Med. 32:46-53.

11. Baader, E.W., and A.J. Bauer. 1951. Industrial intoxication due to pentachlorophenol. Ind. Med. Surg. 20:289-290.

12. Jirasek, L., J. Kalensky, K. Kubec, et al. 1974. Acne chlorina, porphyria cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides, part 2. Czech. Dermatol. 49(3):145-157.

13. Pazderova-Vejlupkova, J., M. Nemcova, J. Pickova, L. Jirasek, and E. Lukaš. 1981. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Arch. Environ. Health 36:5-11.

14. Poland, A.P., D. Smith, G. Metter, and P. Possick. 1971. A health survey of workers in a 2,4-D and 2,4,5-T plant, with special attention to chloracne, porphyria cutanea tarda, and psychologic parameters. Arch. Environ. Health 22(3):316-327.

15. Moses, M., R. Lilis, K.D. Crow, J. Thornton, A. Fischbein, H.A. Anderson, and I.J. Selikoff. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichloro-phenoxyacetic acid: Comparison of findings with and without chloracne. Am. J. Ind. Med. 5:161-182.

16. Suskind, R.R., and V.S. Hertzberg. 1984. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251:2372-2380.

17. Hoffman, R.E., P.A. Stehr-Green, K.B. Webb, G. Evans, A.P. Knutsen, W.F. Schramm, J.L. Staake, B.B. Gibson, and K.K. Steinberg. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. JAMA 255:2031-2038.

18. Stehr, P.A., G. Stein, H. Falk, et al. 1986. A pilot epidemiologic study of possible health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin contamination in Missouri. Arch. Environ. Health 41:16-22.

19. Troxler, R.G., and H.A. Schwertner. 1985. Cholesterol, stress, lifestyle, and coronary heart disease. Aviat. Space Environ. Med. 56:660-665.

20. American Heart Association Steering Committee for Medical and Community Program. 1980. Risk factors and coronary disease: A statement for physicians. Circulation 62:449A-455A.

21. Castelli, W.P. 1984. Epidemiology of coronary heart disease: The Framingham study. Am. J. Med. 76:4-12.

22. Multiple Risk Factor Intervention Trial Research Group (Neaton, J.D., L.H. Kuller, D. Wentworth, et al.). 1984. Total and cardiovascular mortality in relation to cigarette smoking, serum cholesterol concentration, and diastolic blood pressure among black and white males followed for five years. Am. Heart J. 108:759-769.

23. Morton, W.E., E.D. Crawford, R.A. Maricle, D.D. Douglas, and V.H. Freed. 1975. Hypertension in Oregon pesticide-formulating workers. J. Occ. Med. 17(3):182-185.

24. Martin, J.V. 1984. Lipid abnormalities in workers exposed to dioxin. Br. J. Ind. Med. 41:254-256.

25. Ashe, W.F., and R.R. Suskind. 1949, 1950. Reports on chloracne cases, Monsanto Chemical Company, Nitro, West Virginia. In Report of the Kettering Laboratory, December 1949 and April 1950.

26. Lipid Research Clinic Program: The Lipid Research Clinic's Coronary Prevention Trial Results: II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. 1984. JAMA 251:365-374.

27. Stamler, J., D. Wentworth, and J.D. Neaton. 1986. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? JAMA 256:2823-2828.