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USING CAPTURE-RECAPTURE METHOD TO ESTIMATE MULTIPLE SCLEROSIS PREVALENCE IN AREAS AROUND SPOKANE, WASHINGTON

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By

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A THESIS

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CERTIFICATE OF APPROVAL

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This is to certify that the Master's Thesis of

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LIST OF ACRONYMS

CI	Confidence interval
CSF	Cerebrospinal fluid
Ln	Natural logarithm
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSA	Metropolitan statistical area
PPMS	Primary progressive multiple sclerosis
PRMS	Progressive relapsing multiple sclerosis
RPMS	Relapsing progressive multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
TPMS	Transitional progressive multiple sclerosis

ABSTRACT

Background: Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease, which has a profound impact on patients' social roles and quality of life. The etiology of MS is thought to involve both environmental factors and genetic susceptibility. Several studies have implicated exposure to ionizing radiation as one risk factor for multiple sclerosis. Communities around Hanford, a former nuclear site, are concerned about autoimmune diseases attributable to radiation exposure. Eastern Washington State has been suspected to have a high MS prevalence, despite the lack of a systematic survey.

Methods: This study examines the prevalence of multiple sclerosis for the 6-year period of 1998 to 2003 in twelve counties located around Spokane. Data were extracted from medical charts from the primary MS diagnosis and treatment center in Spokane, and a major outpatient treatment system in the city. We applied the capture-recapture technique to these two data sources and estimated the total number of MS cases in the region. Multiple linear regression models were constructed to assess the associations between each county's MS prevalence and demographic and environmental factors.

Results: A total of 1088 cases were identified through the medical records from the two MS diagnosis and treatment systems. The number of female MS cases in the combined list from two sources was 3.1 times the number of male cases. Based on capture-recapture methods, 1626 MS cases were estimated in the study area. In the whole study area, the observed crude MS prevalence was 196.8 (95% CI: 185.1 – 208.5) cases per 100,000 adults; capture-recapture methods yielded a higher estimate of 294.1 (95% CI: 272.1 – 316.0) per 100,000 adults. At the county level, multiple linear regressions indicated that mean per capita income and geographic latitude were associated with total observed MS prevalence; using estimates of total MS

prevalence from the capture-recapture method, only mean per capita income was associated at the 0.05 significance level.

Conclusion: This study confirmed the community's perception of high occurrence of multiple sclerosis. The capture-recapture method using two sources indicated a substantial proportion of "hidden" cases may exist. The combined counts of directly observed MS cases provide a lower bound estimate ("floor"), whereas the estimated MS prevalence based on capture-recapture provides an estimate of the upper bound (or "ceiling"). Analysis of cases from a third source, such as the collective data from neurologist practices in the area, or from the local MS society, would allow more confident determination of the upper range of prevalence. In multivariate analyses, the association between income and MS prevalence may reflect access to health care and care seeking behavior. The high prevalence of multiple sclerosis in this region suggests several intervention opportunities, including health service planning to ensure sufficient and accessible resources for MS diagnosis and care (e.g., MRI facilities, outpatient clinics), and the need to maximize early detection and use of available drug therapies to slow the progression of disease.

CHAPTER 1: INTRODUCTION

Multiple sclerosis is a devastating disease

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease affecting the central nervous system. Patients with MS can have a variety of symptoms including numbness in the extremities, burning and tingling sensations, clumsiness, fatigue, cognitive difficulties, and visual disturbance.

As the disease progresses, severe disability leads to decreased quality of life, as well as increased financial and emotional burden. A recent British study demonstrated the economic burden of MS on persons with MS. Both men and women with MS are less likely to be employed and are more likely to have a low income (Green et al., 2007). In addition to the non-medical cost caused by decreased employment and informal care cost, the mean annual health service and medication cost per MS case in U.S. was estimated at 12,879 dollars in 2004, based on a study with 13,420 MS patients from more than 80 public and private insurance plans (Prescott et al., 2007). An Australian study confirmed an association between MS induced moderate-severe disability and divorce-separation (Hammond et al., 1996). In a word, multiple sclerosis has a profound impact on patients' life and is a big economic burden.

Documented multiple sclerosis prevalence

The most recent estimate of overall MS prevalence in the United States was 85/100,000 persons; prevalence in the western U.S. was estimated at 56/100,000 for men and 139/100,000 for women (Noonan et al., 2002). A recent MS epidemiology in Olmstead County, Minnesota reported an MS prevalence of 177 cases per 100,000 in 2000 (Mayr et al., 2003). The world's highest reported prevalence was 309 cases per 100,000 people in Orkney Island, Scotland (Poskanzer et al., 1980).

Causes of multiple sclerosis and the possible link to environmental exposure

The etiology of MS is thought to be multifactorial, involving both environmental factors and genetic susceptibility (Landtblom et al., 1993). Risk factors include age older than 30 years, female gender, Caucasian race and northern/central European ancestry (Williamson & Henry, 2004). One intriguing phenomenon related to MS prevalence is its variation by latitude. The prevalence of MS was observed to be increasing with distance from the equator. A north-south gradient in prevalence has been demonstrated not only in the U.S., but also in Europe, Australia, New Zealand and Japan (Kurtzke, 1980). Epidemiological study showed that people who have migrated from two islands in the French West Indies to Metropolitan France tended to have increasing rates of MS when they returned to the French West Indies. MS prevalence and incidence were higher on one island in the archipelago with a higher return migration rate, compared with another experiencing lower rate of return migration. The standardized incidence ratio was even higher if the migration to Metropolitan France was made before 15 years of age (Cabre et al., 2005). This result strongly indicates the role of environment in MS etiology. Interestingly, people with higher socioeconomic status tend to have higher rate of MS (Kurtzke & Page, 1997; Wallin et al., 2000). Moreover, some researchers have suggested that MS etiology involves an interaction between socioeconomic and geoclimatic features (Lauer, 1994). Although theories suggesting immunological, environmental, infectious, and genetic causes have been put forward, the underlying cause of multiple sclerosis remains unknown.

Multiple sclerosis near the Hanford nuclear site

Several studies have implicated exposure to ionizing radiation as one risk factor for multiple sclerosis. For example, there are clinical cases of patients who developed demyelinating brain lesions or MS after radiation therapy (Murphy et al., 2003; Peterson et al.,

1993). Myelitis, or inflammation of the spinal cord, can occur within two to four months following high-dose radiation. Radiation is also thought to be especially injurious to patients with pre-existing demyelinating disease (Peterson et al., 1993).

The possible causal linkage between environmental radiation and subsequent multiple sclerosis is the motivation for developing accurate estimates of MS in the counties adjacent to the Hanford Nuclear Site in south-central Washington. The Hanford Nuclear Site is a former production site for nuclear weapons. It was established in 1943 as part of the Manhattan Project in World War II. The plutonium that Hanford facilities produced was used in the nuclear bomb dropped at Nagasaki, Japan. More reactors were built for research and development of peaceful nuclear energy use after the war. These reactors were shut down during the1960s through 1980s. In addition to uranium and plutonium, tritium was produced at the site for a short time as well (U.S. Department of Energy Richland Operations Office, 1997).   Presently, all Department of Energy facilities on the Hanford site have been shut down and are in various stages of decommissioning and cleanup. This massive remediation effort, including waste disposal, will continue for several decades.

Communities around Hanford express concerns about autoimmune diseases that they attribute to exposure to radiation. Multiple sclerosis is one autoimmune disease of concern. A study in the early 1980s suggested that Washington State has a high MS prevalence (Detels et al., 1982). However, there is no active population-based MS surveillance or registry that can directly answer these communities' questions on MS prevalence currently. Therefore it is important to examine the available data to determine whether the prevalence of MS in the area is high.

Defining multiple sclerosis prevalence directly from a single source is difficult

However, the direct determination of MS prevalence or incidence is difficult, due to the complex course of symptom appearance and process of diagnosis. The clinical course of MS is usually long. Eighty-five percent (85%) of multiple sclerosis cases at onset present with a relapsing and remitting course, with partial or complete remission between episodes (Bitsch and Bruck, 2002). When patients are initially evaluated, findings on magnetic resonance imaging (MRI) and patient history may not be sufficient to reach a diagnosis of multiple sclerosis. Patients usually return to their provider or neurologist multiple times due to continuing symptoms before a conclusive diagnosis is reached. Over time the cumulative clinical history, characteristic findings on MRI and results from other supportive tests point to the diagnosis MS. The median time to reach irreversible disability is eight years. Secondary progression, on average, arises after 19 years and sometimes it can be fatal (Confavreux & Vukusic, 2006).

Additionally, two sets of multiple sclerosis diagnostic criteria are used in the medical community, which makes the process of case ascertainments difficult. Prior to 2001, the Poser criteria were used to diagnose MS (Poser et al., 1983) In 2001, an international panel suggested new criteria (McDonald et al., 2001), which integrate clinical, MRI and laboratory findings. The main purpose of setting up new criteria was to facilitate MS diagnosis for the selection of cases for clinical trials (Wiendl et al., 2006; De Seze & Confavreux, 2006). With improved diagnostic criteria, the delay between symptomatic onset and diagnosis of MS has been steadily decreasing (Marrie et al., 2005). It was found that the Poser and McDonald criteria have moderate to substantial agreement (Zipoli et al., 2003), although the Poser criteria yield more combined clinically definite and laboratory supported definite MS cases than the McDonald criteria (Fangerau et al., 2004).

Gaps in the current research

Based on voluntary reports, the Inland Northwest chapter of the National Multiple Sclerosis Society has estimated high prevalence in several counties in eastern Washington. Based on these estimates, Yakima, Kittitas, Benton, Franklin and Klickitat counties have 200 self-reported cases per 100,000 people.   Prevalence estimates for the western counties of the State are reported to be lower, at 65 cases per 100,000 people (Hanford Health Information Network, 2000). Also from earlier studies, Washington State was considered to be a high MS prevalence area (Detels et al., 1982). While it is suspected that MS prevalence is high in eastern Washington, there is no MS surveillance or registry to provide an estimate.   In this study, the prevalence of multiple sclerosis was calculated using data obtained from MS treatment centers and outpatient clinics, and then it was estimated using the capture-recapture method.   This study attempts to calculate the prevalence of neurologist-diagnosed MS in the Spokane area, and reduce underestimation by using multiple data sources.

A recent MS cluster investigation in El Paso, Texas reveals that MS standardized morbidity ratios can range from 1.05 to as high as 8, depending on various comparison populations (Williamson, 2006). Thus, the choice of the reference population is critical to maximize the utility of our estimates.

Prior research by Nelson and colleagues (1986) indicates that neurology practices and treatment centers yield the highest number of cases, as opposed to MS prevalence based on self-report, which underestimates prevalence by 20%-40%. The standardized chart review conducted by trained research assistants in this study increased the consistency and reliability of case ascertainment.

Given the heavy economic and social burden brought by MS to affected families, the prior concerns about high MS prevalence in eastern Washington, and our carefully designed protocol, it is both feasible and important to examine the available data to determine the prevalence of MS in areas around Spokane, Washington.

CHAPTER 2: METHODS

Brief overview

This study examines the prevalence of multiple sclerosis between Jan 1st, 1998- Dec 31st, 2003 in twelve counties located around Spokane: Adams, Ferry, Lincoln, Pend Oreille, Spokane, Stevens, and Whitman from Washington state; and Benewah, Bonner, Boundary, Kootenai, and Latah from Idaho state. The numerator is composed of MS cases, gathered from clinic records of local neurologists and MS treatment centers. The denominator, the area's population, was derived from the 2000 Census.   SPSS 14.0 was used to set up regression models to examine the potential association of MS prevalence with socioeconomic and demographic factors, proximity to Hanford, and latitude.

Study population and area

The study population was the residents of 12 counties adjacent to Spokane, Washington. In 2000, the census estimated that the total population over 18 years old in the study area was 552,941 (U.S. Bureau of Census, 2000). The age and gender of MS cases were obtained from medical records and client rosters.

Our case definition required documentation in the chart of an MS diagnosis, confirmed by a neurologist.   Chart review of patient history, physical exam, imaging studies, and cerebrospinal fluid analysis indicates that a neurologist's diagnosis of MS is equivalent to meeting the Poser criteria, but not all of cases would meet the McDonald criteria. Because people younger than 18 years of age have different channels of medical access—usually pediatrics, MS cases younger than 18 years of age were excluded. Patients residing in other counties in Washington or Idaho, or patients from other states were excluded in this analysis.

There are only two major population centers in the study area: Spokane in Washington, and Coeur d'Alene in Idaho. The corresponding counties of these two cities are classified as metropolitan statistical areas (MSA), according to the definition of the Office of Management and Budget (OMB) in 2003.   The other 10 counties in the study area are considered "micropolitan" or "nonmetro" (U.S. Bureau of Census, 2003).
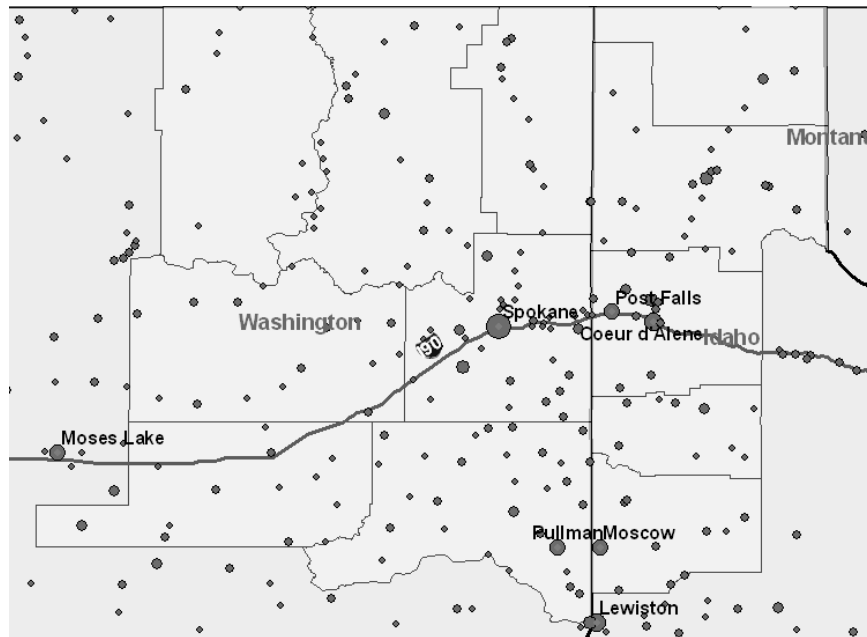
Figure 1. Location of cities with population greater than 10,000 in and near study area

(Figure 1 shows the locations of cities with population over 10,000 within the region according to census 2000. As seen in this figure, Spokane County and Kootenai County are the two counties within the region with the largest population centers.)
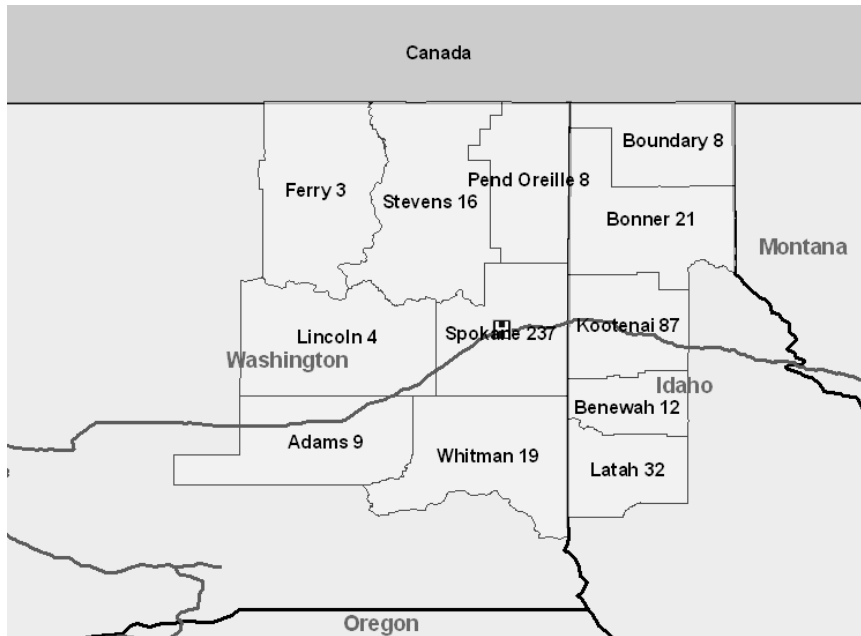
Figure 2. Population densities (people/square mile) of counties in study area

(In Figure 2, the symbol "H" signifies the location of the two major MS diagnosis and treatment centers are located in Spokane from which we obtained data about MS cases.)

Spokane County is the MSA with the highest population density in the study area, and is also the health care service hub for eastern Washington, northern Idaho and western Montana. Holy Family Hospital is the largest diagnosis and treatment center for MS in the region. Neurologists at the Rockwood Clinic also provide diagnosis and treatment for MS through a network of outpatient clinics in the Spokane metropolitan area, however, the total service population is smaller than that of Holy Family Hospital. Outside the study area, the nearest MSAs in Washington and adjacent states are Seattle-Tacoma-Bremerton WA, Yakima WA, Richland-Kennewick-Pasco WA, Bellingham WA, Portland-Salem OR, Boise ID, and Missoula

MT (U.S. Bureau of Census, 2003). Given the long distance to other cities with large medical

facilities, patients living in the study area are likely to be diagnosed and to be treated in Spokane.
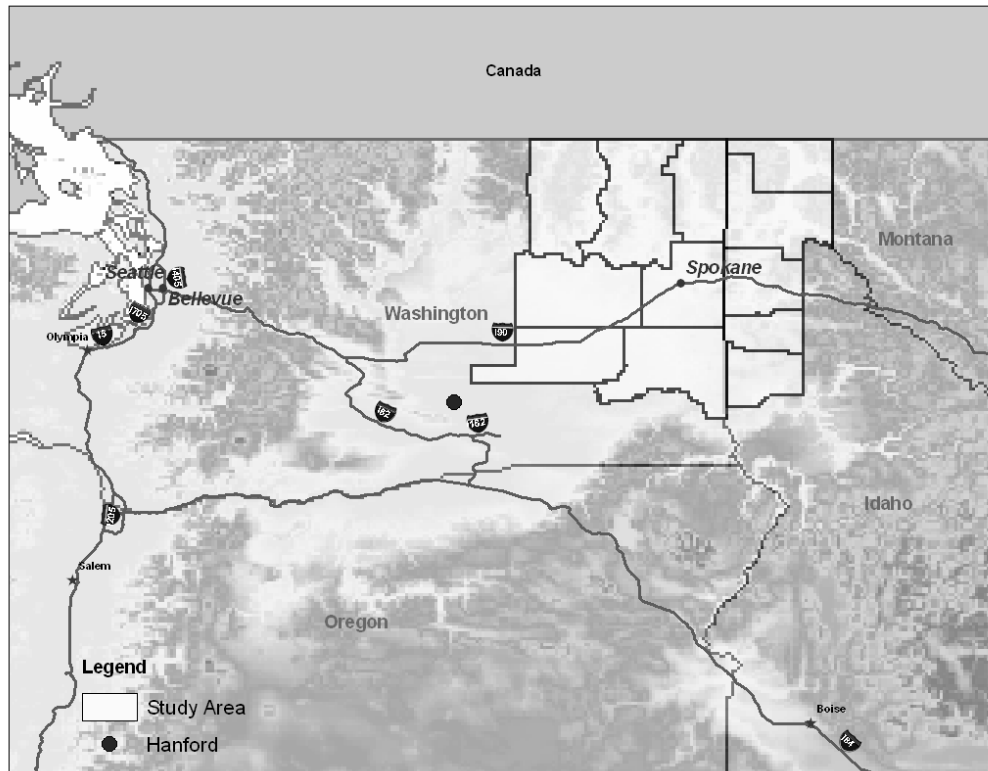
Figure 3. Geographic location of study area in relation to other major population centers in

northwest U.S.

(Figure 3 presents the spatial relationship of our study area and the Hanford site, as well as

showing the interstate highways, the Cascade Range and the Rocky Mountains.)

Data sources and human subject protections

      Data were extracted from medical charts from the Holy Family Hospital Multiple

Sclerosis Center and the Rockwood Clinic, both located in Spokane. Holy Family Hospital is a

272-bed full-service facility, providing advanced medical and surgical care. In 2005, it admitted over 9,500 people for care and provided more than 111,000 visits for outpatient services in 2005. Rockwood Clinic has been in operation for over 70 years, and provides outpatient services at a central facility and 14 satellite facilities. The Rockwood Clinic serves 120,000 patients annually and has 26 specialties, including neurology.

A time window of six years (from Jan 1st, 1998 to Dec 31st, 2003) was selected to establish the period prevalence, assuming that most cases of MS, including slowly progressing and benign cases, would seek care from neurologists at least once in this interval.

To develop lists of potential MS cases, billing records inclusive of patient visits during 1998 through 2003 were searched for the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 340 (multiple sclerosis), 341.8-341.9 (other demylinating disease), 377.3 (optic neuritis), and 323.9 (transverse myelitis). Each chart was then pulled from medical records and abstracted by research assistants trained by the project neurologist. The abstractors reviewed the history section of each chart to find documentation of a neurologist's diagnosis of MS, and to identify clinical events that would constitute attacks (e.g., optic neuritis, spinal cord syndrome, brainstem, and cortex). Objective lesions (e.g., signs of loss of visual acuity, abnormally increased reflexes and presence of Babinski's reflex) were abstracted from review of the physical exam section of the clinic notes. Finally, findings of MRI studies, analysis of cerebral spinal fluid, and visual evoked potential were reviewed.

Information collected through abstraction of clinical records was limited to the minimum amount necessary to complete the project. Name information was necessary to identify individual cases for the purpose of conducting the capture-recapture method of estimation. Name and date of birth were the only two fields of personal identifying information collected.

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Use of the capture-recapture method would not have been possible without this information, and the paper and hardcopy records with these fields were secured and access was limited only to the investigators for the purpose of matching cases from separate sources. Address information includes city and state names only, and was not used for matching.

The study protocol was reviewed and approved by the Spokane Area Institutional Review Board representing both the Holy Family Hospital and the Rockwood Clinics. Additionally, the protocol was reviewed and approved by the IRB of the Oregon Health & Science University and the Office of Science at the Centers for Disease Control and Prevention (CDC).

Capture-recapture analysis

The capture-recapture method, originally developed for use in estimating animal populations, has been applied to epidemiology in recent years. For example, Gjini et al. (2004) applied the capture-recapture method to UK Hospital Episode Statistics and the Public Health Laboratory Services, in order to improve the estimate of incidence and deaths from pneumococcal meningitis. Similarly, Schrauder et al. (2007) estimated the incidence of invasive meningococcal disease in Germany in 2003, using the capture-recapture method to analyze the data from a national lab roster and from a national surveillance system respectively.

In the original application of capture-recapture, animals are captured in traps. Captured animals are marked and then released into the population. At the subsequent trapping, some of the previously captured animals are found bearing the marks from the first catch. Using the number of animals captured in each trapping and the number of animals with marks, we can estimate the number of animals missed from all trappings. In epidemiological studies using this

technique, the marks are replaced with identifiers such as names, social security numbers, birth dates and residence addresses (Martyn, 1998).

There are four key assumptions made when conducting a traditional capture-recapture analysis: (1) the population is closed; (2) the ascertainment data lists are independent; (3) the lists are matched correctly; and (4) the capture probability of each member of the population is homogeneous. These four assumptions are rarely fully met in epidemiological studies. However, capture-recapture provides a quick and inexpensive first estimation of prevalence or incidence in the absence of comprehensive surveillance or registry information.

An estimate of population size, provided that above four assumptions are fully met, can be calculated as (International Working Group for Disease Monitoring and Forecasting, 1995):

$$N = \frac{n_1 \times n_2}{m}$$

In this study, the numbers of total estimated MS cases and their corresponding variances were calculated using an unbiased formula according to Seber et al. (Seber, 2000), which was derived from the above formula due to small numbers:

$$N = \frac{(n_1 + 1) \times (n_2 + 1)}{(m + 1)} - 1$$

$$Var\ (N) = \frac{(n_1 + 1) \times (n_2 + 1) \times (n_1 - m) \times (n_2 - m)}{(m + 1)^2 \times (m + 2)}$$

- N = Estimate of total population size

- n_1 = Total number of patients captured through the first source

- n_2 = Total number of patients captured through the second source

- m = Number of patients captured from the first source that were then recaptured through the second source

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Then the corresponding 95% confidence intervals (ci) were calculated using the following formula:

$$95\% \ ci = \ N \pm 1.96 \times \sqrt{Var(N)}$$

Names, date of birth, sex, and city were the "tags" allowing matching of cases between the lists. Two medical records were considered identical if the patients had the same last name, first name, date of birth and sex. If these fields were the same for two records, but the middle name was missing from one record or if only the middle initial was recorded and this matched the first letter of the middle name on the other record, these two records were considered to be from the same patient. If either the last name or the first name did not match in only one or two letters, but the rest of information plus city was identical, they were considered the same patient. If multiple records were found for a single patient in one of the data lists, duplicate records were deleted. When the same patient was found in the data lists from each of the two health systems, that patient was considered as a match, a "recaptured" patient.

Study variables

Medical record information included each patient's date of birth and sex. Patients' ages were calculated by subtracting their date of birth from April 1, 2000, which was Census Day. Age was rounded to the nearest integer. Confirmed MS patients were grouped into six age categories: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years or older. Resident cities were matched to counties based on U.S. Census Bureau 2000 Census information. The total number of MS cases in each county was determined by de-duplicating and adding the total number of cases obtained from the two sources mentioned above.

The total number of adults by county (the denominator) was obtained from the U.S. 2000 Census. Conveniently, the year 2000 is the mid-point of our six-year window - from 1998 through 2003.

The U.S. 2000 Census also provided information at the county level on: age by sex; number of persons age 18 years and older who reported to be white race alone; population by age; per capita income in 1999; education level among persons age 25 and older; and the latitude and longitude of approximate internal geographic center in each county. Based on this information, gender-, age-, and county-specific MS prevalence was calculated.

For the purpose of age-adjustment, the six age categories listed above were used. The U.S. total population in these six age groups was also extracted from U.S. Census Bureau 2000 Census.

Covariates

Age, sex, and Caucasian race have been implicated as MS risk factors in the medical literature (Williamson & Henry, 2004). By using age-proportion and sex-proportion as independent variables in modeling, the confounding effect of age and sex was evaluated.

Other possible predictor variables include socioeconomic status, latitude and distance of residence from Hanford. Distance to the Hanford site (d) was calculated using the Haversine method (Sinnott, 1984) as follows:

$$R = \text{earth's radius (mean radius} = 6{,}371\text{km)}$$

$$\Delta\text{lat} = \text{lat}_2 - \text{lat}_1$$

$$\Delta\text{long} = \text{long}_2 - \text{long}_1$$

$$a = \sin^2(\Delta\text{lat}/2) + \cos(\text{lat}_1).\cos(\text{lat}_2).\sin^2(\Delta\text{long}/2)$$

$$c = 2.\arcsin(\min(\sqrt{a}, \sqrt{(1-a)}))$$

$$d = R.c$$

Although the main focus of this study was not to investigate the causes of variation in the prevalence of multiple sclerosis, we considered factors known to influence disease prevalence, including socioeconomic status (SES). In this study, SES was approximated by per capita income and average education levels in each county and was assessed through simple linear regression modeling. The percentages of white individuals in the population in each county were considered independent variables in the analysis of potential risk factors. Similarly, the environmental factors of latitude and distance from Hanford were assessed by the simple linear regression.

Variability

The outcome variable - MS prevalence - may have high variability from single source. Therefore, we used two data sources to reduce the variability associated with only one data source. Given the standardized review of medical charts in this study, the variability in the case ascertainment should have been reduced as well. In addition, age-standardization using census data reduces potential confounding associated with varying age distribution.

Statistical analysis

Descriptive analysis was performed on each county's demographic factors. In gender and age groups, the number of observed MS cases from each source and the number of matched MS cases between sources were described.

Age-specific, gender-specific, and county-specific MS aggregated prevalence and associated 95% confidence intervals were calculated. The Poisson distribution was used if the

number of cases was less than 100. For the overall study area, age-adjusted prevalence was calculated. The capture-recapture method was applied to estimate total number of MS cases by age group, sex, and county. Using the estimates cases from the capture-recapture method, prevalence was calculated by age, sex, and county.

In each sex, age group and county, the sensitivity of each data list was calculated by dividing observed cases by the total estimated cases from the capture-recapture method.

Natural logarithm transformations were applied to both observed MS prevalence and estimated MS prevalence based on capture-recapture method, so that normal distribution could be approximated.

Simple linear regression models were set up assessing the associations between each county's natural log of MS prevalence and following factors: the mean per capita income; percentage of population with post-secondary education degrees; percentage of white race population; percentage of female adult population; percentage of population older than 30 years of age among total adult population; latitude; and distance from county to Hanford site. Independent variables were introduced into the multiple linear regression models if they had a p-value less than 0.25 in simple linear regression. The final model was determined through backward stepwise selection.

Associations between each county's natural log-transformed MS prevalence based on capture-recapture and the above mentioned factors were assessed using a similar approach. The final model was determined through backwards selection.

CHAPTER 3: RESULTS

Observed cases and prevalence and estimated cases and prevalence based on capture-recapture

A total of 1088 MS cases were identified through the medical records from the two multiple sclerosis diagnosis and treatment centers. Among all the cases, 912 (83.8%) were ascertained at Holy Family Hospital and 400 (36.8%) were at Rockwood Clinic, with 224 (20.6%) matched cases that were identified through both sources. The number of cases from Holy Family Hospital was 2.3 times (912/400) of that from Rockwood Clinic. More than half (56.0%) of Rockwood Clinic cases matched cases from Holy Family Hospital, while 24.6% (224/912) of Holy Family Hospital cases were also found in Rockwood Clinic records.

The number of female MS cases in the combined list from two facilities was 3.1 times the number of male cases (822/266) among all observed cases. The ratio of female cases to male cases was higher among cases identified through the Holy Family Hospital chart review (3.3), but was lower for the Rockwood Clinic list and those cases identified in both lists: 2.5 and 2.6 respectively.

Most (81.8%) of MS patients in our study were between 30 and 59 years of age. Very few patients aged 70 years and older (3.2%) were identified. The highest proportion (36.3%) of MS cases fell in the 40-49 years age group.

Based on capture-recapture methods we estimated 1626 multiple sclerosis cases in the study area, suggesting that totals based on chart reviews from two clinical sources resulted in an underestimation of 538 cases.

Based on the population of the study area, observed crude multiple sclerosis prevalence was 196.8 (95% CI: 185.1 – 208.5) cases per 100,000 adults. After age-adjustment to the 2000

US Census adult population, the observed age-adjusted MS prevalence in the study area was 197.1 (95% CI: 185.5 – 209.2) cases per 100,000 adults, very similar to the crude unadjusted prevalence estimate. Capture-recapture methods yielded a higher estimate of 294.1 (95% CI: 272.1 – 316.0) per 100,000 adults and did not overlap the confidence interval of observed prevalence.

Female MS prevalence was 291.2 per 100,000 adults, 3.0 times the observed male MS prevalence that was 98.3 per 100,000 adults. Capture-recapture yielded a higher estimate: 435.7 per 100,000 in female adults and 144.4 per 100,000 in male adults. 95% confidence intervals associated with estimated prevalence in both sex groups did not overlap the observed prevalence's confidence intervals.

The observed MS prevalence was lowest in the 70 years and older age group (52.5 per 100,000) and was highest in the 40-49 years age group (342 per 100,000). Again, the capture-recapture method estimates were higher: 94.9 per 100,000 among those 70 years and older and 529.5 per 100,000 among those 40-49 years old. In the 30-39, 40-49, and 50-59 age groups, estimated prevalence based on capture-recapture was also higher than observed prevalence, and 95% confidence intervals associated with estimated prevalence did not overlap with observed prevalence confidence intervals.

Among individual counties, observed MS prevalence ranged from 46.2 per 100,000 adults in Adams County, WA to 328.5 per 100,000 adults in Lincoln County, WA. Capture-recapture methods resulted in a slightly different distribution with a range from 64.7 cases per 100,000 adults in Adams County to 373.5 cases per 100,000 adults in Spokane County. As expected, observed prevalence and estimated prevalence based on capture-recapture are highly

correlated to each other (Pearson correlation 0.908, p<0.001). In Spokane County, the 95%

confidence interval for estimated prevalence did not overlap the interval for observed prevalence.

Overall, the Holy Family Hospital source had a higher sensitivity in MS case capture than

the Rockwood Clinic across all genders, age groups and counties. For several rural counties, the

Holy Family Hospital source demonstrated 100% of sensitivity of capture.
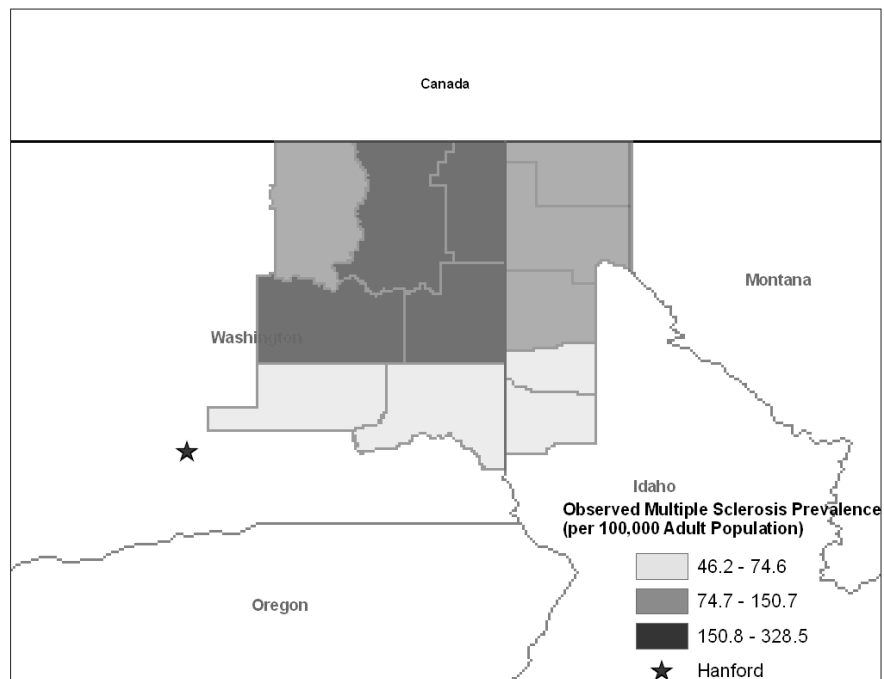
Figure 4. Observed adult multiple sclerosis prevalence, by county

(Figure 4 shows the prevalence based on the combined list of cases from two hospitals. Four out

of twelve counties in our study area had MS prevalence over 150.8 per 100,000, presented in red.)
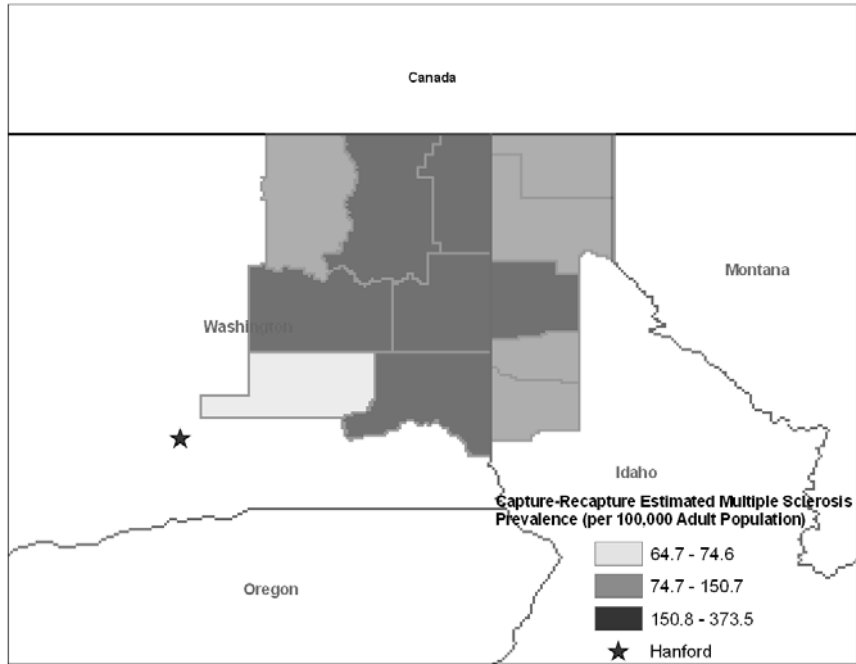
Figure 5. Estimated adult multiple sclerosis prevalence based on capture-recapture, by county

(Figure 5 displays the estimated MS prevalence from the capture-recapture method for each of the 12 counties. Note that two more counties had MS prevalence higher than 150.7 per 100,000, compared with directly observed MS prevalence (Figure 4).)

Figure 6. Plot of estimated multiple sclerosis (MS) prevalence based on capture-recapture vs.

observed MS prevalence

(Figure 6 indicates that there is a high correlation between estimated MS prevalence from

capture-recapture and observed MS prevalence. The fitted Line is:

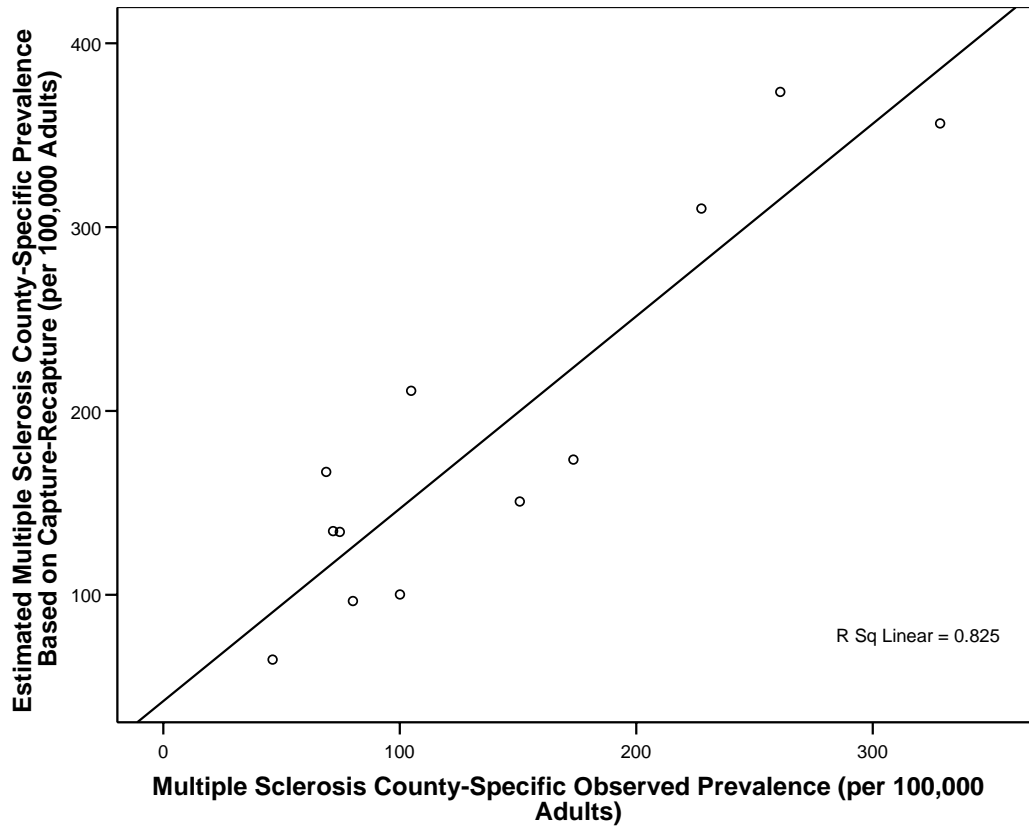*E(Estimated MS prevalence) = 42.1 + Observed MS prevalence*, $p < 0.001$ with $R^2 = 0.825$)

Table 1. Observed multiple sclerosis cases and prevalence, compared with estimated cases and prevalence based on capture-recapture

	Observed Number of Cases in Holy Family Hospital (%)	Observed Number of Cases in Rockwood Clinic (%)	Matched (%)	Observed Total Number of Cases	Capture-Recapture Estimated Number of Cases	Holy Family Hospital Sensitivity %	Rockwood Clinic Sensitivity %	Observed Prevalence (per 100,000 Adults)	95% CI for Observed Prevalence	Estimated Prevalence by Capture-Recapture (per 100,000 Adults)	95% CI for Estimated Prevalence by Capture-Recapture
Gender											
Female	698 (76.3%)	286 (71.5%)	162 (72.3%)	822	1230	56.7	23.3	291.2	271.3 - 311.1	435.7	397.5 – 474.0
Male	214 (23.4%)	114 (28.5%)	62 (27.7%)	266	391	54.7	29.2	98.3	86.5 – 110.1	144.4	124.5 – 164.4
Age Group											
18-29	54 (5.9%)	24 (6.0%)	9 (4.0%)	69	137	39.6	17.6	52.7	41.0 – 66.7	104.3	60.8 – 147.8
30-39	178 (19.5%)	77 (19.3%)	48 (21.4%)	207	284	62.7	27.1	204.7	176.8 – 232.6	280.7	240.1 – 321.3
40-49	326 (35.7%)	147 (36.8%)	78 (34.8%)	395	612	53.3	24	342	308.3 – 375.7	529.5	460.4 – 598.6
50-59	249 (27.3%)	103 (25.8%)	64 (28.6%)	288	399	62.4	25.8	335.8	297.0 – 374.6	465.2	406.0 – 524.5
60-69	81 (8.9%)	32 (8.0%)	19 (8.5%)	94	134	60.3	23.8	177.6	143.5 – 217.3	253.8	194.1 – 313.4
70 and over	24 (2.6%)	17 (4.3%)	6 (2.7%)	35	63	37.9	26.9	52.5	36.6 – 73.0	94.9	50.6 – 139.2
County											
Adams	3 (0.3%)	3 (0.8%)	1 (0.4%)	5	7	42.9	42.9	46.2	15.0 – 107.8	64.7	22.9 – 106.6
Benewah	4 (0.4%)	1 (0.3%)	0 (0.0%)	5	9	44.4	11.1	74.6	24.2 – 174.1	134.2	3.5 – 264.9
Bonner	21(2.3%)	4 (1.0%)	3 (1.3%)	22	27	79.2	15.1	80.2	50.3 – 121.4	96.6	61.1 – 132.1
Boundary	7 (0.8%)	1 (0.3%)	1 (0.4%)	7	7	100	14.3	100.1	40.2 – 206.2	100.1	100.1 – 100.1
Ferry	8 (0.9%)	1 (0.3%)	1 (0.4%)	8	8	100	12.5	150.7	65.1 – 296.9	150.7	150.7 – 150.7
Kootenai	71(7.8%)	20 (5.0%)	8 (3.6%)	83	167	42.5	12	104.8	83.5 – 129.9	210.9	117.9 – 303.9
Latah	13 (1.4%)	10 (2.5%)	3 (1.3%)	20	38	34.7	26.7	71.8	43.9 – 110.9	134.6	52.9 – 216.3
Lincoln	24 (2.6%)	8 (2.0%)	7 (3.1%)	25	27	88.5	29.5	328.5	212.6 – 484.9	356.4	290.1 – 422.8
Pend Oreille	15 (1.6%)	1 (0.3%)	1 (0.4%)	15	15	100	6.7	173.4	97.1 – 286.0	173.5	173.5 –173.5
Spokane	667 (73.1%)	336 (84.0%)	193 (86.2%)	810	1159	57.5	29	260.9	242.9 – 278.9	373.5	344.7 – 402.3
Stevens	63 (6.9%)	6 (1.5%)	4 (1.8%)	65	89	71.1	6.8	227.5	175.6 – 290.0	310.1	181.3 – 438.9
Whitman	16 (1.8%)	9 (2.3%)	2 (0.9%)	23	56	28.7	16.2	68.9	43.7 – 103.4	166.8	40.5 – 293.1
Total	912 (100%)	400 (100%)	224 (100%)	1088	1626	56.1	24.6	196.8	185.1 – 208.5	294.1	272.1 – 316.0

Association between observed multiple sclerosis prevalence and demographic factors

Using 2000 Census data, the average percentage of female adults in the study area population was 50.1% (SD=1.1%, n=12). In Latah, ID, the proportion of females in the adult population was only 48.1%. Spokane County had the highest (51.7%) female adult proportion.

The mean annual per capita income in the study area was $16,242 (SD=$1,686, n=12), with a range from $13,534 to $19,233.

Great disparity in education levels was observed among individual counties. 27.8% (SD=11.5%, n=12) of those age 25 years or older in the study area had an associate or higher level college degree. In Whitman and Latah Counties approximately half of the population over 25 years of age had earned higher education degrees, whereas Adams and Benewah Counties had only 18% of population over 25 years of age earning higher education degrees.

Racial makeup also varied between counties. 97% of Bonner County adults were white race alone. In Adams County, only 69.7% of adult population was white race alone. In the 12-county study area, a mean of 90.5% of the adult population was white race alone (SD=8.3%).

The average latitude of the study area was calculated using county centroids and is N 47.78, with relatively small variation (SD=0.695). Among the 12 counties, Adams is most closely located to the Hanford site (83.7 km), and Boundary County is located furthest away (344.2 km).

Table 2. Observed MS prevalence, estimated prevalence based on capture-recapture and demographic characteristics, by county

County	Ln(Estimated MS Prevalence by Capture-Recapture) (Ln(Cases per 100,000))	Ln (MS Prevalence) (Ln(Cases per 100,000))	Proportion of Female in Population	Mean Per Capita Income (Annual, Thousand Dollars)	Proportion of Population with Higher Education Degree	Proportion of Caucasian in Population	Proportion of Persons Aged 30 or Older in Population	Latitude (° North)	Distance to Hanford Site (KM, Based on Centroid Distance)
Adams	4.17	3.83	0.49	13.53	0.18	0.70	0.75	46.97	83.66
Benewah	4.90	4.31	0.50	15.29	0.18	0.91	0.84	47.24	236.91
Bonner	4.57	4.38	0.50	17.26	0.24	0.97	0.85	48.32	293.70
Boundary	4.61	4.61	0.50	14.64	0.19	0.96	0.83	48.76	344.17
Ferry	5.02	5.02	0.49	15.02	0.21	0.79	0.84	48.50	231.15
Kootenai	5.35	4.65	0.51	18.43	0.27	0.96	0.80	47.70	248.71
Latah	4.90	4.27	0.48	16.69	0.48	0.94	0.59	46.79	214.57
Lincoln	5.88	5.79	0.51	17.89	0.27	0.96	0.88	47.61	149.29
Pend Oreille	5.16	5.16	0.50	15.73	0.20	0.95	0.88	48.45	273.32
Spokane	5.92	5.56	0.52	19.23	0.35	0.92	0.77	47.67	208.51
Stevens	5.74	5.43	0.51	15.90	0.24	0.92	0.85	48.40	244.09
Whitman	5.12	4.23	0.50	15.30	0.52	0.88	0.51	46.92	172.68

Higher education was not associated with MS prevalence at the county level (p=0.73); nor was the distance between county of residence and Hanford (p=0.719).

We attempted to construct a multivariate linear regression model with the following candidate independent variables: percentage of females among the total adult population, percentage of population of white race alone, percentage of persons age 30 or older in the total adult population, mean annual per capita income, and latitude at county centroid. There was a moderate correlation between white race percentage and per capita income (Pearson correlation 0.642, p=0.024), although white population percentage did not reach the significance level of p=0.1 and was therefore excluded from the final model. Moderate correlation between female adult proportion and per capita income was also observed (Pearson correlation 0.653, p=0.021). No interactions were found among these independent variables, except for the one between latitude and percentage of females in the population (p=0.013). However, when main effects of latitude and percent female adult population both were in the model together with the interaction term, neither main effect was significant (p>0.1).

Taking the above results into consideration, the final best model ($R^2 = 0.521$) was:

E (Ln(MS prevalence))= -18.381 + 0.201*income + 0.416*latitude

The first model indicated that, holding latitude constant, every 1000 dollar increase in mean per capita income was associated with 0.201 unit increase in Ln (MS prevalence), i.e., 1.2 cases per 100,000 increases in MS prevalence. Holding per capita income constant, every one degree increase in latitude was associated with 0.416 unit increase in Ln (MS prevalence), i.e. 1.5 cases per 100,000 increases in MS prevalence.

Table 3. Results from simple linear regression analysis with natural log of observed MS prevalence in each county as dependent variable

			95% Confidence Interval	
Factors	Coefficient	Significance	Lower Bound	Upper Bound
Proportion of Females in Population	34.474	0.034	3.150	65.799
Mean Per Capita Income (Annual, Thousand Dollars)	0.198	0.066	-0.016	0.413
Proportion of Population with Higher Education Degree	-0.594	0.730	-4.330	3.141
Proportion of Caucasians in Population	2.875	0.210	-1.908	7.657
Proportion of Persons Aged 30 or Older in Population	2.630	0.097	-0.568	5.827
Latitude (° North)	0.410	0.127	-0.140	0.960
Distance to Hanford Site (KM, Based on Centroid Distance)	0.001	0.719	-0.005	0.007

Association between estimated multiple sclerosis prevalence based on capture-recapture and demographic factors

Higher education was not associated with estimated MS prevalence at the county level (p=0.445). Neither the distance to Hanford (p=0.898), nor latitude (p=0.764) was associated with estimated prevalence.

A multiple linear regression model was constructed using the following candidate independent variables: percent of females among total adult population, per capita income and percent of population of white race alone. There was no correlation between white race percentage and the percentage of female adults among total population (p>0.1). No interactions were found between these independent variables.

Taking the above results into consideration, the final best model ($R^2 = 0.486$) was:

E(Ln(Capture-Recapture Estimated MS prevalence))= 1.475 + 0.224*income

Every 1000 dollars increase in per capita annual income was associated with a 0.224 unit increase in Ln(Capture-Recapture Estimated MS prevalence) i.e. a 1.3 case per 100,000 increase in MS prevalence.

Table 4. Results from simple linear regression analysis with natural log of estimated MS prevalence based on capture-recapture in each county as dependent variable

Factors	Coefficient	Significance	95% Confidence Interval	
			Lower Bound	Upper Bound
Proportion of Females in Population	31.696	0.026	4.716	58.676
Mean Per Capita Income (Annual, Thousand Dollars)	0.224	0.012	0.062	0.386
Proportion of Population with Higher Education Degree	1.149	0.445	-2.072	4.370
Proportion of Caucasians in Population	2.925	0.143	-1.174	7.025
Proportion of Persons Aged 30 or Older in Population	0.696	0.641	-2.532	3.925
Latitude (^{o} North)	0.076	0.764	-0.471	0.622
Distance to Hanford Site (KM, Based on Centroid Distance)	0.000	0.898	-0.006	0.005

CHAPTER 4: DISCUSSION

Main findings

This study confirmed a high prevalence of multiple sclerosis in the study area. Both the observed overall crude prevalence (196.8 cases per 100,000) and the age-adjusted observed prevalence (197.1 cases per 100,000) were close to the estimate of 200 cases per 100,000 reported by the Inland Northwest Chapter of the National Multiple Sclerosis Society for several counties in their service area. In this aspect, our findings confirmed the high prevalence indicated in the self-reported data held by this service organization. However, our capture-recapture method estimate at 294.1 per 100,000 suggests that actual prevalence in the overall area is still higher.

In agreement with previously published studies (Maytr et al., 2003; Noonan et al., 2002; Neuberger et al., 2004), we observed an increasing prevalence with age. As expected, we observed higher prevalence in age groups older than 30 years than in age groups younger than 30 years, and no substantial increase in prevalence as age increased beyond 60 years.

While we expected the prevalence of MS among females to be greater than among males, our ratios are higher than those reported in previous studies. In the larger Spokane area, the prevalence ratio of females-to-males was approximately 3, exceeding the ratios of 2.15: 1 reported for Olmstead County (Maytr et al., 2003). However, female-to-male prevalence ratios higher than 2:1, a figure cited in previously research (Kurtzke & Page, 1997; Maytr et al., 2003), have been reported in several recent studies (Noonan et al., 2002; Neuberger et al., 2004), so our observed female-to-male ratio was consistent with these recent studies.

Correlation analysis indicated that multiple sclerosis prevalence in counties was significantly associated with the counties' mean per capita income in multiple linear regression

models and associated with the proportion of female adult population in simple linear regression models. This result reflected the high women-to-men prevalence ratio and female gender being a risk factor. It could also be an indication that women with MS used health services more than men with MS, a phenomenon observed by other researchers (Travassos et al., 2002). In addition, the association between MS prevalence and income could be the manifestation of the high-income groups' more frequent health service utilization (Baghdadi, 2005; Howard et al., 1996).

Previously established risk factors such as white race, age over 30 (Williamson & Henry, 2004; Kurtzke, 1980; Kurtzke & Page, 1997; Wallin et al., 2000) or exposure to ionizing radiation as represented by distance to the Hanford site in this study, were not correlated to MS prevalence at the county level. White race was expected to be significantly associated with total MS prevalence, but the percentage of white race did not vary sufficiently among counties in the study area to detect a significant change. A south-to-north gradient in MS prevalence was examined, but only a marginally significant association was demonstrated in multiple linear regression using natural log transformed observed MS prevalence as dependent variable. This was not surprising given the very limited range of latitude in the study area.

Comparison to other studies

Our observed MS prevalence had similarities to what has been reported in other studies in United States.

In the Olmstead County study, the MS prevalence (age- and sex- adjusted to the 2000 US white population on December 1, 2000) was 191.2 per 100,000 (Maytr et al., 2003). In addition, the Olmstead study reported female MS prevalence as 239.1 per 100,000, which was lower than our observed female prevalence of 291.2 per 100,000. MS prevalence among males in the

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Olmstead study (111.2 per 100,000) was, on the other hand, higher than our observed male prevalence of 98.3 per 100,000. It is worth noting that the highest MS prevalence observed in Olmstead study was among the 45-54 and 55-64 year age groups (460.0 per 100,000 and 419.9 per 100,000, respectively), and in our study the highest prevalence was found in similar age groups of 40-49 and 50-59 years (342.0 per 100,000 and 335.8 per 100,000). Although our observed prevalence in these two age groups was lower than that in the Olmstead study, our estimated prevalence based on the capture-recapture method (529.5 per 100,000 and 465.2 per 100,000 respectively) was closer to those in the Olmstead study.

Former studies report that about twice as many women are affected as men (Kurtzke & Page, 1997; Maytr et al., 2003), although another study based on the National Health Interview Survey (NHIS) reported a ratio of women to men of 2.6:1 and the ratio was higher (3.6:1) for some specific age groups (Noonan et al., 2002). Our study revealed a higher ratio of female-to-male cases than previous reports: 3.1:1 (822 female cases over 266 male cases). Based on capture-recapture analysis, the estimated ratio of women to men among MS cases was also 3.1:1 (1230 estimated female cases over 391 estimated male cases). The MS prevalence study using NHIS data yielded prevalence estimates (139 per 100,000 for women, 56 per 100,000 for men) for the western United States that were lower than our observed prevalence in northeastern Washington and northern Idaho. However, NHIS is a survey based on a probability sample and the estimate covers a larger geographic area with a substantial range in latitude. The different study design made it impossible to directly compare our observed prevalence to the NHIS estimates.

In another multiple sclerosis prevalence study with environmental hazard concerns (Neuberger et al., 2004), lower MS prevalence was observed in a residential area near an oil

refinery plant in Independence and Sugar Creek, MO (39° N latitude). In the Missouri study, the

combined MS definite, probable and presumed prevalence among women was 177 per 100,000

and among men was 48 per 100,000. The male prevalence reported in the Missouri study was

half of that in our study area. The female-to-male prevalence ratio in their study (3.6:1) was also

higher than the ratio in our study area. The investigators report lower age-specific prevalence in

most age groups, except that the MS prevalence estimates in the 50-to-59 years and 70 or older

age groups, were very close to ours. Our capture-recapture estimated prevalence was higher than

the prevalence reported for Missouri.

Table 5. Comparison of our findings to similar MS prevalence studies

	Maytr et al., 2003	Noonan et al., 2002	Neuberger et al., 2004	Our study observation
Study Time and Areas	December, 2000 Olmstead County, MN	1989 to 1994 Overall U.S.	1998-2001 Sugar Creek and Independence, MO	1998-2003 12 Counties around Spokane, WA
Prevalence (cases per 100,000)				
Total	191.2 (165.6-216.8) (age- and sex-adjusted to the 2000 US white population)	85	113 (93-136) (age-adjusted to 2000 US population)	197.1 (185.5-209.2) (age-adjusted to the 2000 US adult population)
Gender				
Male	111.2	48	48	98.3
Female	239.1	123	177	291.2
Prevalence Ratio (Female: Male)	2.15	2.56	3.68	2.96
Age Group (years)				
18-29	24.8 (15 -24 years)	15 (<30 years)	23 (<30 years)	52.7
30-39	84.1 (25-34 years)	102	110	204.7
40-49	202.3 (35 – 44 years)	209	231	342
50-59	460.0 (45 – 54 years)	182	334	335.8
60-69	419.9 (55- 64 years)	148	127	177.6
70 and over	277.2 (65 and over)	76	52	52.5

Limitations

This study was intended to be descriptive by design. It achieved the objective of providing the community an estimate of MS prevalence in the Spokane region, based on confirmed MS cases.

The cross-sectional study design is not able to establish a cause-effect relationship between any specific factor and multiple sclerosis. However, our correlation analysis provides an initial investigation of whether potential radiation exposure related to Hanford, as represented by distance, is associated with differences in MS prevalence. We did investigate the statistical associations of group-level descriptors of demographic factors that have been associated with prevalence of other diseases. More importantly, some of the demographic factors that we considered in our study have been demonstrated to be risk factors for MS in prior studies (Williamson & Henry, 2004; Kurtzke, 1980; Kurtzke & Page, 1997; Wallin et al., 2000).

Our study has several limitations. First, we cannot link putative exposures to multiple sclerosis at the individual level. Consideration of socioeconomic factors could only be performed at the population level. Adjustment for potential confounders other than age and sex at individual level was not possible. Therefore, we cannot use this study's data to test the hypothesis that a white person with higher income and education is actually at higher risk of MS.

Second, we lack control of other potential confounding factors. Although we did not find associations between MS and any demographic factors other than female gender, it remains possible that actual associations, such as distance to Hanford, are masked by confounding factors that we did not adjust for. We observed an association between the percentage of women and total MS prevalence by county, but could not assess whether female gender was associated with health care seeking behavior, or with the susceptibility to certain agents that might cause

multiple sclerosis. This is important, since both higher levels of health care seeking behavior and higher susceptibility to putative causative agents could manifest as a higher MS prevalence. In our study, prior exposure history to environmental factors among study subjects was unknown. Family history of MS was not evaluated either, although this is expected to have a much smaller contribution to cause.

Third, the exposure levels in this study were averaged among the population. Residence history is not known for individuals and we used county centroids to assign distance from the site as a proxy measurement for exposure to hazards from Hanford. For example, it is reasonable to expect cases to move to Spokane to be closer to needed health services. Some residents may work at or near Hanford but live some distance away from Hanford; therefore distance of residence from Hanford might not always accurately represent the exposure to ionizing radiation. The possible use of P.O. boxes in city locations as addresses may reduce precision in residence distance measurement, but this error should be minimal given that most people rent P.O. boxes in the area where they live. Race/ethnicity for each individual was not available, and white race was only assessed at the population level.

A major strength of our study is that selection and information bias was kept minimal in our study. Instead of relying on patients' self-report, our case ascertainment was based on neurologist diagnosis in the largest MS diagnosis and treatment facility in the region, and a large outpatient clinic system providing neurology services.

It is possible that some assumptions of capture-recapture method were violated. The closed population requirement is rarely satisfied in human epidemiologic research. People migrate both in and out of study areas. If MS patients only moved out of this area and did not move in, the probability of being recaptured would have decreased and overestimation would

have occurred. It is also possible that migration of subjects into and out of the study area occurs, in addition to change of residence location within the study area. The sensitivities of the two case ascertainment sources were different, with Holy Family Hospital having higher sensitivity than Rockwood Clinic in all the sex, age and county categories. Within either one of the sources, the sensitivity varied across all the subgroups as well, which indicated that the population was not homogeneous in catchability according to age and county. Patients in older age groups and rural counties had higher probability of being captured, suggesting that these two health systems (and especially Holy Family Hospital) are more sensitive in the identification of MS patients with these characteristics. However, the sum of the estimated number of MS cases of subgroups in stratified analysis was very close to the overall estimate, which showed that the bias introduced by variable catchabilities according to age and county was small. In addition, if the neurologists in one health system tended to refer their patients to the other, the recapture probability would have increased and underestimation of total cases was likely to occur. Because the positive dependence between two data sources resulting from patient referrals cannot be ruled out, our capture-recapture estimated prevalence was likely to be conservative.

Implications

Given the high prevalence of multiple sclerosis in our study area, and the significantly reduced quality of life brought by MS, it is important to consider improving MS-related health services.

First, the elevated prevalence of multiple sclerosis in this region has implications for the diagnosis of MS in patients presenting with early symptoms. MS is a clinical diagnosis and by

definition, is made as the result of evidence of lesions involving different nerves occurring at different times. In the Spokane Area, the presenting symptoms and signs (e.g., optic neuritis or weakness) should elevate the clinician's index of suspicion, and MS should be considered in the differential diagnosis. Given the benefits of early treatment with the so-called "ABC" and other drug therapies, recognition of MS may reduce unnecessary progression and loss of function.

Improving the medical care delivery for MS should also be considered. Vickrey et al. (1999) explored some issues associated with MS health care: compared with general neurologists, the MS specialists tended to be better advising patients of new treatments and using new therapies for management of side effects; MS specialists involved patients in research studies more than general neurologists; MS patients also had better perceptions of their communication with MS specialists than with general neurologists; patients in general felt a great need for informational support on issues including symptoms, depression, emotional problems, medication-related side effects, exercise, insurance, transportation, employment, and nutrition.

Accordingly, in our study area new neurologists and medical residents should be encouraged to become MS specialists, so that the MS diagnosis and treatment capacity in the area can be enhanced to meet the high demand from the large number of MS patients in the region. To improve MS care quality, current general neurologists need to be given appropriate education on the most up-to-date MS treatments and management. In order to reduce patient uncertainties and anxieties when facing the various symptoms, all MS care providers in this area should give patients more information on the clinical course of MS, available treatments, appropriate supporting health services and prevention of complications.

In addition, safe environments for MS patients and others with disabilities also should be ensured in the Spokane area. Transportation options should be evaluated to ensure MS patients have mobility and assess to care.

Lastly, we observed that the prevalence of MS was associated with mean per capita income, indicating that some MS cases from lower income groups may not be diagnosed, or may have less ability to obtain treatment. The role of public health as a provider of direct services is presently in the midst of change, and still there is no system to ensure universal coverage. Public health and private sector components of the medical care delivery system in the Spokane area should be made aware of this apparent gap in MS diagnosis and care for lower income groups. Adjustments to services for persons receiving Medicaid and Medicare may reduce this disparity.

Future research

Future research could include more data sources and data from a larger geographic area to assess the spatial relationship between MS and the proximity to Hanford site. Since the prevailing winds in the Hanford area are from the northwest and southwest (U.S. Department of Energy Richland Operations Office, 2004), conducting a similar analysis using chart review data from the Yakima Valley, Richland tri-city area and Walla Walla could be useful in evaluating the hypothesis that MS prevalence is related to the distance from the Hanford site across the whole eastern Washington region. Expanding this study and including other counties in eastern Washington would increase sample sizes as well as quantify the dependence between multiple data sources, both of which would make our capture-recapture estimation more robust.

In order to investigate the causal relationship between ionizing radiation and multiple sclerosis, we could conduct a large matched case-control study. Both cases and controls would

come from relatively stable residence locations but varying distances to the Hanford site. Cases and controls would be frequency matched for age and sex. Because a variety of viral infections including Epstein-Barr and human herpes virus 6 (Murray, 2002), and measles-mumps-rubella vaccine (Atkins et al., 2000) have been implicated to be possible causes of MS, it would be ideal to collect information on infection and immunization history. Interviews would be conducted to obtain detailed histories of exposure to ionizing radiation from diagnostic and therapeutic procedures and from employment at nuclear weapons manufacture or nuclear power plants. Other potential opportunities for occupational exposure to ionizing radiation include employment as commercial airline pilots and flight attendants, medical personnel involved in X-ray operations, and employment in plants with nuclear reactors. Odds ratios for the main effect of residence distance to the Hanford site and latitude would be calculated and assessed to determine whether there is an association with multiple sclerosis. If multiple factors such as age, sex and infection history are shown to be related to MS, then stratified analysis on ionizing radiation exposure could be conducted in each age, sex and infection/vaccination category.

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APPENDICES

Table A1. Poser criteria of diagnosing multiple sclerosis (Poser et al., 1983)

- Clinically definite MS
    - 2 attacks and clinical evidence of 2 separate lesions
    - 2 attacks, clinical evidence of one and paraclinical evidence of another separate lesion

- Laboratory supported definite MS
    - 2 attacks, either clinical or paraclinical evidence of 1 lesion, and CSF immunological abnormalities
    - 1 attack, clinical evidence of 2 separate lesions & CSF abnormalities
    - 1 attack, clinical evidence of 1 and paraclinical evidence of another separate lesion, and CSF abnormalities

- Clinically probable MS
    - 2 attacks and clinical evidence of 1 lesion
    - 1 attack and clinical evidence of 2 separate lesions
    - 1 attack, clinical evidence of 1 lesion, and paraclinical evidence of another separate lesion

- Laboratory supported probable MS
    - 2 attacks and CSF abnormalities

Table A2. McDonald criteria of diagnosing multiple sclerosis (McDonald et al., 2001)

Clinical Presentation	Additional Data Needed
• 2 or more attacks (relapses) • 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
• 2 or more attacks • 1 objective clinical lesion	Dissemination in space, demonstrated by: • MRI • or a positive CSF and 2 or more MRI lesions consistent with MS • or further clinical attack involving different site
• 1 attack • 2 or more objective clinical lesions	Dissemination in time, demonstrated by: • MRI or second clinical attack
• 1 attack • 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by MRI or positive CSF and 2 or more MRI lesions consistent with MS *and* Dissemination in time demonstrated by MRI or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	Positive CSF *and* Dissemination in space demonstrated by: • MRI evidence of 9 or more T2 brain lesions • or 2 or more spinal cord lesions • or 4-8 brain lesions and 1 spinal cord lesion • or positive VEP with 4-8 MRI lesions • or positive VEP with <4 brain lesions plus 1 spinal cord lesion *and* Dissemination in time demonstrated by: • MRI or continued progression for 1 year

Figure A1. Clinical subgroups of multiple sclerosis (Bitsch & Bruck, 2002)

An upward direction over time indicates progression of disability.

PPMS =primary progressive MS; **PRMS** = progressive relapsing MS; **RPMS**= relapsing progressive MS; **RRMS** = relapsing-remitting MS; **SPMS** = secondary progressive MS; **TPMS** = transitional progressive MS.
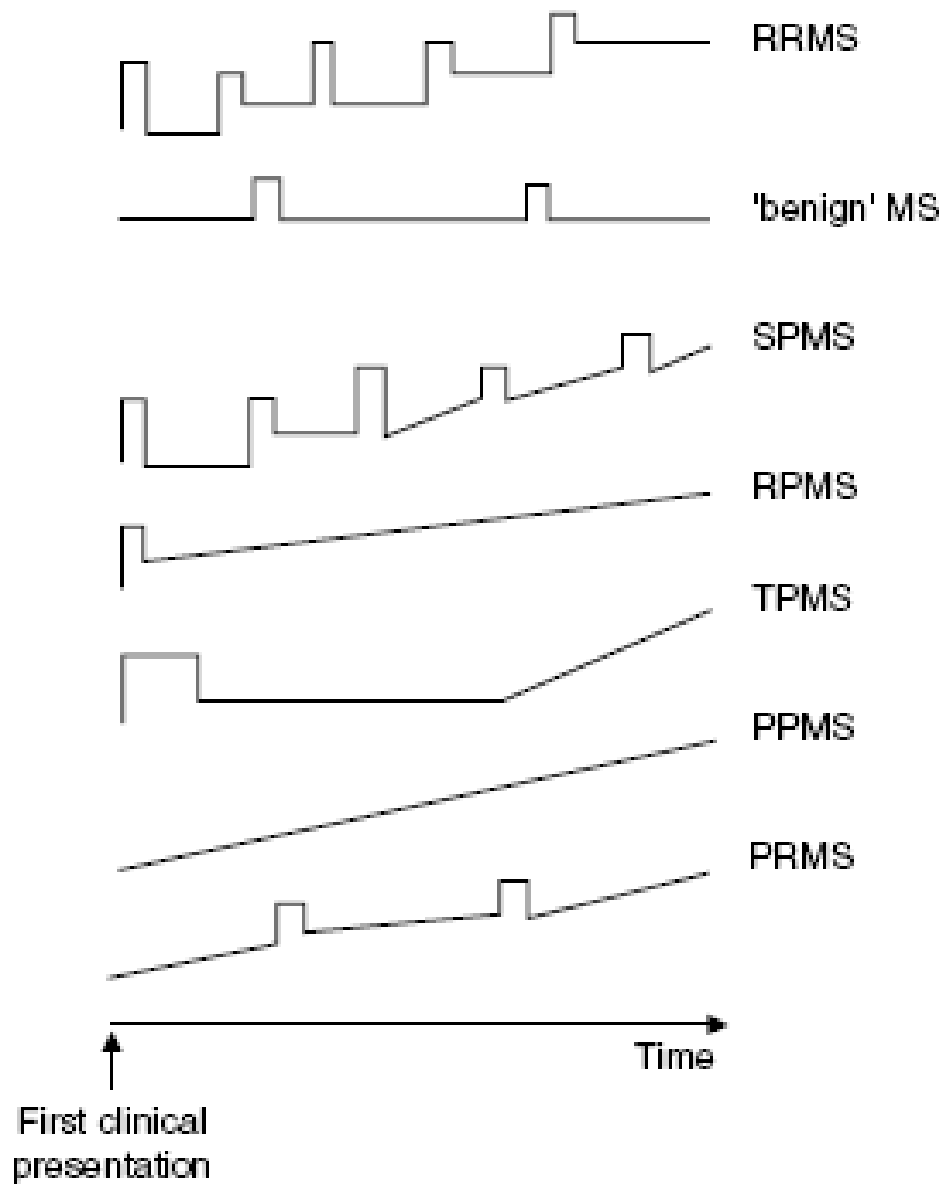
Figure A2. Scatter plot of dependent variable natural log of MS prevalence vs. proportion of

females in population as the independent variable
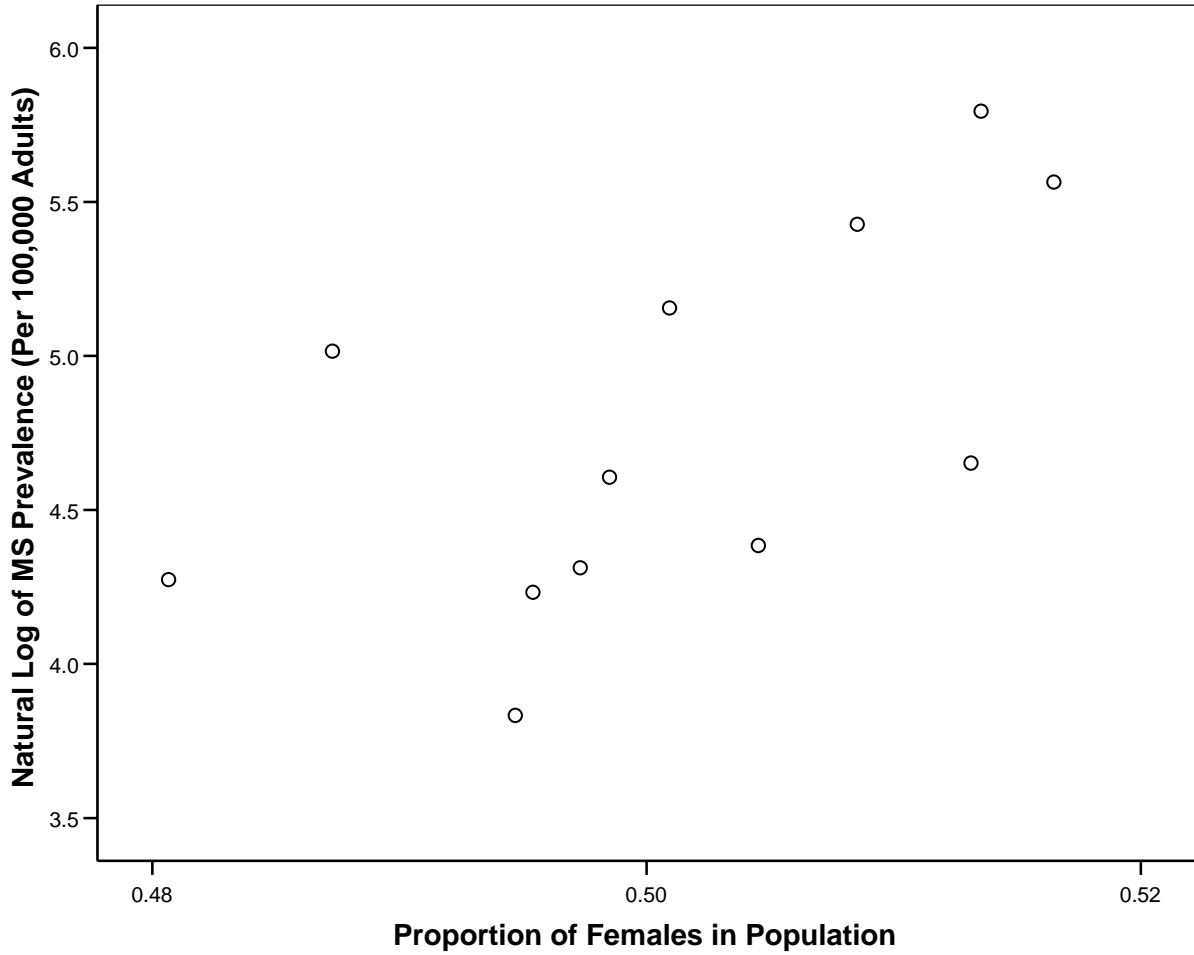
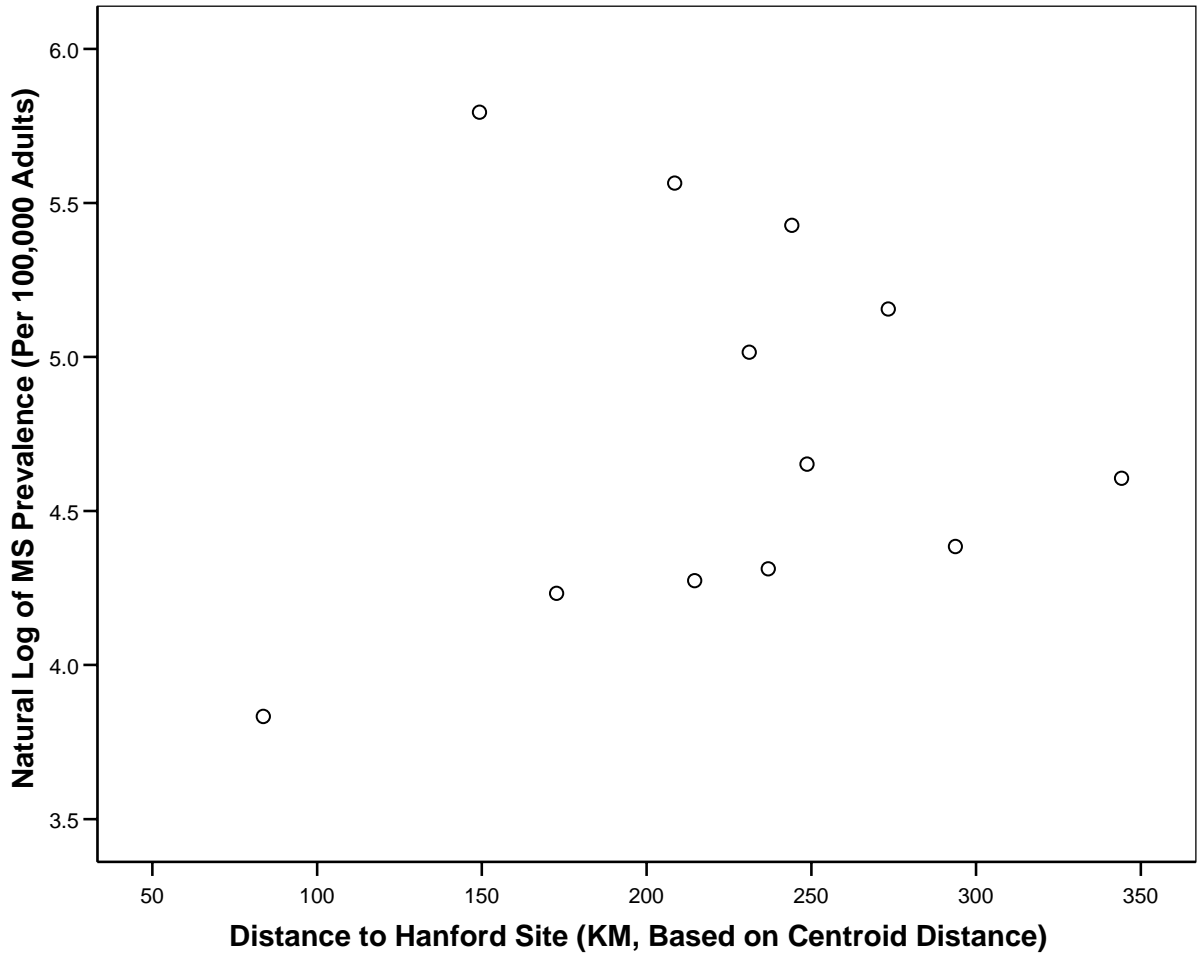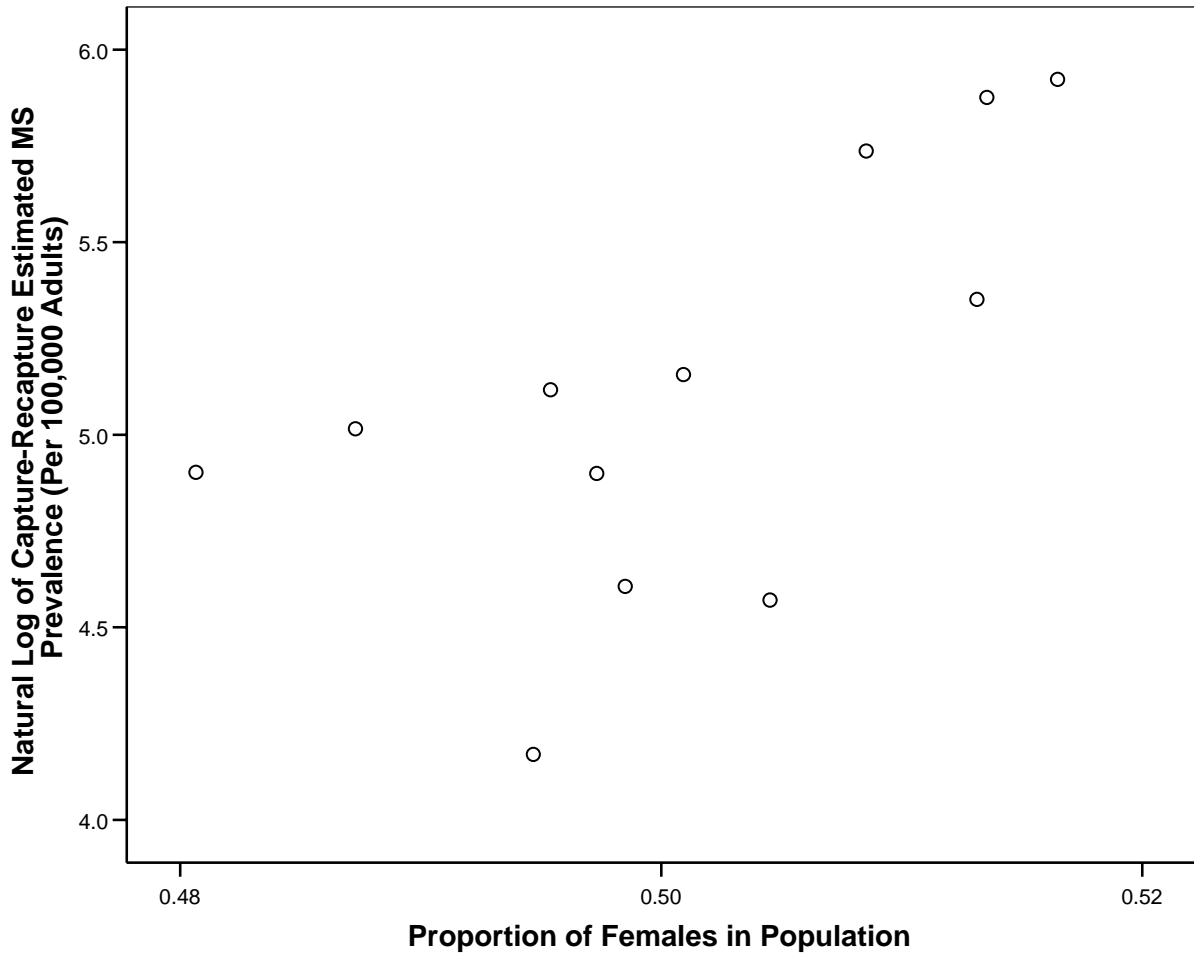Figure A3. Scatter plot of dependent variable natural log of MS prevalence vs. independent variable mean per capita income
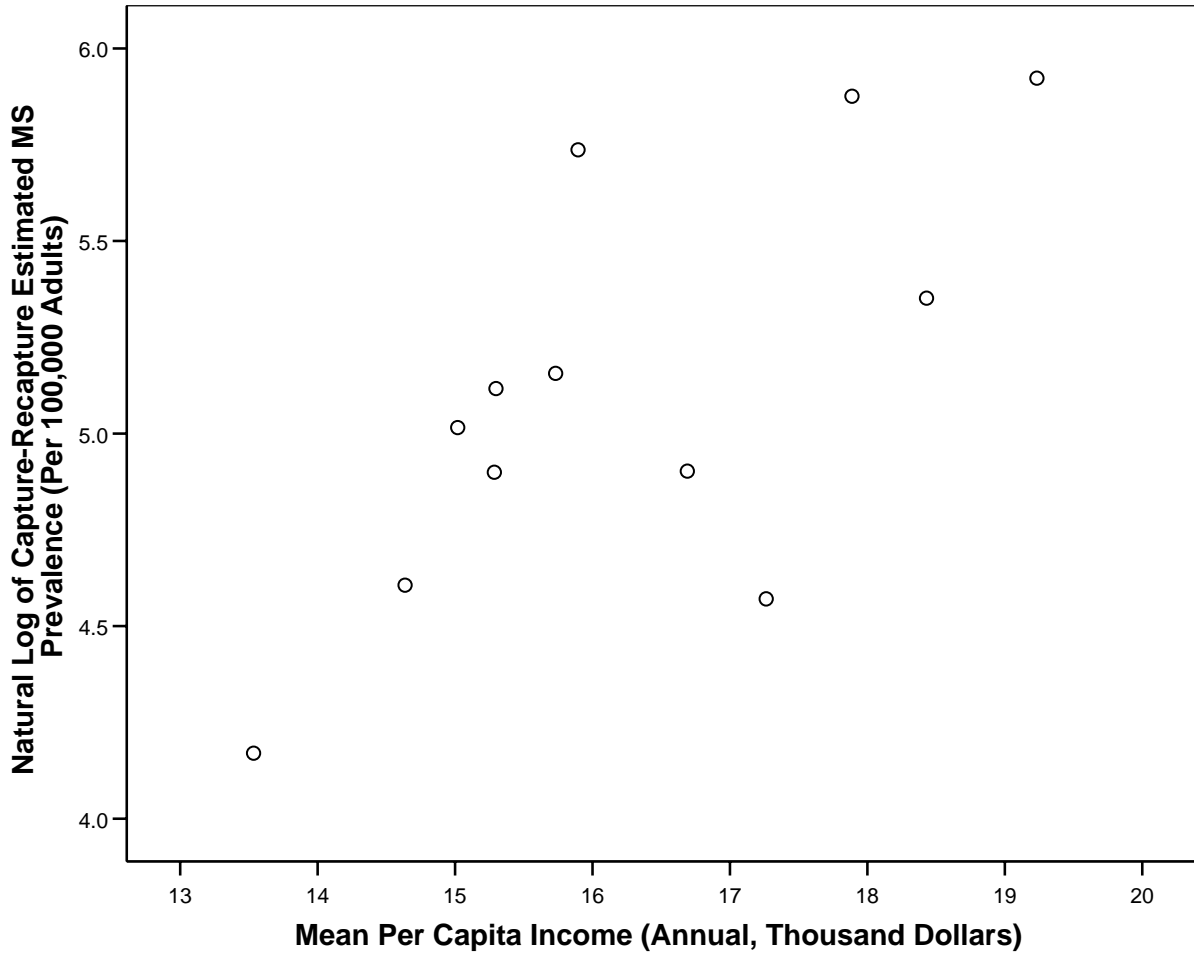

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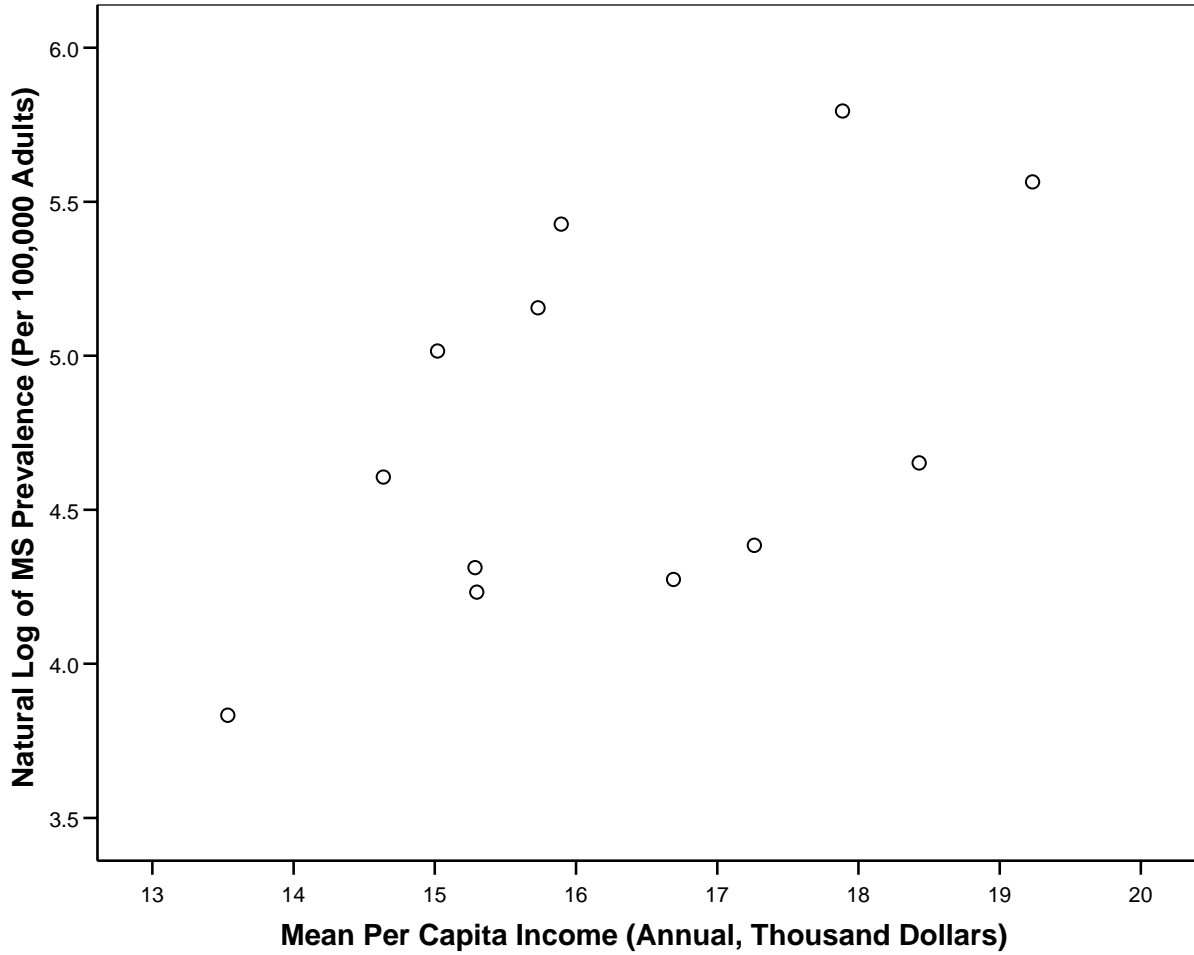
Figure A4. Scatter plot of dependent variable natural log of MS prevalence vs. independent
variable proportion of population with higher education degree
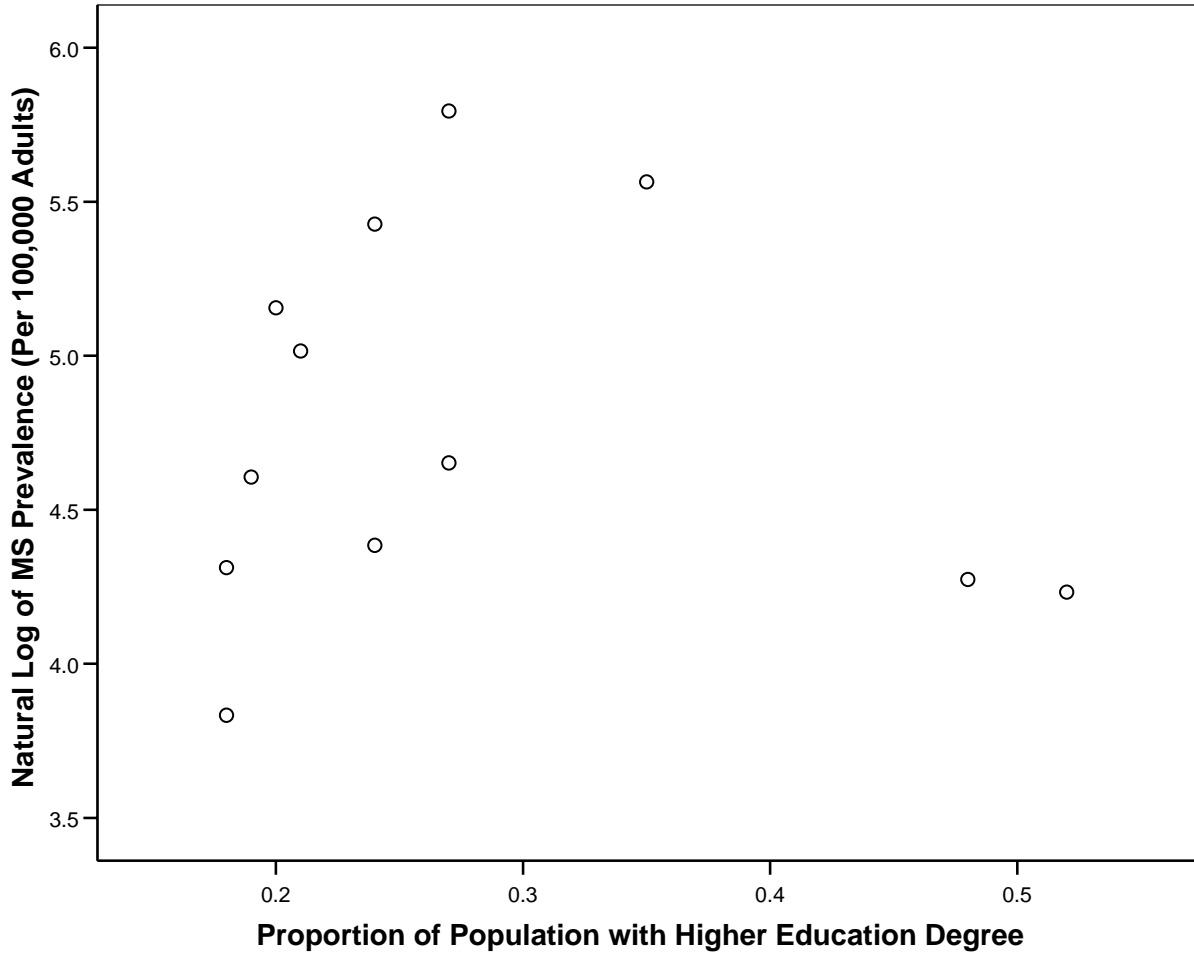
Figure A5. Scatter plot of dependent variable natural log of MS prevalence vs. independent variable proportion of Caucasian population

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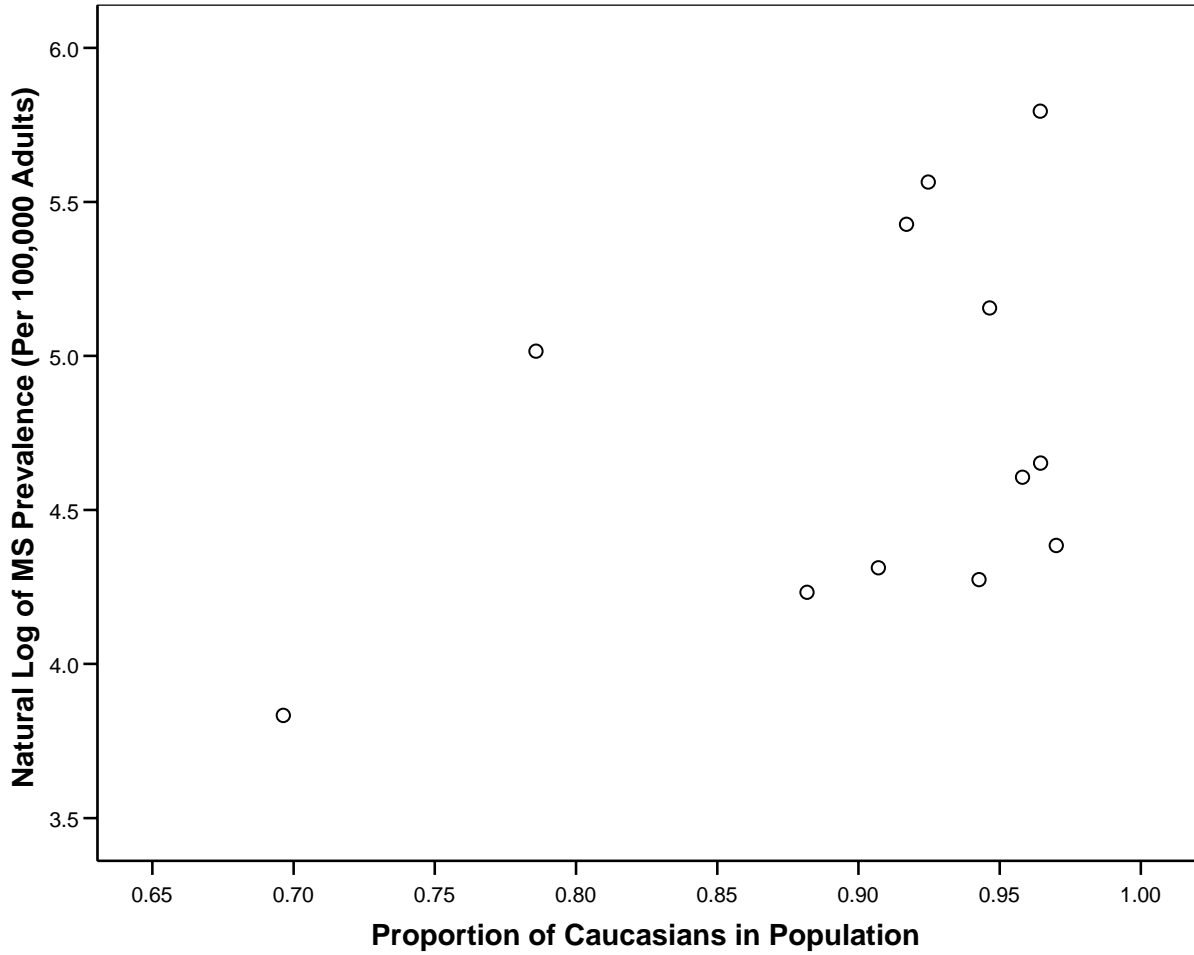
Figure A6. Scatter plot of dependent variable natural log of MS prevalence vs. independent

variable proportion of total adult population 30 or older
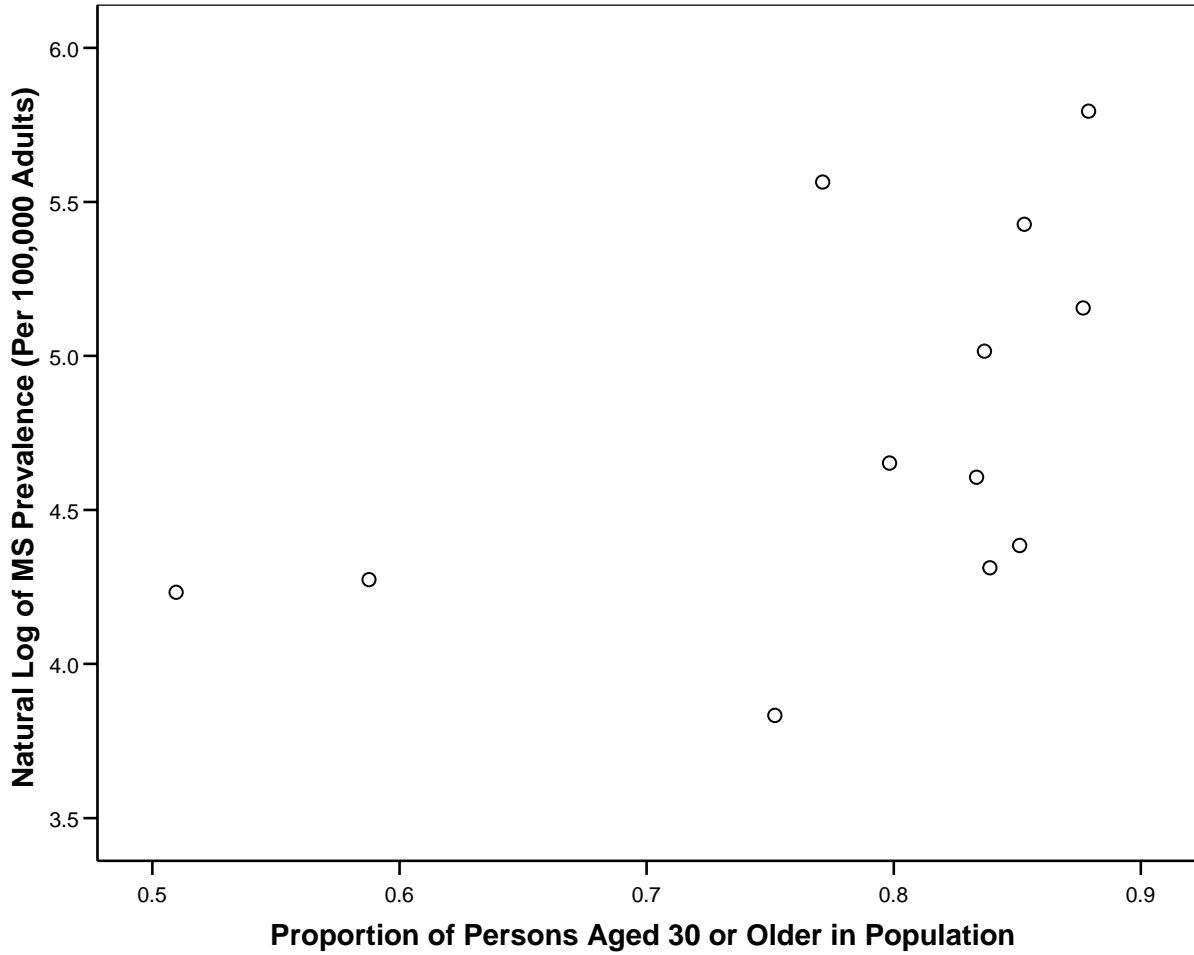
Figure A7. Scatter plot of dependent variable natural log of MS prevalence vs. independent

variable latitude

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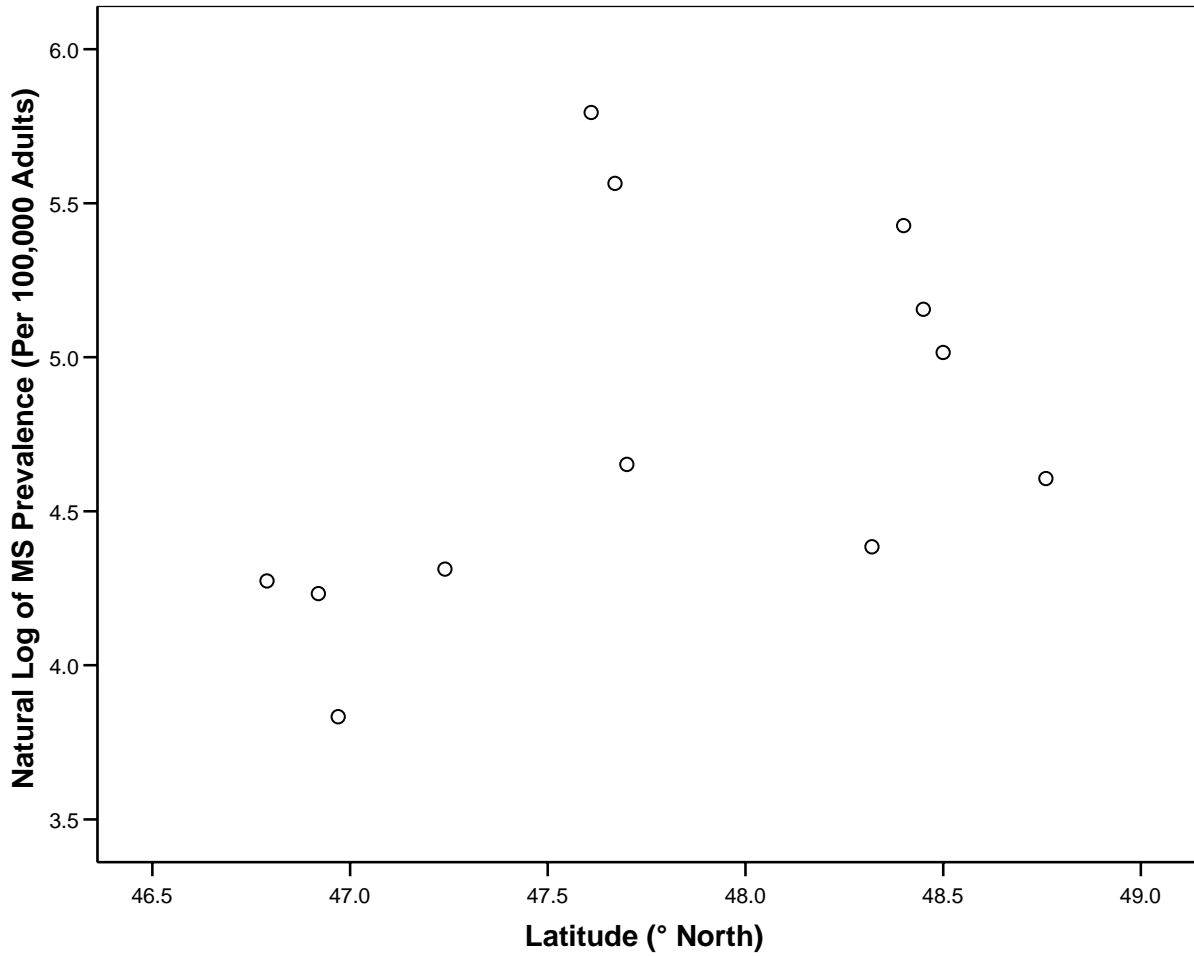
Figure A8. Scatter plot of dependent variable natural log of MS prevalence vs. independent

variable distance to Hanford

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Figure A9. Scatter plot of dependent variable natural log of capture-recapture estimated MS

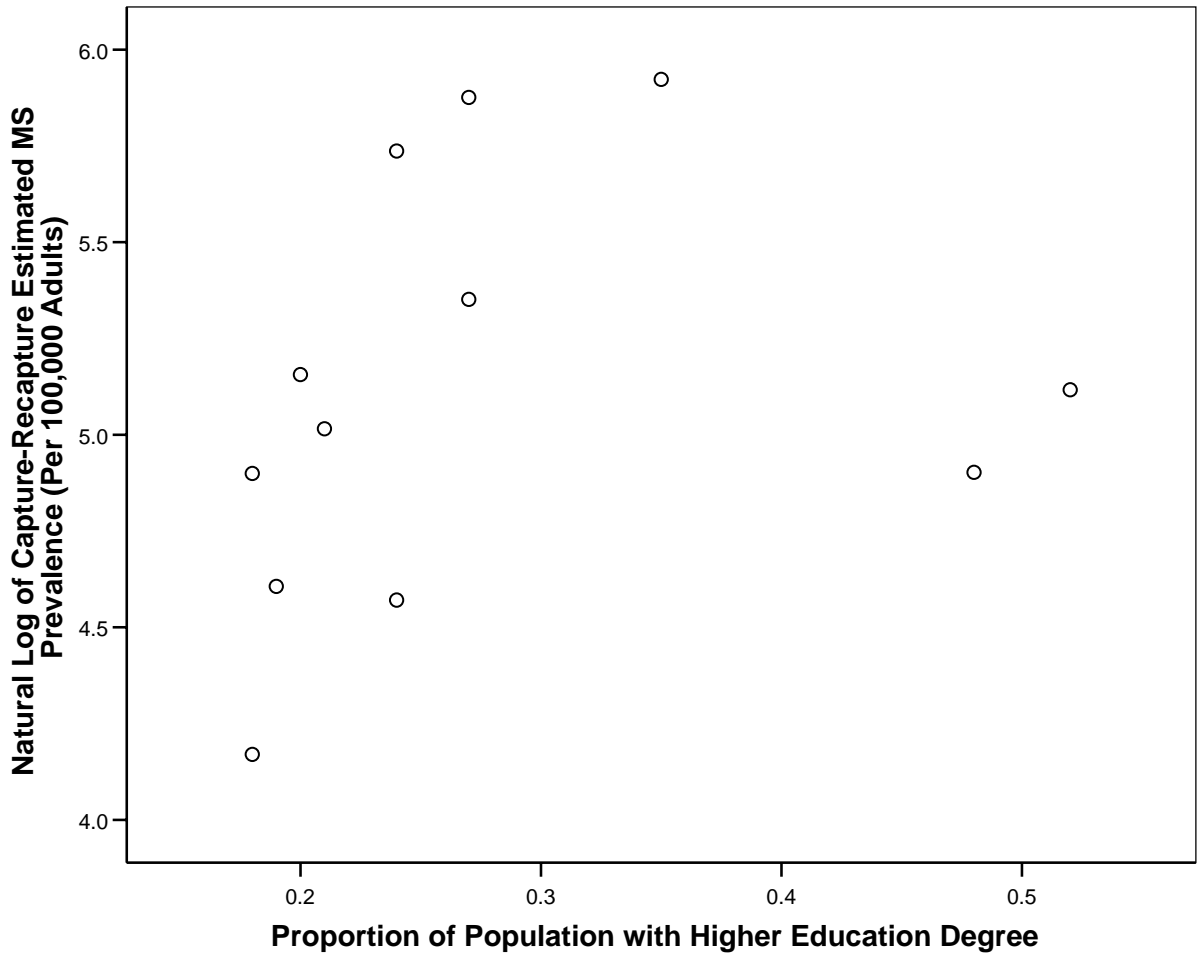prevalence vs. independent variable proportion of female population

Figure A10. Scatter plot of dependent variable natural log of MS prevalence vs. independent

variable mean per capita income

Figure A11. Scatter plot of dependent variable natural log of capture-recapture estimated MS

prevalence vs. independent variable proportion of population with higher education degree

Figure A12. Scatter plot of dependent variable natural log of capture-recapture estimated MS

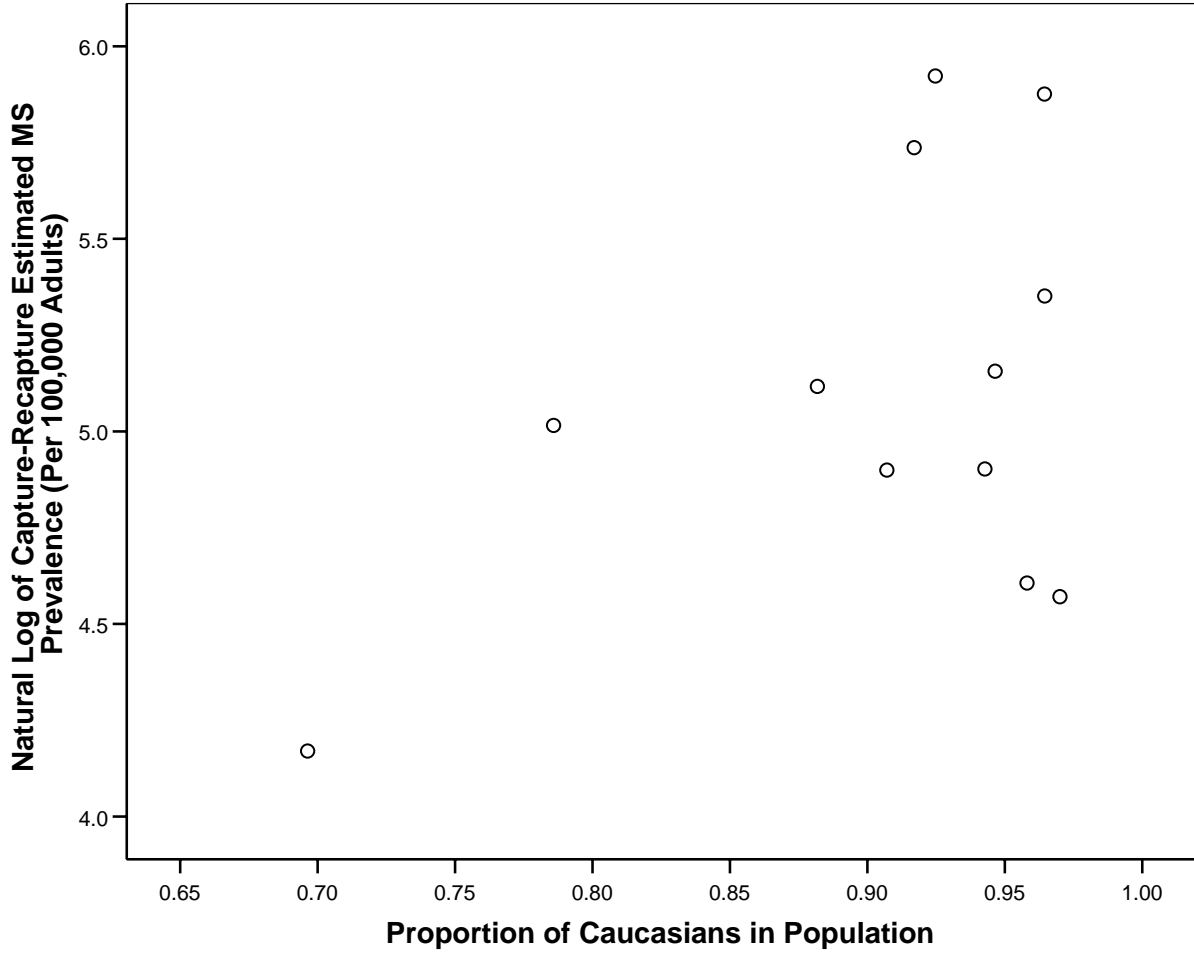prevalence vs. proportion of Caucasians in population as the independent variable
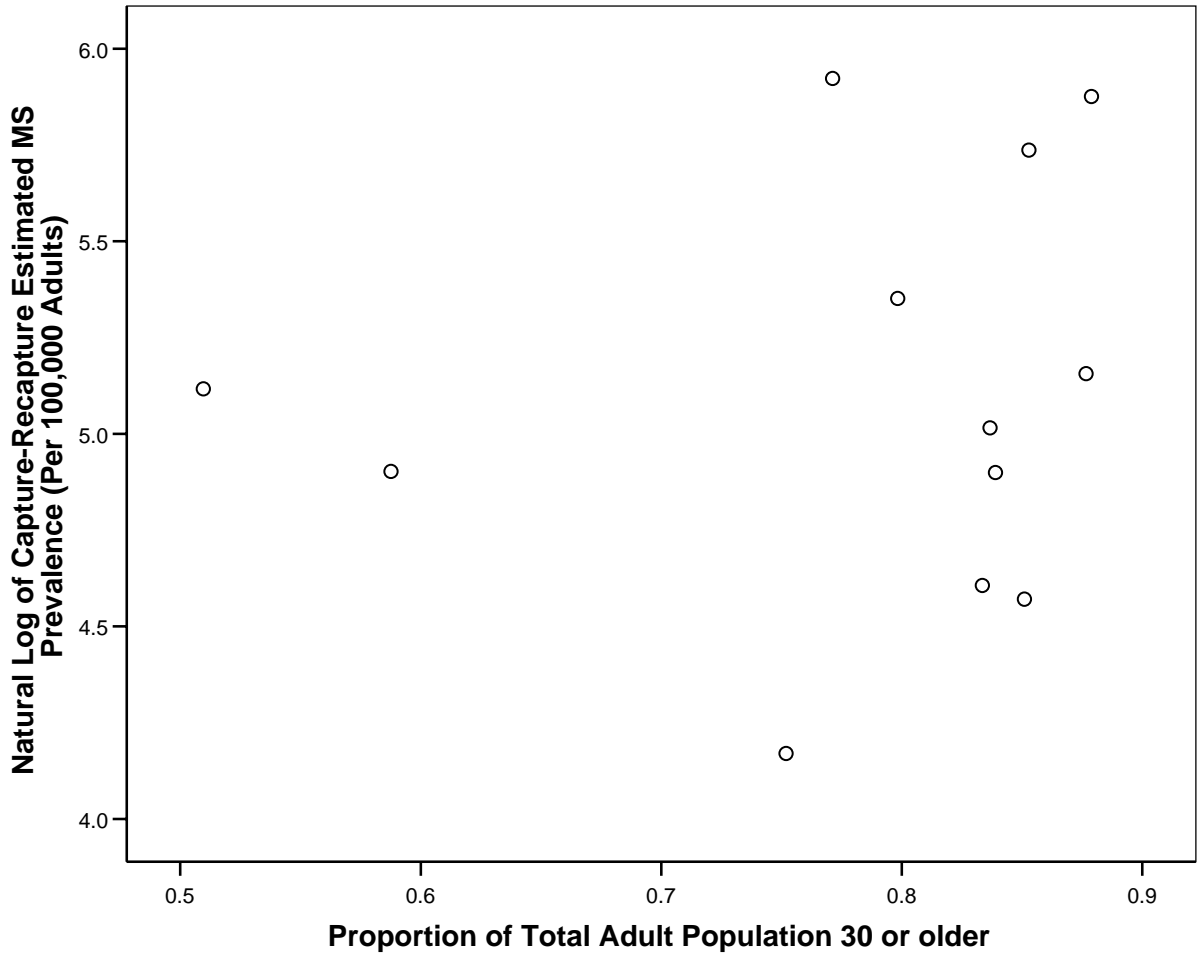
Figure A13. Scatter plot of dependent variable natural log of capture-recapture estimated MS

prevalence vs. independent variable proportion of total adult population 30 or older

Figure A14. Scatter plot of dependent variable natural log of capture-recapture estimated MS

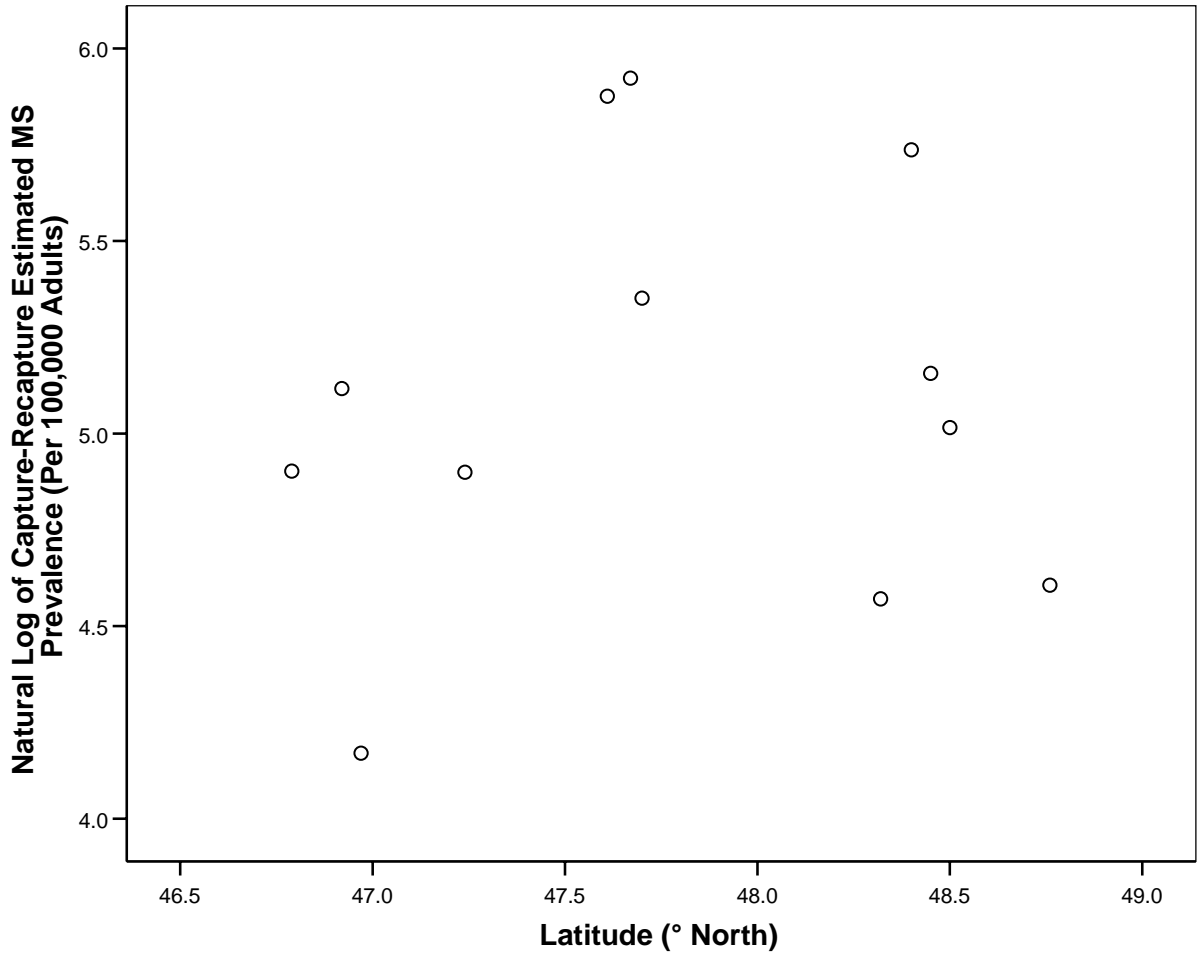prevalence vs. independent variable latitude

Figure A15. Scatter plot of dependent variable natural log of capture-recapture estimated MS

prevalence vs. independent variable distance to Hanford