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Meta-Analysis, Spatial, and Temporal Models to Analyze the Possible Association between Childhood Leukemia in Proximity to Nuclear Facilities

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META-ANALYSIS, SPATIAL, AND TEMPORAL MODELS TO ANALYZE THE POSSIBLE ASSOCIATION BETWEEN CHILDHOOD LEUKEMIA IN PROXIMITY TO NUCLEAR FACILITIES

By

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ABSTRACT

The purpose of this dissertation was to gain a better understanding of the possible association between childhood leukemia and nuclear facilities by conducting a meta-analysis and by the use of spatial and temporal models with respect to Pickering Nuclear Generator (PNG) in Ontario, Canada.

The meta-analysis was conducted to combine and statistically analyze the many studies of childhood leukemia in the vicinity of nuclear facilities. Our focus was on studies that calculated SMRs or SIRs for individual nuclear sites. Due to variability between studies in defining age and geographic zones, eight separate analyses were performed based on age and zone stratification levels. One hundred and forty-six sites were used in at least one analysis. Unadjusted models, fixed effects models, and random effects models were used for each of the eight analyses. Meta-rates greater than one were found in all models at all stratification levels. Further, statistical significance at 95% confidence intervals was often achieved. Within geographic zones (as established by the meta-analysis), the 0-9 age group experienced higher rates than the 0-25 age group. There does not appear to be publication bias in the meta-analysis.

To better understand the temporal and spatial relationship between radiation from PNG and childhood leukemia, smoothed moving rates through time and a spatial model (Score Test of Lawson and Waller) were used that allowed for a more comprehensive description of disease patterns. No apparent relationship between childhood leukemia and PNG was detected. In the temporal analysis, moving SIRs remained near one for the entire time-period for the census subdivisions of Pickering and Ajax (which contain PNG). Zones based on distance from PNG were created for the spatial analysis. The

highest rates were found in the innermost and outermost zones, with the highest population in the outer zones. No significant results were found with the Score Test of Lawson and Waller.

1. INTRODUCTION

In response to the cluster of childhood leukemia reported near the Sellafield nuclear site in Great Britain in 1984 (1), there have been numerous studies assessing the possible risk of childhood leukemia due to irradiation from nuclear sites. Some studies have found positive associations, though few results have been significant. Although there is little doubt that exposure to radiation increases the risk of developing leukemia (2-5), there is disagreement on whether the amount of exposure received by children living near nuclear sites is sufficient to increase risk. The purpose of this dissertation is to gain a better understanding of the possible association between childhood leukemia and nuclear facilities by conducting a meta-analysis and by the use of spatial and temporal models with respect to Pickering Nuclear Generator in Ontario, Canada.

Meta-analysis

Determining individual exposure in proximity to nuclear sites is problematic. Parameters that need to be considered include, type of nuclear site, wind speed and direction, topography, facility emissions, and distance from the site. For the child, parameters include age and lifestyle (i.e. whether the individual spends more time outdoors or indoors). Due to the difficulty of determining individual exposure levels, researchers have largely relied on identifying cases or deaths in a predefined area and calculating a standardized rate without a specific reference to exposure, instead, using geographic zones in proximity to the nuclear site as a surrogate for exposure.

Within the multitude of studies, many type of inconsistencies in methodology have surfaced including:

- Age—The choice of age group to study has not only varied between studies in different countries, it has also varied between studies of a single nuclear site. This may reflect the uncertainties in determining at which age a child is no longer more susceptible in developing leukemia than an adult.
- Area—Past studies have used: 5 km, 10 km, 12.5 km, 16 km, 25 km, 35 km, county, and even a single village. Since the selection of area is often arbitrary (defined by an area with available census data), the choice naturally lends itself to selection bias. Too small an area may underestimate risk to children living outside the area and too large an area may miss a slight increase in risk if that risk is found near the nuclear site and much of the study area is not in the actual exposure zone.
- Time-interval—Duration of time analyzed varies greatly from study to study. The primary barrier is the length of time the site was operational and the availability of incidence/mortality data and population counts.
- Endpoint—Incidence data is generally preferable to mortality data as incidence data includes the census area where the person lived at date of diagnosis. This is a better indicator of where the person may have resided at time of exposure. Mortality data, on the other hand, may more easily be affected by a migration bias. Survival rates have also increased for childhood leukemia making incidence a better indicator than mortality.

Another difficulty arises because childhood leukemia is a rare disease and nuclear sites are frequently found in sparsely populated areas leading to small sample sizes and, consequently, low power to detect small increases in risk. One method to increase sample size and power is to pool several cohorts that share common study characteristics and conduct a meta-analysis.

Although there exists papers that summarize the many cohort and case-control studies on childhood leukemia in proximity to nuclear sites, as well as report other potential causes such as the possibility of an infectious origin associated with population mixing (6-7), there has not been an attempt to combine and statistically analyze these many studies, which is the purpose of this analysis.

Spatial and Temporal Analysis of Pickering Nuclear Generator

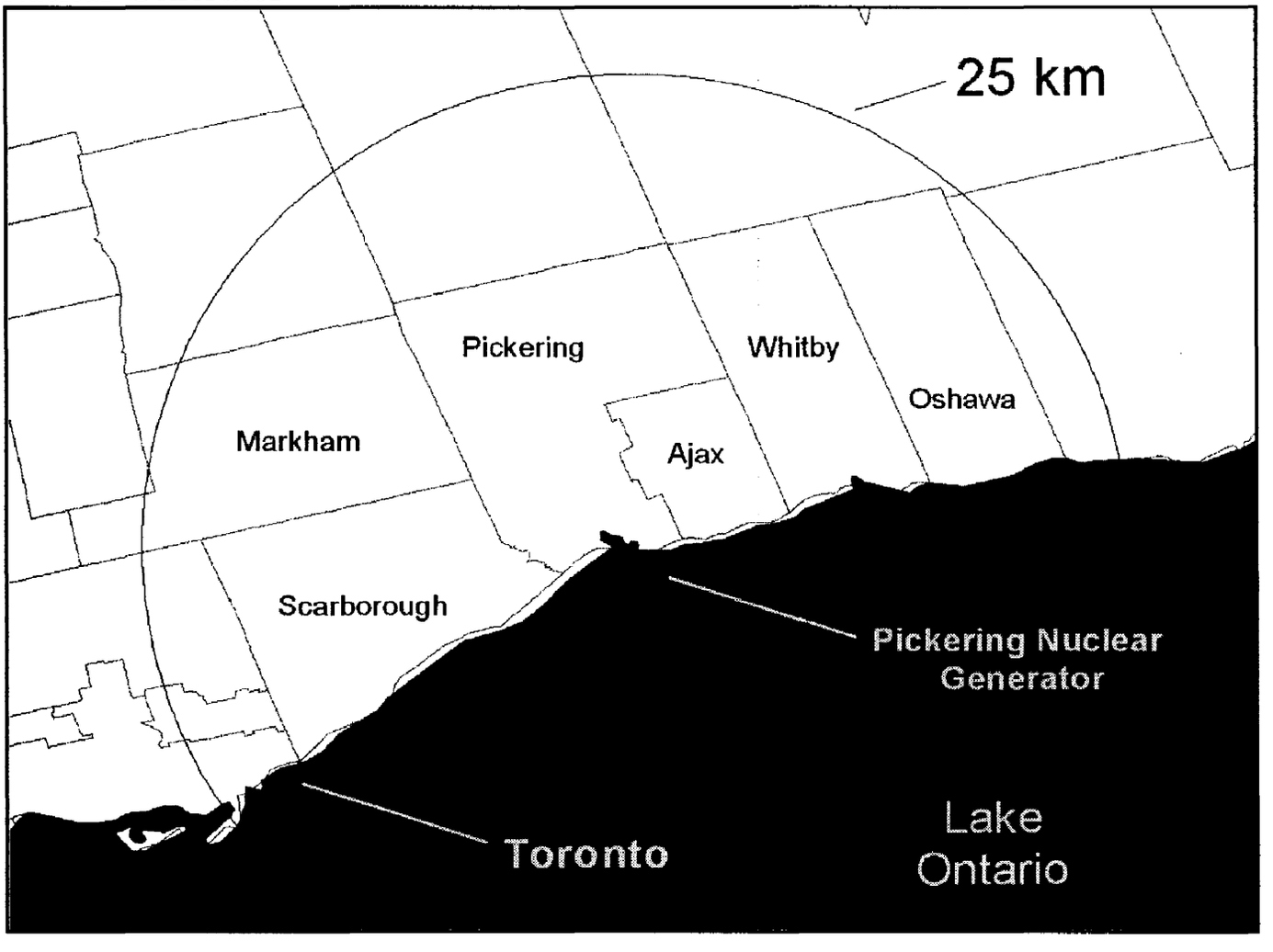
There have been several statistical methods used in cohort studies of childhood leukemia and nuclear facilities. The most common method is the standardized mortality rate (SMR) or standardized incidence rate (SIR). Generally the rate is calculated for the longest time frame that data is available, occasionally it is broken down into pre-defined time-intervals (i.e. 10 year intervals). The population studied is dependent on the geostatistical unit, on which census data is available for that region, ranging from county level to postal codes. The size of the census area is important. If the excess risk is only to those residing near the facility, including a large unexposed population may not allow detection of the excess risk; similarly, if the area of study is too small and the excess risk exceeds the study area, the study may lack the power to find a statistically significant excess (8-10). Another common method used in the cohort studies is to choose control

areas that have similar census characteristics to the area under investigation, and calculate a relative risk. A third, and rarely used method, spatial analysis, considers distance from the source when determining exposure and consequently, risk.

Canadian researchers conducted two studies to analyze childhood leukemia in the vicinity of nuclear facilities in Canada; Phase I included the 0-4 age group (11) and Phase II analyzed the 0-14 age group (12). Nuclear facilities were categorized into one of three groups: nuclear research and development facilities, uranium mining, milling and refining facilities, or nuclear generating stations. For SMRs, the researchers looked at residence at birth and residence at death; and for SIRs, only residence at birth was used. No statistically significant increases in childhood leukemia at the alpha=0.05 level of significance were found; however, the Phase II study's pooled mortality analysis for the population living "nearby" (<25 km) to two nuclear generating stations, Pickering Nuclear Generator (PNG) and Douglas Point Nuclear Generator had an SMR of 1.4 with a lower confidence band of 0.98 when using residence at birth. Further, each generator had a non-significant SIR greater than one, suggesting that more research was needed. Although the researchers would have preferred to use a smaller area than <25 km for the nearby population, they were not able to do so due to the sparse population found near most of the nuclear facilities; and at the time of the study, census subdivision was the smallest geostatistical unit available for census data. For most facilities, the census subdivision in which the site was located was close to the 25 km radius. However, PNG is located near Toronto, in an area more densely populated than other Canadian nuclear facilities. Six census subdivisions were included in the <25 km area (Figure 1.1). The majority of the population in the PNG area is found in Scarborough, a district of Toronto

located west of PNG. If exposure were related to prevailing wind direction, one would expect the largest risk would be to children living northeast of PNG; therefore, including the population of Scarborough would lessen the power to find an increased risk due to PNG. Conversely, if childhood leukemia was positively correlated with population density and radiation from PNG was too low to affect leukemia rates, including Scarborough would increase the probability of a Type I error when the primary hypothesis is testing radiation from PNG as the risk factor.

Figure 1.1 – Six Census Subdivisions within 25 Kilometers of Pickering Nuclear Generator



Another potential issue is the use of a two-sided statistical test. Choosing whether to use a one-sided or two-sided test must be considered carefully. If one is certain that the

exposure in question may only be harmful or have no effect at all, then choosing a one-sided test is plausible. If Clarke selected a one-sided test, the SMR for the nuclear generating stations would have been significant.

The nuclear generating stations of Canada are pressurized heavy water reactors (13). Pressurized heavy water reactors produce greater amounts of tritium than the more commonly used pressurized (light) water reactors and boiling water reactors per unit power production (14,4). Tritium presents many challenges to the scientific community. In the gas form, tritium may diffuse through most any container and is difficult to detect in its oxide form. It may also bond to any molecule that contains hydrogen. Although tritium occurs naturally in the environment, little is known about the impact of low-level tritium exposure (14). Grosche hypothesized that the excess cases of childhood leukemia near the Kruemmel nuclear power station in Germany may be either directly or indirectly related to tritium release from the facility. The researchers compared local childhood leukemia rates to the amount of tritium release from Kruemmel and the Savannah River Site, a weapons facility that produced plutonium and tritium in the United States. Although Savannah River Site released greater amounts of tritium than Kruemmel, increased rates of childhood leukemia were only found near Kruemmel (15). One disadvantage in comparing Kruemmel and Savannah River Site is that Kruemmel is located near a town and Savannah River Site is located in a rural area. Further, cases and deaths near Savannah River Site may only be analyzed at the county level, possibly too large an area to detect a small increased risk near the facility.

The advantages of studying PNG include:

- PNG is a pressurized heavy water reactor that produces tritium.

- PNG is located near a large urban area and has the advantages associated with large sample sizes, in particular greater power to detect a smaller increased risk.
- Ontario's cancer registry began in 1964.
- Ontario population and cancer registration data is available at levels smaller than counties, including census subdivisions and enumeration areas.

Since much of the data used in this analysis overlaps the data used by Clarke, the purpose of our research is exploratory and designed to better understand the temporal and spatial relationship, if any, of childhood leukemia and PNG.

2. REVIEW OF LITERATURE

In 1983, a British television reporter visited the Sellafield nuclear site in West Cumbria, England. The reporter's purpose was to make a documentary on the health of the Sellafield workers with respect to radiation exposure. While visiting the site, the reporter learned from the local residents that there might be an excess of childhood leukemia in the village of Seascale located 3 km to the south. After investigating the residents claim, the reporter aired the program suggesting a ten-fold increase in childhood leukemia in Seascale; and alleged that the cases were linked to the nuclear facility's release of radioactive liquids into the Irish Sea, leading to contaminated beaches and seafood. The British government established an independent investigation led by Sir Richard Black to further investigate the reporter's claims (16). The following year, the Black report confirmed the excess cases of leukemia in the 0-24 age group in Sellafield and stated the excess was highly statistically significant (1). Since the Black report, epidemiologic studies around the world have been undertaken to analyze the risk of leukemia to children living near nuclear facilities. Following is a summary of descriptive studies by nation and a list of potential risk factors (many studies are represented in tabular form in Appendix B).

Studies by Nation

Great Britain (England & Wales)

Prior to the Black report, Baron examined the temporal change in cancer rates in counties containing fourteen nuclear facilities in England and Wales (including

Sellafield). He concluded there was no significant increased risk of cancer (including childhood leukemia) in these counties. Baron, aware of the unpublished results of the Black report, stated the contrast to the Black report is due to the size of the area chosen—Baron used county level data, while the Black report concentrated on a much smaller area around Sellafield (17).

In 1987, researchers found a significant excess of childhood leukemia (age range 0-14) within the overlapping 10 km radii of two nuclear facilities, Aldermaston and Burghfield. The excess was primarily attributed to the 0-4 year olds (18). Another study, this one focusing on Hinkley Point nuclear power station (0-24 year olds), found a statistically significant excess of leukemia and non-Hodgkin's lymphoma with most of the excess attributed to the first ten years after the facility began operation (19).

A 1987 study of 14 nuclear sites in England and Wales (age 0-24), using control areas to determine relative risk, reported a statistically significant relative risk of 2.0 for all nuclear sites combined (20). Two years later, a similar study of 15 nuclear facilities in England and Wales (age 0-24) found a relative risk of 1.15 ($p=0.01$) for all facilities combined (21). However, the researchers also found a statistically significant relative risk of 1.4 in areas that were considered by the British government as possible sites for nuclear installations (22).

In 1992, a study was published that investigated the areas around 21 nuclear sites and restricted the age group to 0-9 years of age. The study used two methods: 1) Expected cases calculated using regional data—since regional data have a much larger population at risk in the denominator, the Poisson distribution was used to determine risk. 2) Expected cases based on comparison areas with approximately the same population

size—since population at risk is equal, the Binomial distribution was used to determine risk. Using childhood leukemia incidence data, Sellafield was significant under the Binomial distribution (p=0.029), Aldermaston was significant using the Poisson distribution (p=0.020); only the Amersham facility indicated statistically significant results for both methods. Further, only Amersham showed a significant excess of childhood leukemia when examining mortality data (Binomial, p=0.0054) (23).

In 1993, a study was published that re-examined Sellafield from 1963-83 and added data for the years 1984-90. The data used the 0-24 age group and both leukemia and non-Hodgkin's lymphoma. The combined data continued to indicate a significant excess of cases. Although the 1984-90 data introduced only two new cases, the 1984-90 time-period produced a statistically significant excess of cases (p=0.007) (24). The Committee on Medical Aspects of Radiation in the Environment (COMARE) used data through 1992 to show that the excess persisted (25,7).

In 1994, a study looked at 29 sites in England and Wales. The researchers used tests that would be more sensitive to the spatial patterns of the disease (known as focused cluster tests). Only the areas around Sellafield (p=0.00002) and Burghfield (p=0.031) showed an excess of leukemia and non-Hodgkin's lymphoma in the 0-14 age group (9).

In 1997, Busby and Cato examined seven districts in the vicinity of Aldermaston and Burghfield nuclear sites. The researchers used leukemia mortality data for the 0-14 age group. The highest relative risks were found in the two districts that COMARE determined would be most affected by radiation, South Oxfordshire (R.R.=2.45, p=0.0047) and Newbury (R.R.=1.93, p=0.031) (26). The same year, Draper looked at leukemia incidence data for the 0-9 age group in the same seven districts. The study also

presented incidence rates for all districts in England, Wales, and Scotland. The authors concluded that the incidence rates in the two districts that Busby and Cato found elevated rates, were not unusually higher than the adjacent districts (27).

Great Britain (Scotland)

A study was undertaken by COMARE to evaluate leukemia in the area that contains the Dounreay nuclear installation. The study looked at people aged 0-24 in three non-overlapping time-periods (1968-73, 1974-78, and 1979-84) and two categories of distance of residence from the facility (<12.5 km and 12.5 to < 25 km). Five cases were observed in the time-period 1979-84 and the distance category <12.5 km while 0.513 cases were expected (p=0.001). No other significant results were found (8,28). Eight years later, another study was published that included additional incidence data for 1985-91. The author combined the time-periods and used only the distance, <25 km. Twelve cases were observed and 5.2 were expected (p=0.007). In the latest period, 1985-91, four cases were observed and 1.4 expected (p=0.059) (29)

In 1996, incidence of leukemia and non-Hodgkin's lymphoma in children between 0-14 years of age residing near seven nuclear sites was analyzed with a focused cluster test, the authors reported that the increase reported previously near Dounreay showed a significant result (p=0.030) when considering distance (30).

France

The first French study to examine cancer around nuclear sites was published in 1989 and focused on mortality in the area of the La Hague nuclear facility. The study

used a zone of 10 km. There was no excess found for any cancer (31). A year later, researchers looked at the La Hague site exclusively for mortality from childhood leukemia. Again, no excess was found (32). The first study near La Hague to use incidence data for leukemia in young persons (age group 0-24) was published in 1993. The time-period used was 1978-90 and case ascertainment was done without a cancer registry. Although a standard incidence ratio (SIR) of 2.5 was found, it was not significant (33). Another La Hague study was published in 1995. Three statistical tests were examined that are designed to detect the presence of clusters around a putative source. The first, a conventional test examining incidence rates for subregions and searching for patterns; the second is a focused cluster test known as Stone's Test; and the third, extraction mapping techniques based on kernel regression smoothing. The results were close to significant when using Stone's Test ($p=0.06$); the other tests were further from significant (34). The latest study reported no new cases of leukemia between 1993-96 (7,35).

Bouges investigated the relationship of childhood hematological cancers and the French Marcoule nuclear reprocessing facility using traditional SIRs and Bayesian methods. No significant increases in disease were found (36).

Two multi-site studies took place in 1992 and 1995. Standard mortality rates were calculated but no significant increase was found (37-38).

Germany

A multi-site study was published in 1992 that looked at areas containing 20 nuclear facilities throughout Germany. There were three distance groups considered (5

km, 10 km, and 15 km radii) (39). Similar to Cook-Mozaffari (21), incidence in areas containing nuclear facilities were compared with incidence in control areas. Increased risk of acute leukemia was found in the 0-4 age group at 15 km (p=0.037) and 5 km (p=0.015) radii, as well as increased risk of non-Hodgkin's lymphoma at 15 km (p=0.017) and 10 km (p=0.012) radii. The results were for all sites combined—individual sites were not considered. The results may have reflected the unexpected low incidence rates in the control areas (39). Between February 1990 and May 1991, six years after the start-up of the Kruemmel nuclear power generator, five cases of leukemia were found in the rural community of Elbmarsch, within a five km radius of the Kruemmel site and on the opposite side of the river. A sixth case was diagnosed in 1995. Although 80% of the population lives north of the site, five of the sixth cases lived south of the site (the sixth case had moved from the south region to the north region a few months before diagnosis). The SIR for 1990-1995 was 460 (95 % CI: 210, 1,030) (40). Between 1994 and 1996, four more cases of childhood leukemia were found in proximity to Kruemmel (15).

United States

The earliest epidemiology studies of the general population near nuclear facilities began in 1949. Tokuhata and Smith give a brief summary of the 1949 study as well as 10 other similar studies that were conducted before 1978. The overall conclusion was that the rates of cancers, infant mortality and birth defects were similar to the general population or control areas (41). A national study was conducted in 1991 that looked at counties that contained a nuclear facility or that was near one of 62 nuclear sites. Each

county was compared to three control counties. Mortality data for all cancers, leukemia (all ages), and childhood leukemia from 1950-1984 was used. Incidence data was also used for the few sites that were in areas with cancer registries. There was no overall excess found. The author concludes, "If any excess cancer risk was present in US counties with nuclear facilities, it was too small to be detected with the methods employed" (42).

Grosche compared the Kruemmel site in Germany to the Savannah River Site in South Carolina, both sites release tritium into the environment. Although tritium releases from the Savannah facility were several orders of magnitude higher than the Kruemmel site, there was not an excess of leukemia cases near the Savannah site between 1991 and 1995. Tritium release from Kruemmel is primarily airborne while tritium release from the Savannah facility is primarily through water (15).

A 2003 study by Boice examined two former nuclear materials processing facilities in Western Pennsylvania. Using a method similar to Jablon, no significant results were found before, during, or after the facilities closed (43).

Mangano studied counties near nuclear reactors in the eastern United States. Statistically significant elevated incidence of childhood leukemia was found in the 0-10 age group (44).

Canada

Canadian researchers studied areas around five nuclear facilities in Ontario: an atomic energy research and development facility, a uranium refinery, a uranium mining and milling facility, and two nuclear power. Incidence and mortality data was available

through the Ontario Cancer Registry. Birth certificates and death certificates were also ascertained for leukemia cases in children between 0-14 years of age. The main objective was to "investigate whether the frequency of leukemia among children born to mothers residing in the vicinity of nuclear facilities differed from the provincial average." A secondary objective was to determine, where possible, if rates for leukemia was different before and after a facility opened. Census subdivisions within a radius of 25 km from the nuclear facilities were used in the analysis. The pooled SMR, by residence at birth, in the 25 km radius around Pickering Nuclear Generator (PNG) and Douglas Point Nuclear Generator was 1.40 (95% CI: 0.98, 1.9) for all birth cohorts combined. The SIR, by residence at birth, in the same area was 1.15 (95% CI: 0.90, 1.44). The SMR, by residence at birth, in the 25 km radius before Pickering was in operation was lower (SMR=1.08; 95% CI: 0.86, 1.34) than after the facility began operation (SMR=1.34; 95% CI: 0.92, 1.89). Douglas Point Nuclear Generator and the uranium refinery also showed increase risk but the lower confidence bands were well below one. Due to the low population density in the Douglas Point and uranium refinery areas, the increased risk would need to be very large for a significant result (45,11-12).

Other Countries

Researchers in Japan conducted a national study where the municipalities around several nuclear sites were examined for mortality from leukemia in the 0-14 age group. Between the years of 1973 and 1987, there was no overall excess risk when compared to control municipalities (46,7).

Waller used several methods of cluster analysis to identify if there was an excess of leukemia in children 0-14 years of age near four nuclear facilities in Sweden. Between 1980 and 1990, no significant clusters were found (47).

Researchers looked for spatial and temporal trends in the Negev region of Israel, where a nuclear facility is located. Although childhood leukemia rates (age: 0-9) were consistently higher over time in Western Negev (as compared to Eastern Negev), no excess cases were found in the towns near the facility (48).

A Spanish study looked at seven nuclear power generators and five nuclear fuel facilities during the period 1975-93. Using towns lying between 50-100 km from the facilities as controls, no excess mortality was found near the nuclear power generators. However, one uranium-processing facility in Anujar (R.R.= 1.30; 95% CI: 1.03, 1.64) found a significant excess of mortality from leukemia; and the uranium-processing facility in Cuidad Rodrigo (R.R.= 1.68; 95% CI: 0.92,3.08) found a slightly non-significant increase in mortality. Excess risk of mortality from multiple myeloma was found in the area of the Zorita nuclear power generator Lopez-Abente, Aragones, et al. 1999 (49).

Zaridze examined former nuclear weapons test sites in Kazakhstan (formerly of the Soviet Union). Increased rates of childhood leukemia were found for children living within 200 kilometers of the former test areas when compared to children living more than 400 kilometers from the areas (50).

In response to the 1986 accident at Chernobyl located in Ukraine, studies from neighboring countries have been conducted, including Hungary (51) and Belarus (52). No increased rates of childhood leukemia were reported.

Large Geographical Studies

According to Dockerty, over 30 studies from around the world have examined whether there is large scale spatial and /or temporal clustering of childhood leukemia. Of the 33 known datasets (including Dockerty's New Zealand dataset), 15 indicated statistically significant evidence of clustering, 13 presented no evidence of clustering, and five found possible clustering in one to several subgroups (53-63).

A 1993 study by Alexander lists several small clusters that have been reported as early as 1930 (56).

The largest study to determine whether childhood leukemia show a general tendency to cluster was the EUROCLUS project. Between 1980 and 1989, EUROCLUS collected incidence data for 13,551 cases of childhood leukemia in seventeen European countries. The key findings in the 1998 EUROCLUS report include:

- Childhood leukemia does not show strong spatial clustering; however, statistically significant results of spatial clustering were found but of small magnitude.
- Clustering focused in areas of intermediate population density (150-500 persons/km^2)
- Compared to control areas, cluster areas have demographic characteristics that indicate: isolation (initially) and population mixing possibly indicating an infectious aetiology for childhood leukemia (to be discussed in more detail below) (64).

Risk Factors

Paternal preconceptional exposure

Gardner conducted a case-control study with 52 cases (age: 0-25) of leukemia, 22 of non-Hodgkin's lymphoma, and 23 of Hodgkin's disease occurring in people born near Sellafield and diagnosed in the area in 1950-85 and 1001 controls matched for sex and date of birth taken from the same birth registers as the cases. For those leukemia cases born within 5 km of Sellafield, the statistically significant relative risk was 2.44. For children of fathers employed at Sellafield at the time of conception and who received greater than 100 mSv of radiation, the statistically significant relative risk for leukemia was 6.42. The idea that paternal preconceptional exposure can cause leukemia in offspring became known as the Gardner hypothesis. However, eating seafood or homegrown vegetables or playing on the beach did not increase risk (65-66).

The concept that paternal preconceptional exposure can cause lethal mutations goes back to at least 1927, when Muller conducted a study of the common fruit fly (67). Mouse studies indicate that it would take an acute dose of 1,500-3,000 mSv (15-20 times the accumulated dose of the most heavily exposed Sellafield workers) for "spermatozoa or spermatogonia to double the spontaneous rate of a wide range of single gene defects" (68). However, germline mutations in humans (due to an environmental exposure) are more difficult to investigate (68-69).

One difficulty in human studies is to accurately account for all radiation that nuclear workers are exposed to and where in the body the radionuclides accumulate. Although the Sellafield workers wore external monitoring badges, it may be possible for internal contamination of radionuclides to be greater than that recorded on the film badge.

An increased risk of more than 10-fold (similar in size to the Black report (1)) was seen for prostatic cancer in workers of the United Kingdom Atomic Energy Authority and the Atomic Weapons Establishment who had at least 100 mSv of radiation recorded on their film badges. These workers also were monitored for possible internal contamination and it was suggested that some radionuclides might be concentrated in the prostate (70-72).

The atomic bomb data contains 7400 children of Japanese men that survived the bomb; there was no increased risk of leukemia in the offspring (73-74). It should be noted that atomic bomb survivors received a single high-level dose of radiation; whereas, the nuclear industry workers receive chronic fractionated low-doses of radiation. Greaves suggest that if a germline mutation is responsible then we could expect to see an increase in fetal death, other pediatric cancers, and congenital malformations. These should be more common than the leukemias since they can arise from a single dominant mutation; unlike acute leukemia in children, which most likely requires at least two independent mutations (75-76).

Roman conducted a case-control study of leukemia and non-Hodgkin's lymphoma near Aldermaston and Burghfield atomic weapon establishments. Of the cases and controls with fathers who wore film badges, a slightly significant relative risk of 9.0 (CI: 1.0, 107.8) was found. However, the authors caution that the small number of cases, three, are not enough to discount chance (77).

McKinney performed a case-control study in three areas of Great Britain that had recently reported clusters of childhood leukemia (not including Seascale). Although odds ratio for preconceptional exposure of fathers to ionizing radiation was increased (but not significant), there were significant associations to the fathers' exposed to wood dust

(O.R.=2.73; 95% CI: 1.44, 5.16), all types of radiation (O.R.=3.23; 95% CI: 1.36, 7.72), and benzene (O.R.=5.81; 95% CI: 1.67, 26.44) (78).

Parker conducted a cohort study consisting of 10,363 children born in West Cumbria to fathers employed at Sellafield between 1950-89 and concluded that the there was no increase in leukemia in other villages near Seascale, where many of the workers lived; therefore, they could not find evidence to support the Gardner hypothesis (79).

Draper conducted a case-control study that included 35,949 children diagnosed with cancer and matched controls. Fathers of children with leukemia and non-Hodgkin's lymphoma were significantly more likely than fathers of controls to have been radiation workers (R.R.=1.77; CI: 1.05, 3.03) and a significant five-fold increase in relative risk for children of female workers (R.R.=5.00; CI: 1.42, 26.94); however, there was no dose-response relation for any of the exposure periods studied. The authors concluded that the Gardner hypothesis was not supported (80). A case-control study of children with leukemia (or non-Hodgkin's lymphoma), living near the Dounreay facility (Scotland), failed to find evidence to support the Gardner hypothesis (81). Nor did the 1993 Canadian case-control study, conducted by McLaughlin, find evidence to support the Gardner hypothesis (82).

Infectious Agent

The idea that leukemia can be caused by an infectious agent is not new. Many animal leukemia's are caused by viruses (83). There are also examples of viruses associated with hematological diseases in humans. The list includes Epstein Barr virus

with Burkett lymphoma and human T-cell lymphotrophic virus type 1 with adult T-cell leukemia (7,84-85).

In 1988, Kinlen hypothesized that "childhood leukemia may be a rare response to an unidentified mild or subclinical infection, the transmission of which is facilitated when large numbers of people come together, particularly from a variety of origins." The idea is that herd immunity to a possible widespread viral infection would tend to be lower than average in isolated areas. The study looked at an area in Scotland that was rural until an influx of people in the 1950s. The area received the population growth at the same time as the area around the Dounreay nuclear facility (which was also rural), where an increased risk of childhood leukemia was found. Similar to the area around Dounreay, a significant increase of leukemia below age 25 was found (10 observed, expected 3.6), with a greater excess below age 5 (7 observed, 1.5 expected) (6). More evidence for the Kinlen hypothesis was presented in 1990 when Kinlen, studied fourteen British "New Towns." Nine of the New Towns were built in response to wartime air raids and maintenance neglect in London. Congestion and housing conditions were poor and the New Towns were to provide housing and jobs to those dispersed from London. The New Towns were built close to the city and attracted a "well-mixed" group from the city. Five "rural" New Towns were created to increase population near industrial development areas. The incomers to these towns had a wider variety of origins than the overspill nine New Towns. The study was categorized into two time periods (1945-64 and 1965-85). There was a significant excess of leukemia, for the 0-4 years old, in four of the rural New Towns during the first time period. No excess was found in the people age 5-24 in either period. Nor was there excess in any of the nine overspill New Towns. Although the

cases were not confined to a single cell type, the only significant excess was in acute lymphatic leukemia (86).

The Kinlen hypothesis has been supported in several studies. In 1949-50, British servicemen were concentrated in densely populated rural military camps. A significant excess of childhood leukemia was evident (87). During 1969-73, local authority areas in England and Wales that had a population increase of more than 50% also experienced an excess of childhood leukemia. These excesses were mostly in rural areas (88). Construction workers of the North Sea oil terminals, who would work and live in a worker's camp for four weeks and then go to their homes for one week, were studied. Excess cases were found in the rural areas where many of the "oil" workers lived (89). Also in Britain, an excess of cases were found in the rapidly growing residential areas where many people would live and then commute to work in another town (90). During World War II, Britain evacuated large numbers of children to rural areas. A study was conducted to look at leukemia in the rural areas for the period 1945-49. The areas were categorized by increasing proportion of evacuees and a significant positive trend was found (91). Childhood leukemia and non-Hodgkin's lymphoma near large rural construction sites in Britain were compared to the Sellafield nuclear site. A 37% increase in leukemia and non-Hodgkin's lymphoma (age 0-14) was recorded during construction and the following year. There was a 72% increase in cases during the time when construction workers and operating staff overlapped, particularly in areas of high social class (92).

Italy and Greece had very high levels of rural migration in the 1950s and 1960s. During this time, both countries also had unusually high mortality rates from childhood

leukemia. Researchers suggest that the rural population mixing may have contributed to the excess mortality (93). The EUROCLUS project also suggests an infectious aetiology (63-64), as well as a study similar in methodology to Kinlen carried out in Canada (94).

Despite the fact that no possible infectious agent has been identified, several hypotheses have emerged to explain the transmission route. These ideas are based on the collective studies that suggest the childhood peak of leukemia (mainly ALL) appear at ages two to four years at different times this century yet still do not appear in developing countries (7). Greaves suggests that the "peak has been produced by socioeconomic improvements which have resulted in the delay of exposure to infections from infancy until the ages represented in the childhood peak, when lymphocytes may be more vulnerable to spontaneous mutations" (95). Smith focused on the infection history of women of childbearing age. The researchers hypothesized "that under the improved hygiene conditions that occur with increased socioeconomic status, more women of childbearing age are likely to be unexposed to a putative leukemia-inducing agent(s), leading to increased opportunity for in utero transmission due to primary infections during pregnancy or leading to a higher frequency of infections during early infancy due to the absence of protective maternal antibodies, and consequently resulting in more children at risk for developing ALL " (96). After the Smith paper, Naumberg reported an association between exposure to maternal lower genital tract infection in utero, and risk of developing childhood leukemia (97).

Environmental exposure to ionizing radiation from man-made sources

Exposure from ionizing radiation to prenatal individuals is a recognized risk factor for cancer (98-100). Studies have also shown that postnatal exposure to nuclear workers (101-102), individuals treated by radiotherapy (4), and atomic bomb survivors (5) can lead to leukemia. The Life Span Study (LSS) of atomic bomb survivors also recognized an increased risk of leukemia in young people (age 0-24) with a relatively short latency period (7,5). However, there has been a debate whether the amount of radiation released into the environment has been enough to cause the excess of childhood cancers that have been reported in proximity to nuclear facilities.

Case-control studies have been conducted near Sellafield (66), Dounreay (81), and La Hague (103) nuclear facilities to determine risk from environmental contamination. The Sellafield study was unable to find increased risk from eating seafood or visits to the beach (66). The Dounreay study reports a statistically significant increased risk for use of the beach within 25 km of the facility ($p<0.04$). The authors did caution that the results were based on small numbers, multiple hypothesis testing, and possible systematic bias (81). Near La Hague, increased trends were found for use of local beaches by mothers and children ($p<0.01$), consumption of local seafood ($p<0.01$), and a relative risk of 1.18 (95% CI: 1.03, 1.42) for length of residence in a granite-built house (103). Although case-control studies such as these may raise questions about possible risk of leukemia from environmental contamination, at best, they provide only indirect evidence. Stronger evidence would come from studies designed to determine a dose-response relationship (7).

Several studies have attempted to reconstruct the doses of ionizing radiation to the population living near nuclear facilities and to determine risk of cancer associated with the radiation. Unlike the studies that use distance as a surrogate to actual dose estimates (usually by classifying exposure zones as a fixed radius around a putative source), dose-response studies use mathematical models to adjust for temperature, wind, terrain, etc. allowing for different distribution of radioactive emissions across areas at similar distances from the source (104). Expected cases must be determined from dose-response relationships found in other studies. Studies used in the past include: the Life Span Study (105), the British ankylosing spondylitis patients treated with high doses of x-rays (106), and the Oxford Survey of Childhood Cancers (107). In the Life Span Study (adults versus children below the age of 5 years), it has been calculated that for a given dose of radiation, the relative risk for leukemia increases with younger age by a factor of 4-5 (40,105). For prenatal exposure, a factor of approximately 70 can be derived from the data of the Oxford Survey of Childhood Cancers (40,107).

Unfortunately, many of the dose-response studies near nuclear facilities were published as technical reports, not readily attainable (1,8,108-118). However, Goldsmith (23) and Laurier (7) have presented summaries of the results of several of these studies. The studies consistently found that the doses attributable to nuclear facility waste discharge were not high enough to account for the excess cases of hematologic cancers found in those areas. For example, estimated doses from the Sellafield facility were 40 times to 300 times lower than would be needed to account for the excess cases (1,110). Near Dounreay, "the total risk of radiation induced leukemia in an estimated 4550 young people resident in the village of Thurso between 1950 and 1984 will have been well

below one case (0.34)" (8,112). However, six cases were found in Thurso during that time period (23). Excess cases of leukemia in children between the ages of 0-14 years of age, based on the estimated discharge from Aldermaston and Burghfield, is between 6 x 10^{-5} and 6 x 10^{-4} (109). Furthermore, bone marrow dose attributable to waste discharge from the facilities (within 5 km radius) was at least 1,000 times lower than the dose due to natural exposure (115).

There are disadvantages in determining excess risk from dose-response studies. For example, synergistic effects of multiple environmental exposures are not well understood. Gibson and Wheldon suggest synergistic effects between irradiation and chemical exposures may increase the potential of either factor to cause leukemia (40,119-120). Furthermore, Hoffman believes exposure assessments in the dose-response studies completed to date are generally limited because "routine environmental radiation surveillance can fail to detect chronic exposures from short-lived β-emitters or from extremely inhomogeneous spatial/temporal distributions of radionuclides. In fact, elevated rates of structural chromosomal aberrations in a casual sample of five parents of leukemia cases and four other adult Elbmarsch residents would be compatible with past releases of short-lived fission products, which might have been missed by routine surveillance (2.4 dicentric chromosomes/1,000 metaphases observed, 0.4/1,000 expected $p<0.0001$)" (40).

Other potential risk factors

There have been several studies that have identified other risk factors that have not been mentioned to this point. A list of the potential risk factors follows:

- Electromagnetic fields (121-124)
- Pesticides (125-129)
- Benzene (leukemia risk factor for all ages) (130)

Methodological Inconsistencies

Since many researchers and a large portion of the general population believe environmental contaminants (e.g. radiation, benzene, and pesticides) are a risk factor for several diseases including leukemia, childhood leukemia is often viewed as a marker for these environmental contaminants. Largely for this reason, clusters of childhood leukemias near nuclear facilities have become a "hot" topic that has lead to a multitude of studies. Within the multitude of studies, many types of bias and inconsistencies in methodology have surfaced:

- Age—the choice of which age group to study has not only varied between studies in different countries, it has also varied between studies of a single nuclear site. For example, French studies have consistently analyzed people between 0-24 years of age, German and Canadian studies have used the 0-14 age group, and British studies have chosen several age groups: 0-4, 0-9, 0-14, 0-24. The Sellafield studies alone have included the following age groups: 0-24 (as first published in the Black report (1)), 0-14, and 0-9.
- Endpoint—The most common cancer endpoints are all leukemias, acute leukemias, acute lymphatic leukemia (ALL), and non-Hodgkin's disease. Significant results have been found for each above stated group of cancers and for

different combinations (ex. ALL + non-Hodgkin's disease). The only neoplasm that has been included in every study is ALL. Although ALL is included in all studies, many studies have not been able to report results alone for ALL. This is often the case for mortality studies because data differentiating between types of leukemias is either missing or unreliable.

- Area—The choice of the area to study is arbitrary. Past choices have included: 5 km, 10 km, 12.5 km, 16 km, 25 km, 35 km, county, and even a single village. Since the choice of area is arbitrary (defined by an area with available census data), the choice naturally lends itself to selection bias. Too large a study area may also lead to a loss of power for detecting localized effects if the effect to be detected is small.
- When a single village is studied (ex. Seascale near Sellafield), they are usually chosen after a cluster has already been reported in the village. This is often the case for the studies that "revisit" an area around a putative site. Therefore, "they have as their goal the verification of the existence of this excess, and not the evaluation of the probability of rejecting the null hypothesis. This could exaggerate the proportion of excess leukemia cases in these areas" (7).
- Time-periods—Length of time studied varies greatly from study to study. The primary barrier is the availability of incidence/mortality data.
- Incidence/Mortality—Incidence data is generally preferable to mortality data because incidence data includes the address or census area where the person lived at date of diagnosis. This is a better indicator of where the person [may have] resided at time of exposure. Mortality data is more easily affected by a migration

bias. Incidence data also provides more confidence in determining the histologic type of neoplasm. However, mortality data also has an advantage—because of the publicity generated by health effects and nuclear facilities, registration/case ascertainment bias has appeared in some areas. Cook-Mozaffari found evidence of more complete ascertainment near British nuclear sites than in control areas chosen for comparison (21). Alexander noted clear indications of better case ascertainment in the 5 km area around the Kruemmel nuclear site (Germany) compared to other areas: 42% of the cases in the 5 km area were reported by three or more institutions compared to 20% in the 5-10 km area and 29%, 25%, and 31% in distant areas (64).

- Source of reference rates—The choice of reference rate effects the expected cases in an area. One must consider whether to use local or national rates and which covariates to include in determining the expected cases.
- Lack of information on exposure level has made dose-response relationships nonexistent in most studies.

Biology, Etiology, and US Incidence Rates

Biology of Leukemia:

Similar to many types of cancer, the leukemias can be defined by certain abnormal characteristics as described by (160):

- Monoclonal origin
- Acquired Gene Mutation
- Genetic instability, clonal diversification, and progressive subclone selection

- Dysregulation or uncoupling of critical cellular functions: proliferation, differentiation, and cell death
- Net growth advantage, clonal dominance, vascular and extravascular spread, and comprise of normal tissue functions.

In leukemia, only one abnormal stem cell is necessary to lead to the disease. The suspect cell must experience the mutation or more likely sequential series of mutations. Over 100 genes have been identified that are candidates for mutations leading to certain leukemia subtypes. Approximately 10^{11} blood cell divisions take place on a daily basis and when that is considered with respect to the probability of a gene mutation occurring in one cell cycle is 10^{-6}, it is likely that gene mutations are occurring all the time. However, most mutations are either functionally neutral for the cell or happen in non-important cells. In fact, it is the rarest of mutations that is truly a candidate for proliferation. The mutation must happen in a hematopoietic cell with renewal capacity and the necessary gene must be altered in a certain sequence that confers net growth and/or survival advantage on the clonal descendants of the original cell. While most carcinomas appear to require 5 to 15 mutations that may take several years, the leukemias may take only a few mutations, and in extraordinary cases perhaps only one. Age differences exist when considering the probability of developing leukemia (Table I.1). As an example, the lymphoid-restricted stem cells that can cause ALL, the dominant childhood leukemia, undergo extensive self-renewal early in life and therefore are at their most vulnerable.

As described by the American Cancer Society, the four major types of leukemia are acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic

lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). For our purposes, acute can be defined as rapidly growing cells that do not mature properly. On the other hand, chronic is a condition where the cells live too long and cause a build-up of white blood cells. Lymphocytic leukemias originate from lymphocytes in the bone marrow and myelogenous leukemias originate from one of two types of white blood cells: granulocytes or monocytes.

Etiology (161):

Chronic leukemias: Radiation can induce CML but not CLL. According to the Life Span Study, rates of ALL, AML, and CML increased among Japanese exposed to the atomic bomb. However, CLL rates did not increase in the same population, nor has CLL rates increased in other irradiated populations. (162) The majority of the CML cases in the Life Span Study were developed 5-10 years after exposure and concentrated in persons under 45 years of age. It appears that ionizing radiation at doses greater than 0.5 Grays may cause CML in humans. Although studies have found significant increases in acute leukemias in people exposed to certain chemicals, mainly benzene, the evidence does not support an increase in the chronic leukemias. Familial studies suggest that genetics play a larger role in the development of CLL than CML. Further, CLL patients are more likely to develop second cancers including melanomas, soft tissue sarcomas, and lung cancer. The excess of second cancers may be attributed to various reasons including genetic predisposition to other cancers, carcinogenic effects of treatment for CLL, or increased ascertainment due to medical attention for CLL. In the SEER population CLL incidence rates are less than 1 in 100,000 among persons under

age 50 and then quickly increase. For CML, one would expect between 1 and 2 in 100,000 between ages 20 to 50 years and a slower rise than CLL after that.

Acute leukemias: Studies have shown that radiation from nuclear reactions, occupational radiation, and therapeutic and diagnostic medical radiation can cause both ALL and AML. The use of certain chemotherapy agents has also been shown to cause AML, usually peaking 4-5 years after therapy. The only other chemical besides chemotherapy that has persuasive evidence that it may cause leukemia is benzene, mainly AML. Other positive associations have been found in petroleum refining, rubber manufacturing, and a slight increase in AML in smokers. However, these studies are only suggestive of a possible association. Familial studies have found that both ALL and AML may be caused by genetics. Acute leukemias can occur at all ages. Until age 25, ALL is the dominant leukemia. ALL has a distinctive peak at about age 2-5; whereas AML begins to increase after age 50.

Table I.1 - SEER Age-specific Incidence Rates, 1973-1991, per 100,000 (163)				
Age at Diagnosis	Acute Lymphatic Leukemia	Acute Myeloid Leukemia	Chronic Lymphatic Leukemia	Chronic Myeloid Leukemia
0-4	5.7	0.6	0.0	0.1
5-9	3.1	0.4	0.0	0.1
10-14	1.7	0.3	0.0	0.1
15-19	1.2	0.5	0.0	0.2
20-24	0.6	0.5	0.0	0.3
25-29	0.5	0.7	0.0	0.4
30-34	0.5	0.8	0.1	0.6
35-39	0.5	1.1	0.2	0.9
40-44	0.5	1.4	0.8	1.2
45-49	0.5	1.8	1.4	1.3
50-54	0.8	2.7	3.4	2.1
55-59	0.9	4.0	5.9	1.8
60-64	1.0	5.6	8.7	2.8
65-69	1.1	8.5	12.8	4.4
70-74	1.5	11.7	18.5	5.9
75-79	1.9	14.8	22.0	8.5
80-84	2.5	18.1	27.3	10.8
85+	2.1	15.7	34.5	12.7

3. MATERIALS AND METHODS

Meta-analysis

Study Identification

Studies were identified by a comprehensive literature search, review of references, government publications, and recommendations from researchers active in the field. The criteria used for inclusion were:

1. The study must be a cohort study examining leukemia in proximity of a nuclear site. A study must differentiate between leukemia and lymphoma.
2. The study must include at least two of the following three variables: observed, expected, or endpoint (SMR/SIR) for individual nuclear sites, as opposed to a summarization that includes multiple sites.
3. If a site has zero observed cases or deaths, it will be considered 0.01 for calculations. Using 0.01 is conservative in that it will never allow the rate to be greater than one (expected are only displayed to two decimal places).
4. The study must have at least one age category less than 26 (if a study includes age categories over the age of 26, only ages less than 26 will be used in the meta-analysis).
5. The study must indicate geographic zones in which cases or deaths occurred.

For multiple studies on the same cohort, the most complete study was used that met the study characteristics of interest for each analysis (defined below). The primary

criterion used to identify the most complete study was the longest time-interval, and the secondary criterion was the most recent publication.

Thirty-seven studies were identified for possible inclusion. Seventeen studies covering 146 nuclear sites in nine countries or former countries (East Germany) met the criteria for at least one analysis.

Statistical Methods

Since one of the inclusion criteria is that an endpoint had to be reported for individual nuclear sites, each site was considered as an individual study in the meta-analysis. After the appropriate subset of sites had been identified for each analysis, three separate models were used to calculate a meta-SMR and meta-SIR: an overall unadjusted (unweighted) model, a fixed effects model, and a random effects model.

The unadjusted (unweighted) model is the total observed cases or deaths divided by the total expected cases or deaths,

$$T = \frac{\sum O_i}{\sum E_i}$$

where:

T = effect size of pooled data (meta-SMR or meta-SIR)

O_i = observed cases or deaths in the i^{th} study

E_i = expected cases or deaths in the i^{th} study.

An alternative model to adjust for sample size is a fixed effects model using the inverse variance-weighted method (131). The model is:

$$T = \frac{\sum_{i=1}^{k} w_i T_i}{\sum_{i=1}^{k} w_i},$$

where:

T = effect size of pooled data (meta-SMR or meta-SIR)

T_i = observed effect size in the i^{th} study

w_i = weight in the i^{th} study.

The weight commonly used to minimize the variance of T is:

$$w_i = \frac{1}{v_i},$$

where v_i = variance in the i^{th} study (131-132).

The meta-analysis combines nuclear sites that perform different functions and are located in a multitude of environmental settings (with respect to topography, wind, etc.). It is unlikely that all studies estimate the same underlying effect size, a fixed effects model assumption. One way to account for variation in effect size is to use a random effects model. The random effects model is (131,133):

$$T_i = \theta_i + e_i,$$

where:

T_i = estimate of effect size in the i^{th} study

θ_i = true effect size in the i^{th} study

e_i = error with which T_i estimates θ_i , and

$$\text{var}(T_i) = \tau_\theta^2 + v_i ,$$

where:

τ_θ^2 = between study variance

v_i = within study variance in the i^{th} study.

The random effects model is weighted by the inverse of the sum of the between study variance and variance in the i^{th} study.

Forest plots were used to show each site's SMR or SIR and corresponding 95% confidence intervals on a logarithmic scale. Ninety-five percent confidence intervals were calculated by the method of exact Poisson confidence intervals for standardized mortality ratios (134). The forest plot contains several sites and visually represents the variability between estimates (131).

Heterogeneity was analyzed with a Chi-Square Test for Homogeneity (135) and graphically, with radial plots, which plot the z-statistic for each study against the reciprocal of its standard error (136):

$$Z = \frac{\log(\mathrm{SMR}_i) - \log(\mathrm{S}MR_{\mathrm{T}})}{\text{standard error}}, \qquad \text{and standard error} = \frac{1}{\sqrt{(O_i)}}$$

where:

$\mathrm{SMR_i}$ = may be either SMR or SIR for the *i*th study

$\mathrm{SMR_T}$ = may be either meta-SMR or meta-SIR

$\mathrm{O_i}$ = observed cases or deaths in the *i*th study.

The radial plot also includes an unweighted regression line constrained through the origin and corresponding 95% confidence regions. Studies located outside the 95% confidence regions contribute greatly to the heterogeneity (131).

Publication bias was analyzed with funnel plots, which plot the log of the treatment effect from individual studies and the inverse of their standard error (131). Publication bias results from a generally accepted belief that studies with significant results are more likely to be published than studies with non-significant results. If this is true for studies of childhood leukemia in proximity of nuclear sites, the funnel plot will be skewed.

Analysis

If childhood leukemia from radiation exposure is more likely in young children (i.e. 0-9 age group), an analysis of the 0-25 age group may not allow the excess risk to be identified. Similarly, if the population living within 10 km of the nuclear site is at a much higher risk than the population residing 10-25 km from the site, a study including all children residing within a 25 km radius of the nuclear site may again miss a small or even moderate excess risk to the 0-10 km population. Since the numerous studies examined several different age groups, geographic zones, and endpoint, it was not possible to calculate an overall meta-SIR or meta-SMR. Therefore, we developed multiple subsets of interest as defined in Table 3.1.

Table 3.1 - Stratification of Analysis

Analysis	Age Group[a]	Geographic Zone[a]	Endpoint
1	0-9	All	SIR
2	0-9	All	SMR
3	0-9	< 16 km[b]	SIR
4	0-9	< 16 km[b]	SMR
5	0-25	All	SIR
6	0-25	All	SMR
7	0-25	< 16 km[b]	SIR
8	0-25	< 16 km[b]	SMR

a. Contains all subsets within the defined range. If more than one study exists for a cohort, the study with the largest range within the defined range is used. For example, 0-9 age group may include a study that contains only 0-4 age group.
b. Rounded to the nearest kilometer. For example, 10 miles converts to 16.09 km; therefore it is considered 16 km.

Spatial and Temporal Analysis Near Pickering Nuclear Generator

Temporal Analysis

The traditional method used to analyze childhood leukemia around nuclear facilities is to calculate SIRs for blocks of time since the facility began operation, for example, the first 10 years after initial operation and then 11 years to present, or simply, before and after the facility began operation. A limitation with the method is that choosing time periods is arbitrary and may lead to bias. An alternative method to avoid the bias of arbitrary time frames is to use smoothed moving SIRs where researchers select a time width (ex. 5 or 10 year width) and calculate an SIR. Next, move the window by a

certain increment (ex. 3 years at a time) and again calculate the SIR. Breslow and Day suggest the following equation:

$$\hat{\theta}(t) = \frac{1}{y}\sum_{i=1}^{I} K\left(\frac{t-t_i}{b}\right)\frac{d_i}{R_i^+},$$

where, $\hat{\theta}(t)$ is the SIR estimate at time t, K(x) = smooth, positive kernel function, b = bandwidth that determines the degree of smoothness in the estimate, y = number of years for which a rate is calculated, d_i = the number of cases at time t_i, and R_i^+ is the total standard risk at time t_i (137). Rothman suggests using the following kernel:

$$K(x) = 1 - x^2, \qquad \text{when} \quad |x| < 1$$

$$= 0 \text{ otherwise.}$$

Note, using this weight, observations close to t are given the most weight, and observations at the end of the bandwidth (t_i close to b) are given less weight (138).

The standard error is

$$SE\,\hat{\theta}(t) = \frac{1}{y}\left[\sum_{i=1}^{I} K^2\left(\frac{t-t_i}{b}\right)\frac{d_i}{(R_i^+)^2}\right]^{1/2},$$

One could form a 100(1-α)% confidence interval using

$$\hat{\theta}(t) \pm Z_{\alpha/2} SE\,\hat{\theta}(t),$$

where $Z_{\alpha/2}$ = upper 1 - α/2 probability from a standard normal distribution.

Alternatively, we can use the log scale to better approximate a normal error distribution and get more accurate confidence intervals. The confidence intervals on the log-scale are given by

$$\log\hat{\theta}(t) \pm Z_{\alpha/2} * \left\{ SE(\hat{\theta}(t)) \right\} / \hat{\theta}(t).$$

Transforming back to the SMR scale, the confidence intervals for θ(t) are

$$\exp[\log\hat{\theta}(t) \pm Z_{\alpha/2} * \left\{ SE(\hat{\theta}(t)) \right\} / \hat{\theta}(t)]$$

Smoothed SIRs for 0-4 and 0-14 age groups were calculated and displayed graphically for the Pickering Nuclear Generator (PNG) area (within a 12.5 km radius) and three control areas.

Spatial Analysis

If one is testing whether there is increased risk due to a putative source (i.e. PNG), it makes sense to take the spatial relationship between the cases and the source into account (by giving greater weight to cases closer to the source). Focused cluster statistics have been designed for this reason. The Score Test of Lawson and Waller will be used in our study, as the test is more robust than other focused cluster tests. Generally, the Score Test has better power to detect increased risk in a variety of situations including smaller sample size, and a gradual decrease in risk with increased distance to the putative source. When the cases are clustered into only a few cells, commonly referred to as a 'Hot Spot', the Score test performs equal to similar tests (139).

In order to perform a focused cluster test, zones must be created around the source. The zones are aggregations of census regions. Any census region that has its centroid in a given zone can contribute only to that zone. The test statistic is:

$$U = \sum_{i=1}^{I} g_i (O_i - E_i)$$

where g_i is the exposure to the focus for an individual residing in region *i*. It has been shown, that the inverse of the distance (from the centroid of the region) may be used as a surrogate for exposure (140-141).

The expectation of *U* is zero under the null hypothesis and the variance is approximated by the Fisher information:

$$Var(U) \cong \sum_{i=1}^{I} g_i^2 E_i \ ,$$

U has an asymptotic standard normal distribution (139).

Exposure zones were created based solely on distance from the source. Five zones were used that were 2.5 km wide with the furthest zone 12.5 km from PNG. Exposure zones were also created based on prevailing wind direction at PNG (142).

Subject Selection

Data was obtained from Cancer Care Ontario. Criteria for inclusion into at least one of the analyses conducted included subjects less than 15 years of age that were diagnosed with leukemia (ICD-9, 204-208) between the years of 1971 and 2000.

Although childhood leukemia incidence data exists from 1964, Cancer Care Ontario was not confident in the completeness and accuracy of the data prior to 1971.

Geographic Area Selection

For the smoothed SIR analysis, the exposed population was comprised of census subdivisions that had their centroid within 12.5 km of PNG. The census subdivisions of Pickering (in which PNG is located) and Ajax met the criteria and were considered the primary exposed population.

Three control areas consisted of census subdivisions that are similar to Pickering/Ajax except for exposure to a nuclear facility. Using 1996 data, Pickering/Ajax and the control areas were matched on population density and geographic size. All census subdivisions in Ontario, without a nuclear facility, were examined individually for possible inclusion into the study. If a census subdivision met the criteria for population density but was too small in area, the next most densely populated adjoining census subdivision was combined with the selected census subdivision until the combined area met the criteria for density and area. The adjoining census subdivision must reside in the same census division as the selected census subdivision. The three control areas are as follows: Vaughan, Stoney Creek/Grimsby, and Niagara Falls/Welland/Thorold. Census Division population counts were also collected for the census divisions that contained the selected census subdivisions (Table 3.2). Census division and census subdivision population counts are collected every five years; therefore, linear interpolation was used to estimate counts for non-reported years.

Table 3.2. Exposed Study Area and Control Areas

Census Subdivision	Census Division
Pickering/Ajax	Durham
Vaughan	York
Stoney Creek/Grimsby	Hamilton-Wentworth
Niagara Falls/Welland/Thorold	Niagara

For the spatial analyses, enumeration areas were used. Enumeration areas are the smallest geographical area for which census data are reported in Canada. Enumeration areas have a maximum of 440 dwellings in urban areas and a minimum of 125 dwellings in rural areas. Since enumeration area data was not collected until 1986, the analyses were performed on data from 1986-2000. Similar to census subdivisions, enumeration areas population counts are collected every five years and linear interpolation was used to estimate population counts for non-reported years.

Software

All statistical analyses were conducted with SAS 8.2. All mapping, including assigning enumeration areas to zones was done with ArcView 3.2.

4. RESULTS

Meta-analysis

Table 4.1 lists the studies that appeared in at least one analysis. Individual sites and values are listed in the Appendix. Table 4.2 shows the number of sites included for each analysis.

Table 4.1: Studies of Childhood Leukemia and Nuclear Facilities used in the Meta-Analysis

Study	Country	Endpoint	Age Group[a]	Zone (km)[a]
COMARE III, 1989 (109)	Great Britain	I/M	0-9, 0-14, 0-24	<10, <16
Goldsmith, 1992 (23)	Great Britain	I/M	0-9	<16
Ewings *et al.*, 1989 (19)	Great Britain	I	0-24	District[b], <12.5
Baron, 1984 (17)	Great Britain	M	0-14	<8
Clarke *et al.*, 1989 (11)	Canada	I/M	0-4	County[b]
Clarke *et al.*, 1991 (12)	Canada	I/M	0-14	County[b]
Viel et al., 1995 (34)	France	I	0-4, 0-24	<10, <35
Viel and Richardson, 1990 (32)	France	M	0-4, 0-24	<35
Hattchouel *et al.*, 1995 (38)	France	M	0-25	<16
Jablon *et al.*, 1990 (143)	USA	I/M	0-9, 0-19	County[b]
Mohner and Stabenow, 1993 (144)	East Germany	I	0-14	<15
Heasman *et al.*, 1987 (145)	Scotland	I	0-24	<12.5
COMARE II, 1988 (8)	Scotland	I	0-24	<12.5, < 25
Hole and Gillis, 1986 (146)	Scotland	I	0-14	Adj Post Codes[b]
Kaletsch *et al.*, 1997 (147)	West Germany	I	0-14	<15
Iwasaki *et al.*, 1995 (46)	Japan	M	0-14	District[b]
Lopez-Abente *et al.*, 1999 (49)	Spain	M	0-24	<15, <30

a. Categories used in at least one analysis.
b. Considered greater than 16 km.

Table 4.2 - Number of Sites by Analysis

Analysis	Age Group	Geographic Zone	Endpoint	Number of sites
1	0-9	All	SIR	22
2	0-9	All	SMR	76
3	0-9	< 16 km	SIR	13
4	0-9	< 16 km	SMR	14
5	0-25	All	SIR	50
6	0-25	All	SMR	115
7	0-25	< 16 km	SIR	41
8	0-25	< 16 km	SMR	37

A total of one hundred forty-six sites were used in at least one analysis (Burghfield was included in Aldermaston data due to the close proximity of the sites). Seventeen studies reported 70 SIRs and 193 SMRs that met the analysis criteria for the various sites. Five sites in the USA were excluded due to zero observed deaths and expected could not be calculated because only observed and SMR were reported. When all geographic zones were used, SMRs were reported at least twice as often as SIRs. However, when geographic zones were restricted to < 16 km, SIRs were reported more often than SMRs. The great disparity between reporting SIRs and SMRs can be attributed to the sites in the USA. Jablon reported 116 SMRs for USA sites, as compared to 8 SIRs, that met the criteria (143). The USA study was conducted at the county level and the sites are assigned to 'All' geographic region, which also accounts for the disparity in number of sites between 'All' and '< 16 km' geographic regions.

Analysis 1

Analysis 1 was restricted to the following conditions:

- SIR
- 0 - 9 age group
- All zones

Twenty-two sites from Great Britain, Canada, France, and the United States met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.794, suggesting that the effect sizes are homogenous. This is further confirmed by studying the radial plot in Figure 4.1.1. All studies are scattered homoscedastically within two standard deviations of the line, whose gradient represents the meta-rate from a fixed effects model. The radial plot also can be used to indicate the size of the study. The smaller the study, the larger the standard error and consequently, the closer the study will be to the y-axis (131). In this case, studies 006, 169, and 353 are far from the y-axis and contribute greatly to the meta-rate. Meta-rates are presented in Table 4.3 for all three models described in the methods section. Meta-rates are significantly greater than one at the alpha=0.05 level of significance.

Table 4.3 – Meta-SIR, Age Group = 0-9, Geographic Zone = 'All'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.21	(1.10, 1.33)	1.25	(1.13, 1.38)	1.24	(1.12, 1.38)

The Forest Plot (Figure 4.1.2) indicates that the site-specific rates were consistently greater than one. Forest Plots contain the site-specific rates and the overall meta-rate and their corresponding 95% confidence intervals. Forest Plots can be misleading in that the smaller the horizontal bar representing the confidence range, the larger the study. Therefore, the site with the smallest bar contributes greatly to the

pooled rate and the site with the largest bar contributes the least. In this analysis, site 006 is the largest study (smallest bar) and site 018 is the smallest study (largest bar). Looking at the forest plot, it is difficult to rule out heterogeneity.

An important bias to consider when conducting a meta-analysis is publication bias. It is often the case that statistically significant results are more likely to be published than nonsignificant results. Publication bias is unlikely with regard to childhood leukemia and nuclear sites as many of the nuclear sites in the world have had a study conducted and published in either a scientific journal or government document. However, to be prudent publication bias was checked with the aid of a funnel plot (Figure 4.1.3). A "funnel" shaped scattering of the studies with approximately equal tails indicates that publication bias is not present. There does not appear to be publication bias.

Figure 4.1.1 – Radial Plot for Meta-SIR, Age Group = 0-9, Geographic Zone = 'All'

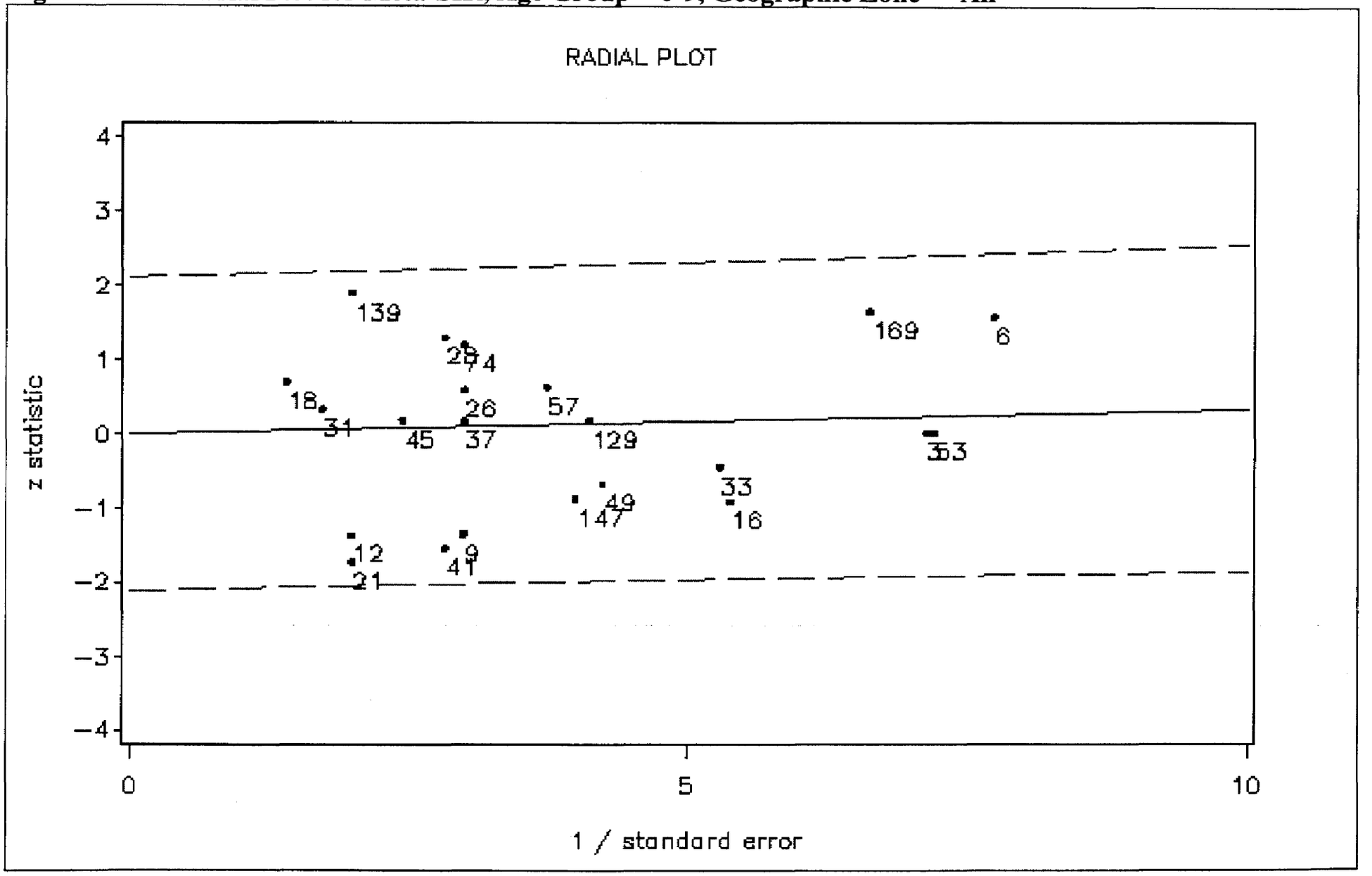


Figure 4.1.2 – Forest Plot for Random-Effects Meta-SIR, Age Group = 0-9, Geographic Zone = 'All'

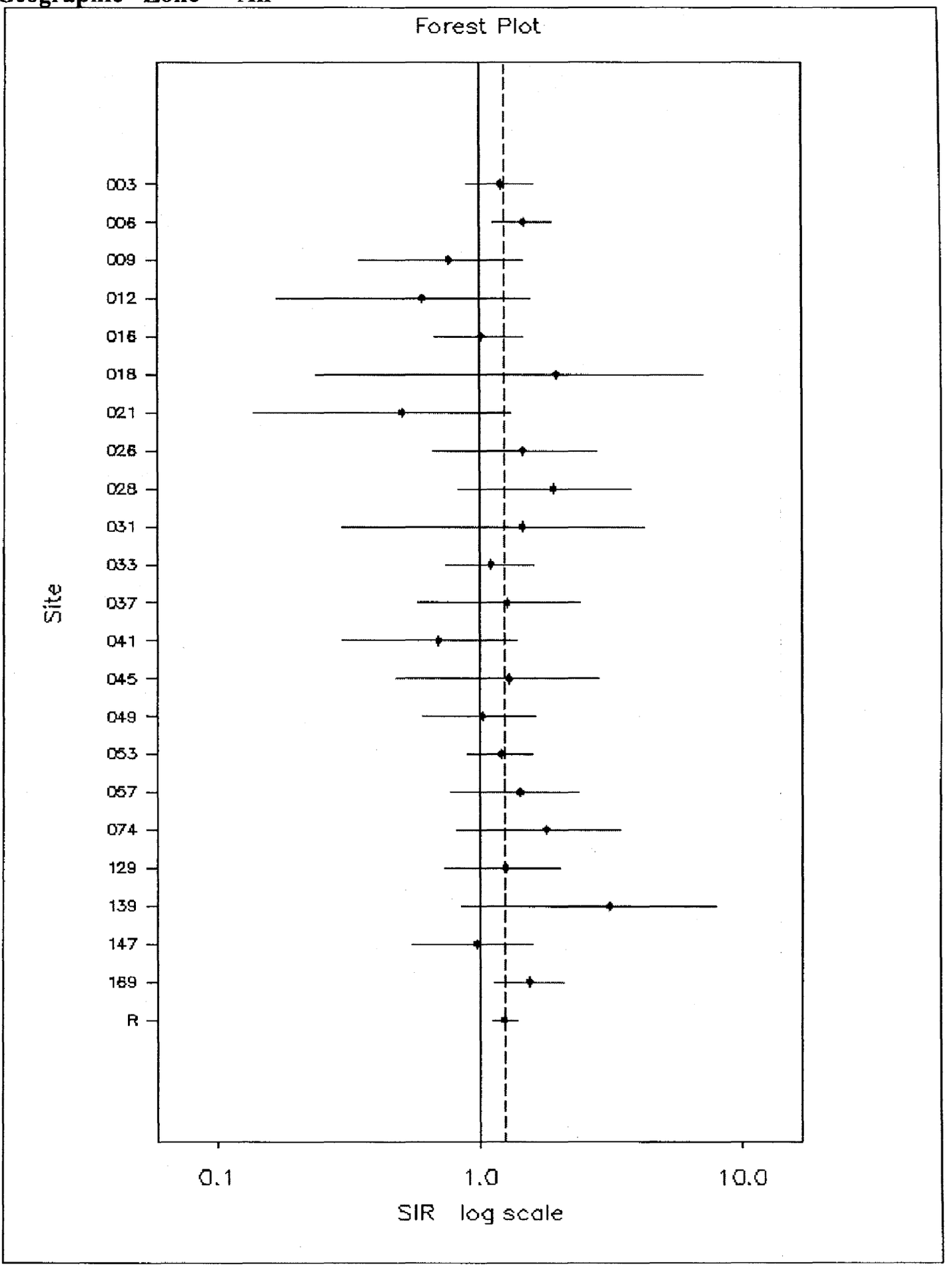
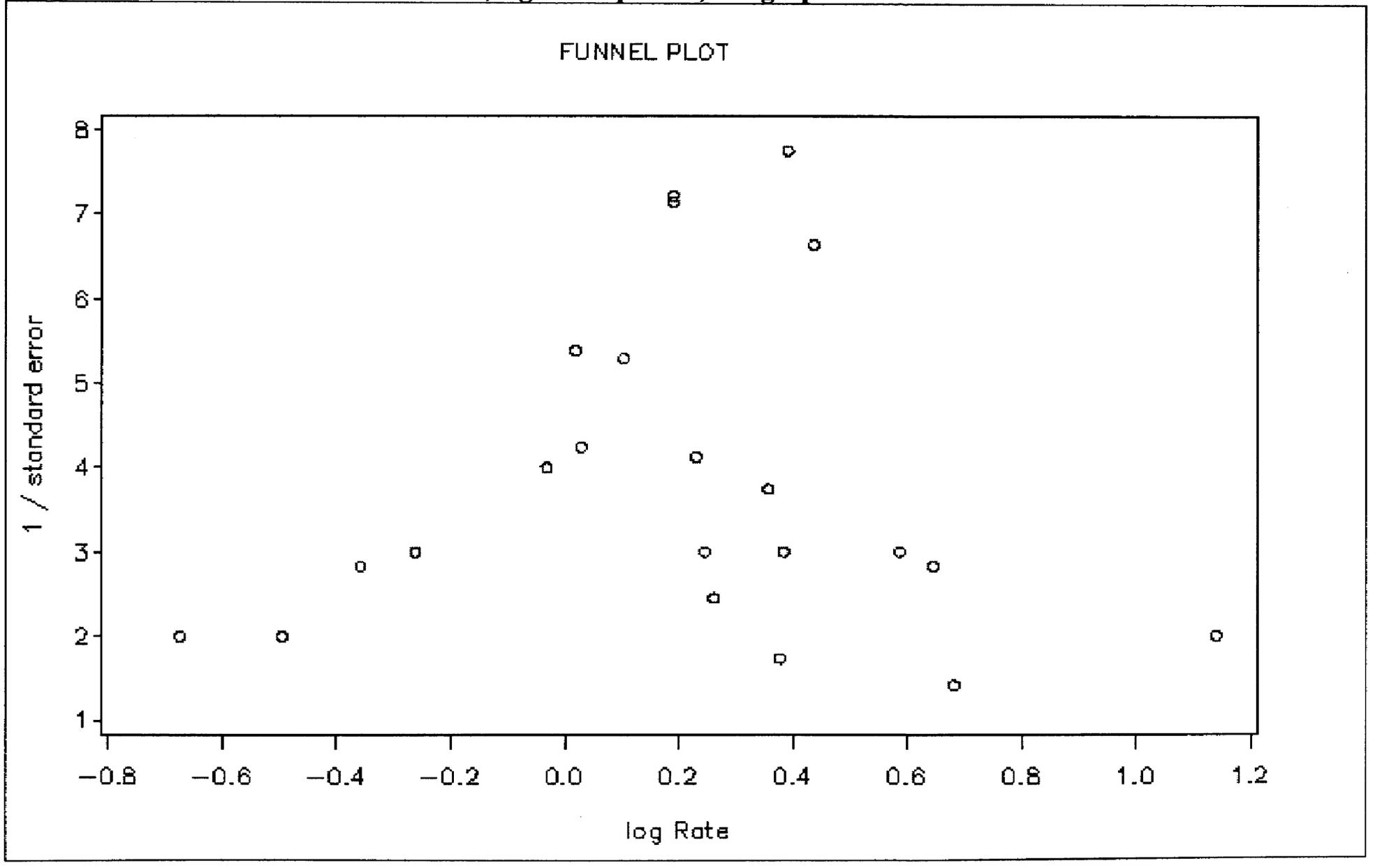


Figure 4.1.3 – Funnel Plot for Meta-SIR, Age Group = 0-9, Geographic Zone = 'All'



Analysis 2

Analysis 2 was restricted to the following conditions:

- SMR
- 0 - 9 age group
- All zones

Seventy-six sites from Great Britain, Canada, France, and the United States met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.302, suggesting that the effect sizes are homogenous. However, the radial plot in Figure 4.2.1 indicates sites 203 and 233 may be contributing to heterogeneity. Since sites 135, 173, and 211 are located far from the y-axis, they may be contributing greatly to the meta-rate. Meta-rates are presented in Table 4.4.1 for all three models described in the methods section. Meta-rates are significantly greater than one for the fixed effects and random effects model. The unadjusted model has a lower confidence band below one.

Table 4.4.1 – Meta-SMR, Age Group = 0-9, Geographic Zone = 'All'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.03	(0.98, 1.08)	1.06	(1.01, 1.11)	1.06	(1.01, 1.12)

The analysis was rerun without sites 203 and 233. Although the change in overall results was slight, the fixed effects model was no longer statistically significant (Table 4.4.2).

Table 4.4.2 – Meta-SMR, Age Group = 0-9, Geographic Zone = 'All', Excluding Sites that may be Contributing to Heterogeneity

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.03	(0.98, 1.08)	1.05	(1.00, 1.11)	1.05	(1.01, 1.11)

The Forest Plot (Figure 4.2.2) indicates that the site-specific rates generally remained near one, although many of the larger studies had rates greater than one. The funnel plot (Figure 4.2.3) does not indicate evidence of publication bias.

Figure 4.2.1 – Radial Plot for Meta-SMR, Age Group = 0-9, Geographic Zone = 'All'

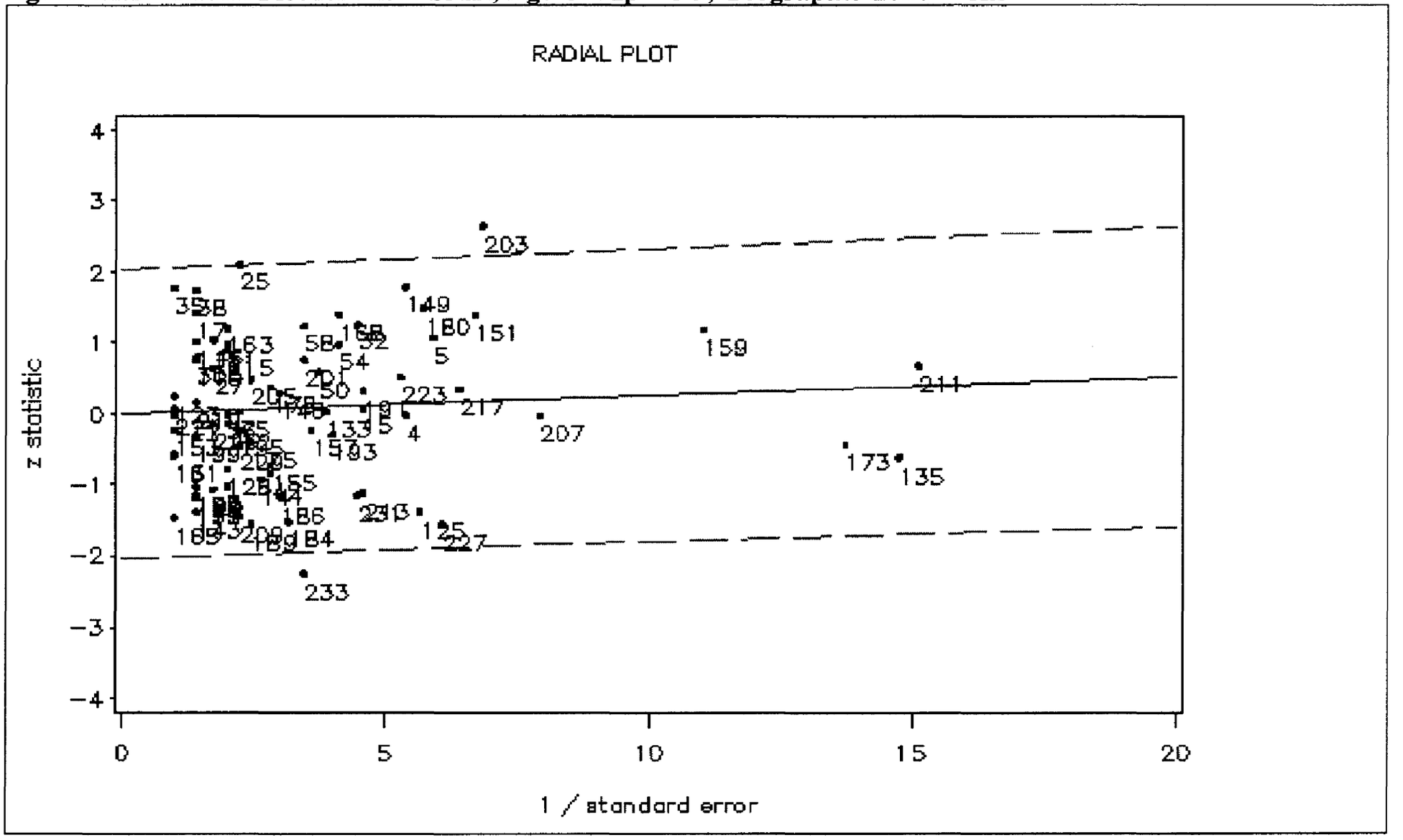


Figure 4.2.2 – Forest Plot for Random-Effects Meta-SMR, Age Group = 0-9, Geographic Zone = 'All'

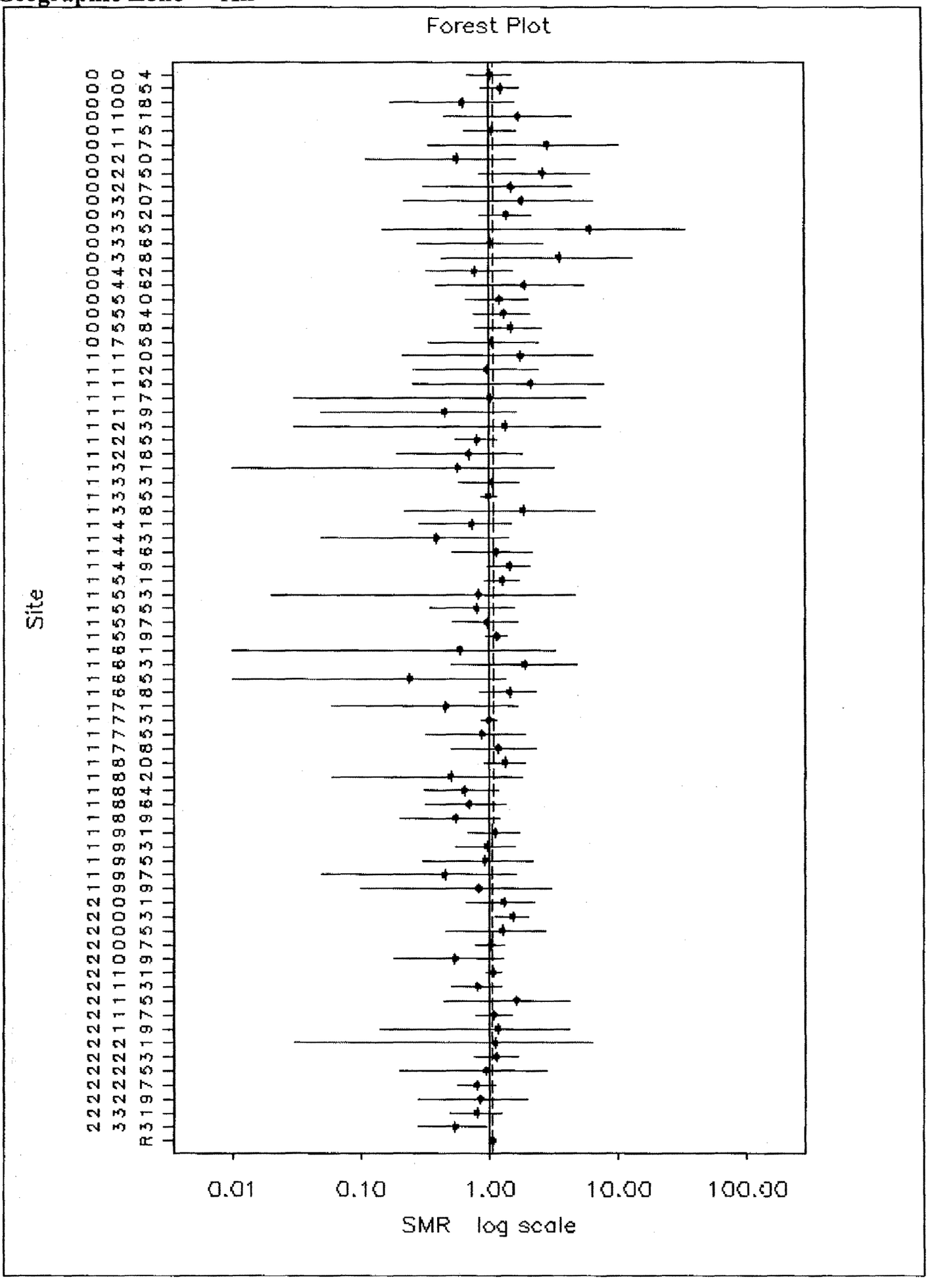
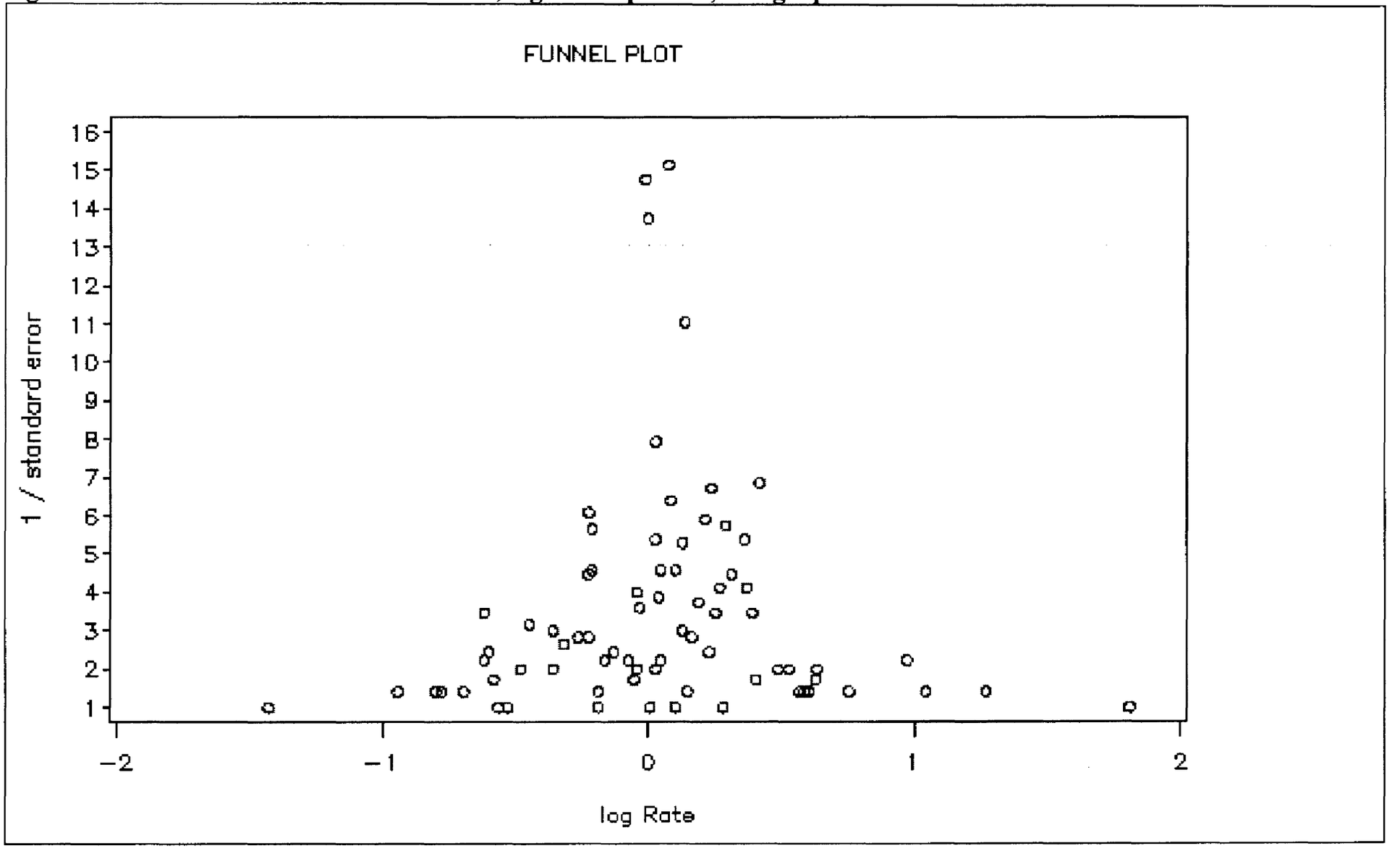


Figure 4.2.3 – Funnel Plot for Meta-SMR, Age Group = 0-9, Geographic Zone = 'All'



Analysis 3

Analysis 3 was restricted to the following conditions:

- SIR
- 0 - 9 age group
- < 16 km geographic zone

Twelve sites from Great Britain and one site from France met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.314, suggesting that the effect sizes are homogenous. This is further confirmed by studying the radial plot in Figure 4.3.1 where all studies are scattered homoscedastically within two standard deviations of the line. Since sites 003 and 006 are located far from the y-axis, they may be contributing greatly to the meta-rate. Meta-rates are presented in Table 4.5 for all three models described in the methods section. Meta-rates are significantly greater than one for all models.

Table 4.5 – Meta-SIR, Age Group = 0-9, Geographic Zone = '< 16 km'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.18	(1.04, 1.35)	1.23	(1.07, 1.40)	1.22	(1.05, 1.41)

The Forest Plot (Figure 4.3.2) indicates that the site-specific rates were generally greater than one. Although there are only thirteen sites, the funnel plot (Figure 4.3.3) does not indicate evidence of publication bias.

Figure 4.3.1 – Radial Plot for Meta-SIR, Age Group = 0-9, Geographic Zone = '< 16 km'

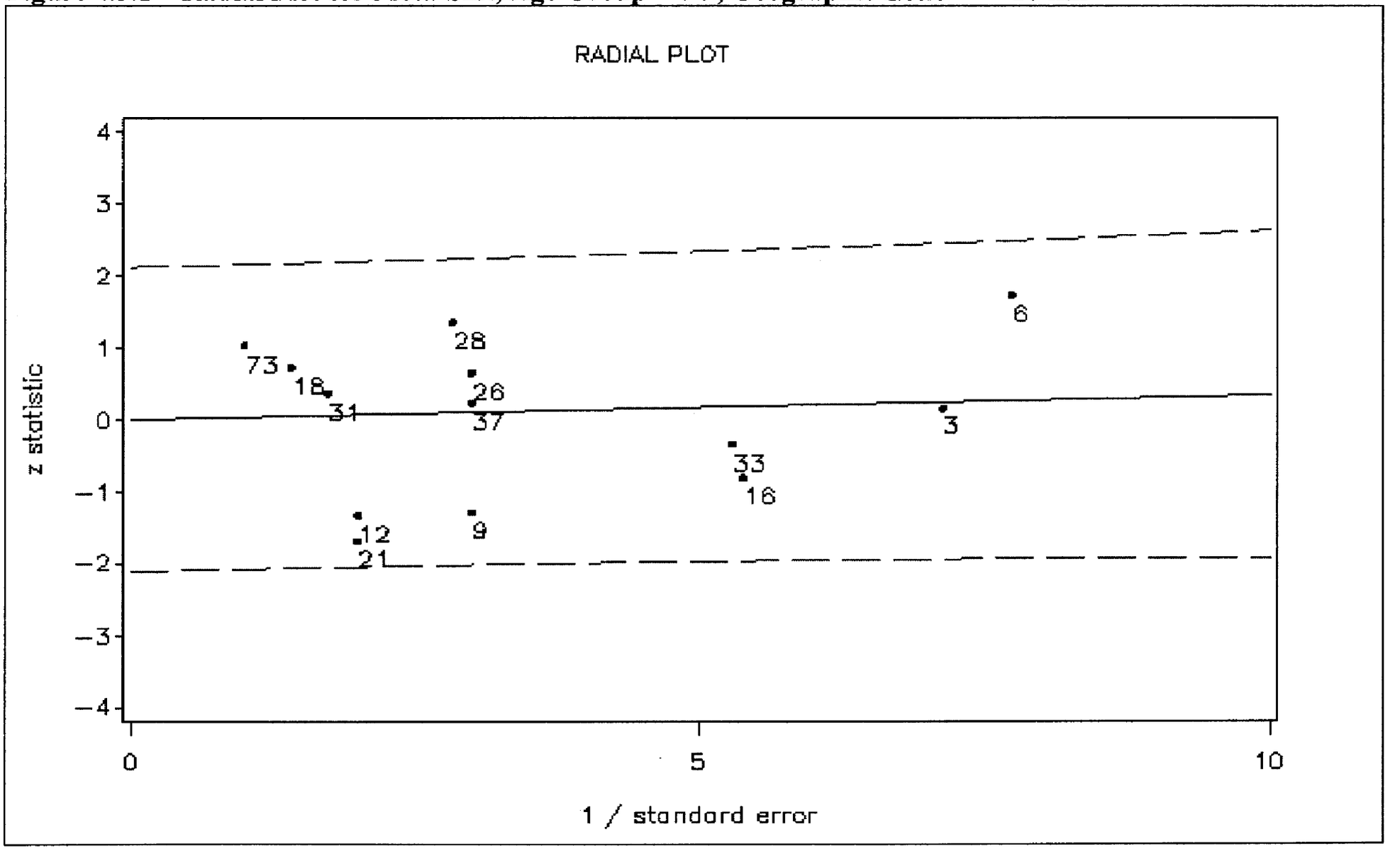


Figure 4.3.2 – Forest Plot for Random-Effects Meta-SIR, Age Group = 0-9, Geographic Zone = '< 16 km'

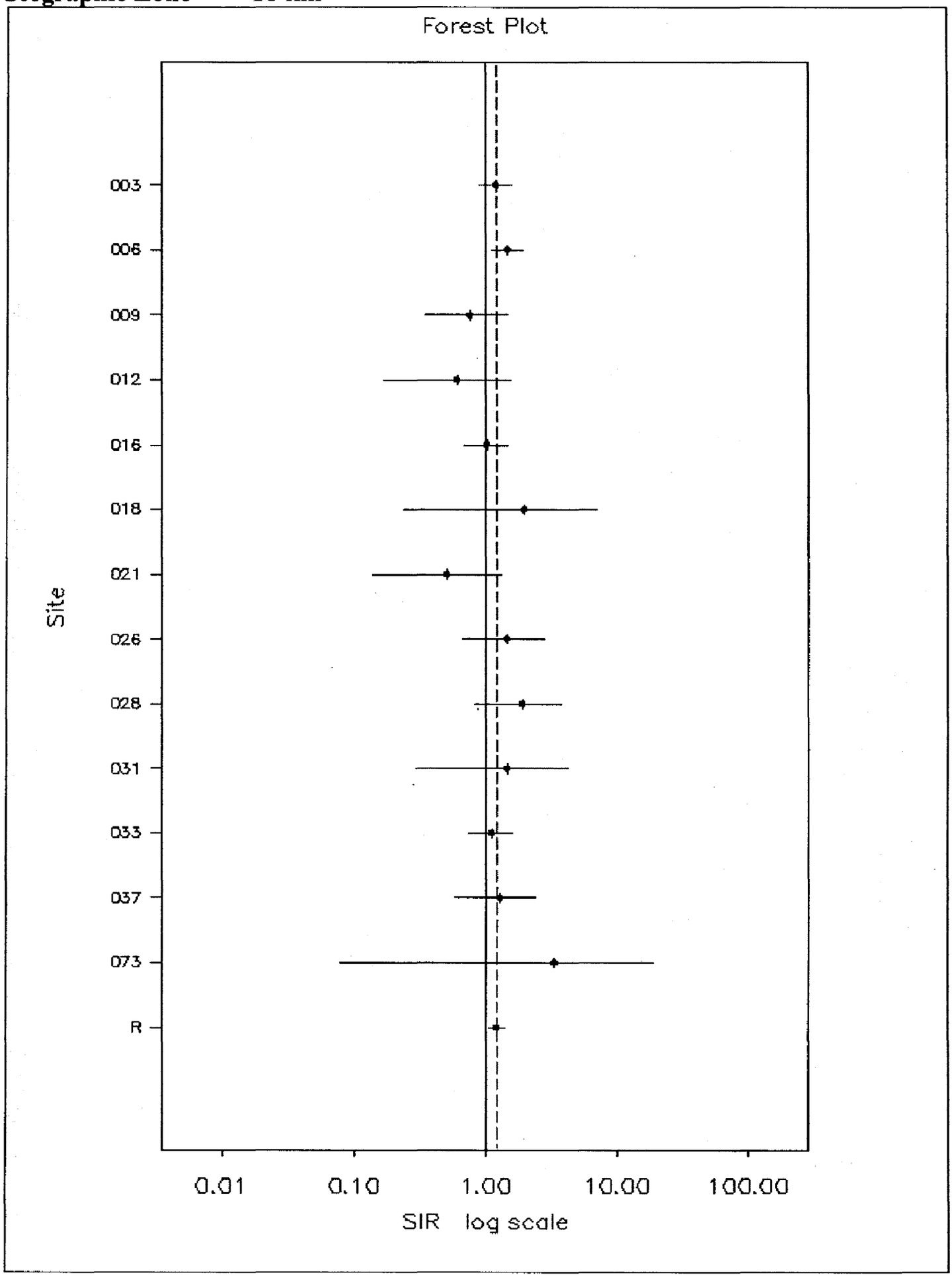
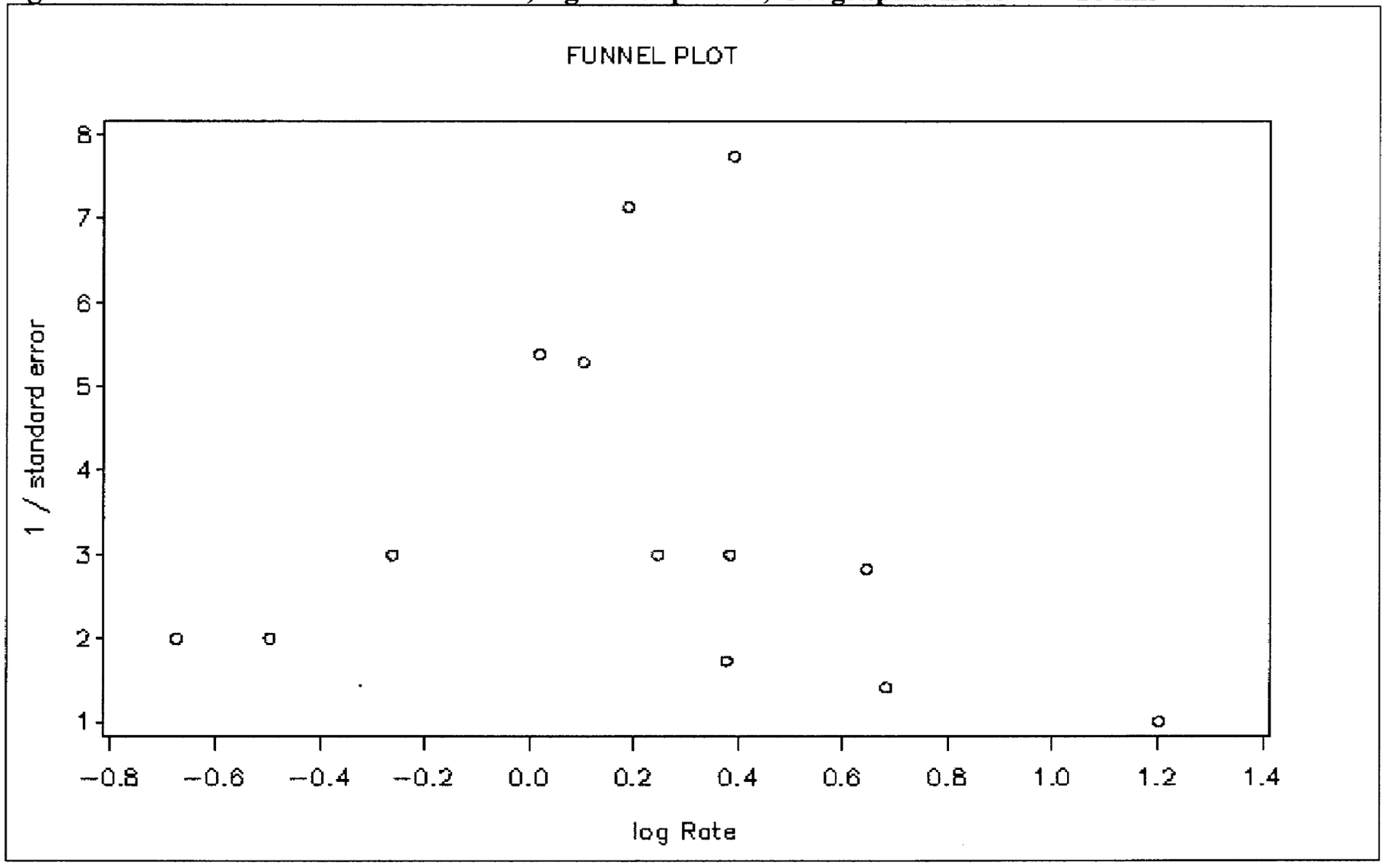


Figure 4.3.3 – Funnel Plot for Meta-SIR, Age Group = 0-9, Geographic Zone = '< 16 km'



Analysis 4

Analysis 4 was restricted to the following conditions:

- SMR
- 0 - 9 age group
- < 16 km geographic zone

Fourteen sites from Great Britain met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.275, suggesting that the effect sizes are homogenous. This is further confirmed by studying the radial plot in Figure 4.4.1 where all studies are scattered homoscedastically within two standard deviations of the line. Since sites 004, 005, 015 and 032 are located far from the y-axis, they may be contributing greatly to the meta-rate. Meta-rates are presented in Table 4.6 for all three models described in the methods section. Meta-rates are significantly greater than one for the fixed effects and random effects model. The unadjusted model has a lower confidence band below one.

Table 4.6 – Meta-SMR, Age Group = 0-9, Geographic Zone = '< 16 km'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.17	(0.99, 1.38)	1.23	(1.04, 1.46)	1.24	(1.03, 1.50)

The Forest Plot (Figure 4.4.2) indicates that the site-specific rates were generally greater than one. Although there are only fourteen sites, the funnel plot (Figure 4.4.3) appears to be skewed to the left indicating there may be publication bias. However, this could be an artifact of too few studies appearing in the funnel plot.

Figure 4.4.1 – Radial Plot for Meta-SMR, Age Group = 0-9, Geographic Zone = '< 16 km'

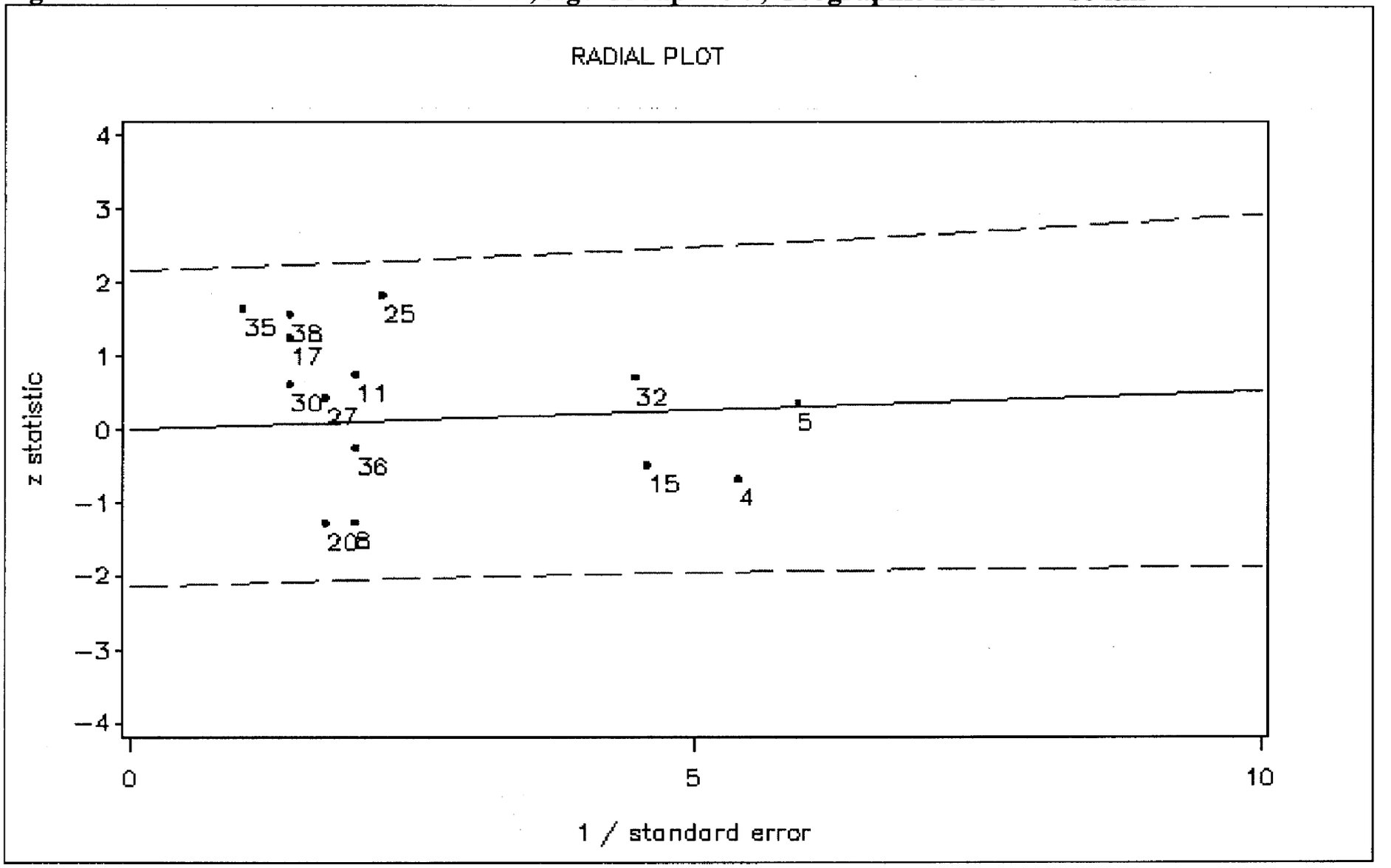


Figure 4.4.2 – Forest Plot for Random-Effects Meta-SMR, Age Group = 0-9, Geographic Zone = '< 16 km'

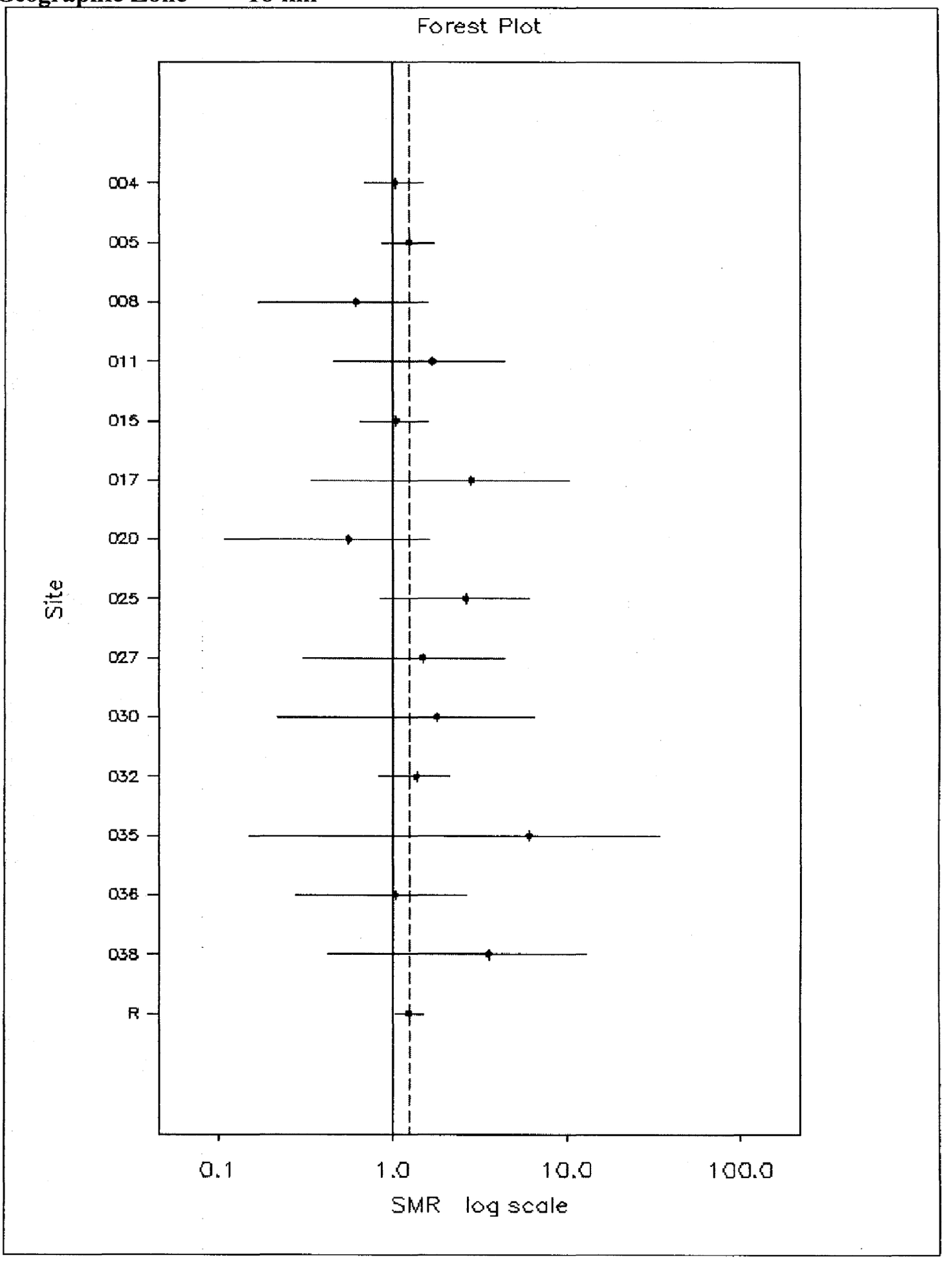
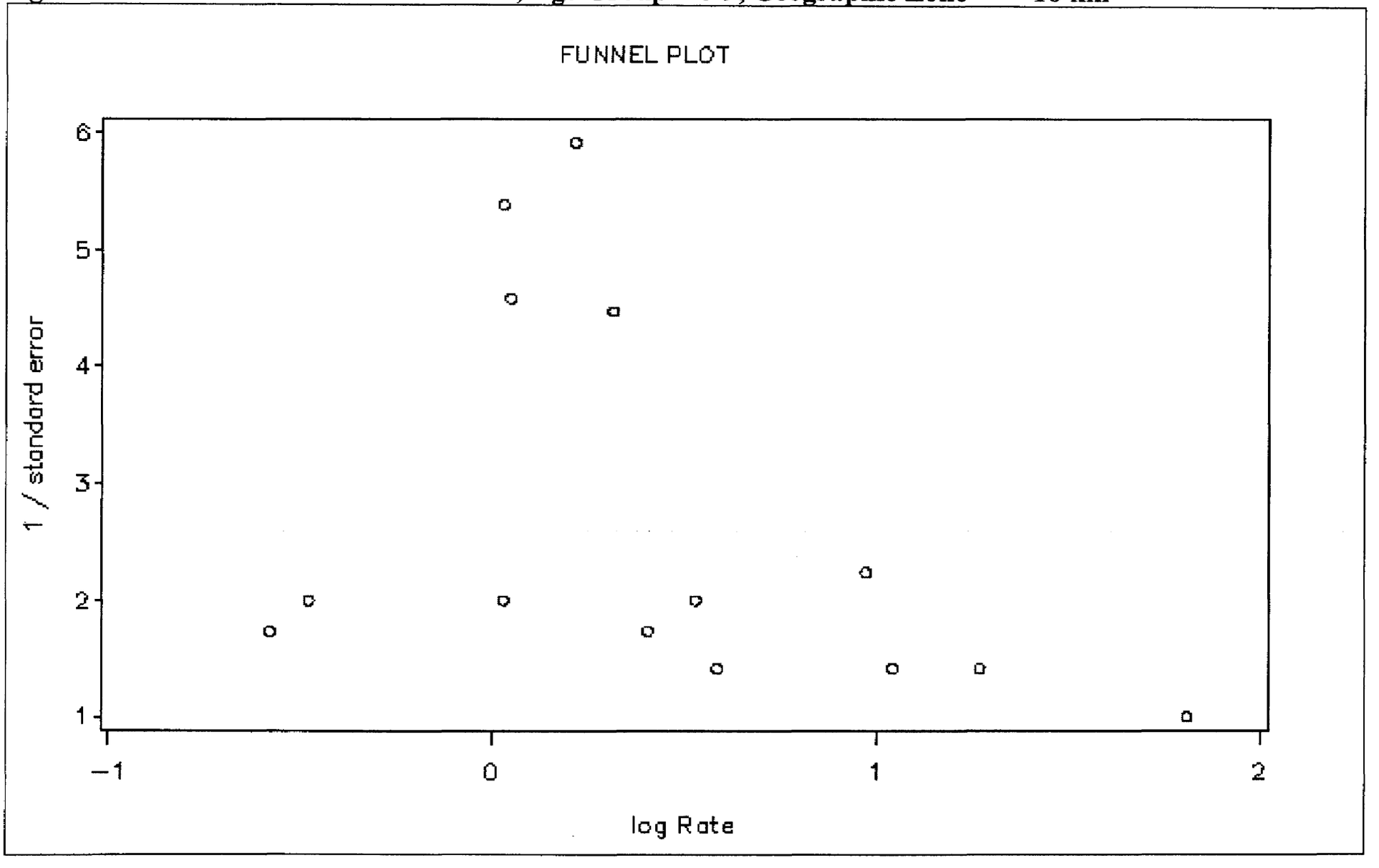


Figure 4.4.3 – Funnel Plot for Meta-SMR, Age Group = 0-9, Geographic Zone = '< 16 km'



Analysis 5

Analysis 5 was restricted to the following conditions:

- SIR
- 0 - 25 age group
- All geographic zones

Fifty sites from Great Britain, Canada, France, United States, Scotland, West Germany, and East Germany met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.598, suggesting that the effect sizes are homogenous. However, the radial plot in Figure 4.5.1 indicates that site 006 may be contributing to heterogeneity. Since sites 001, 024, 051 and 242 are located far from the y-axis, they may be contributing greatly to the meta-rate. Meta-rates are presented in Table 4.7.1 for all three models described in the methods section. Meta-rates are significantly greater than one for all models.

Table 4.7.1 – Meta-SIR, Age Group = 0-25, Geographic Zone = 'All'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.10	(1.04, 1.16)	1.12	(1.06, 1.18)	1.12	(1.06, 1.18)

The analysis was rerun without sites 006. There was no change in statistical significance for the three models (Table 4.7.2).

Table 4.7.2 – Meta-SIR, Age Group = 0-25, Geographic Zone = 'All', Excluding Sites that may be Contributing to Heterogeneity

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.08	(1.02, 1.15)	1.10	(1.04, 1.17)	1.10	(1.04, 1.17)

The Forest Plot (Figure 4.5.2) indicates that the site-specific rates generally remained near one, although many of the larger studies had rates greater than one. The funnel plot (Figure 4.5.3) does not indicate evidence of publication bias.

Figure 4.5.1 – Radial Plot for Meta-SIR, Age Group = 0-25, Geographic Zone = 'All'

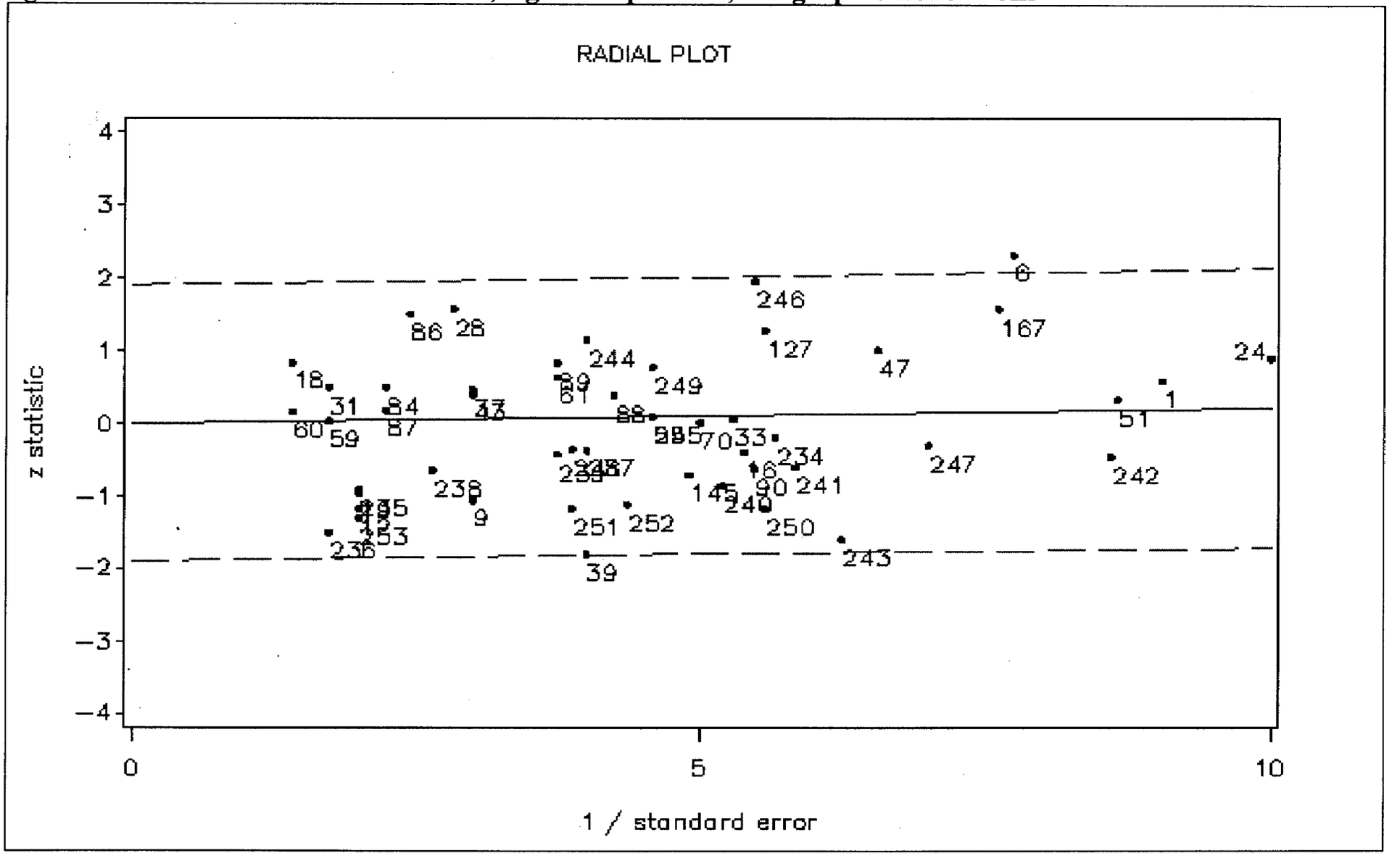


Figure 4.5.2 – Forest Plot for Random-Effects Meta-SIR, Age Group = 0-25, Geographic Zone = 'All'

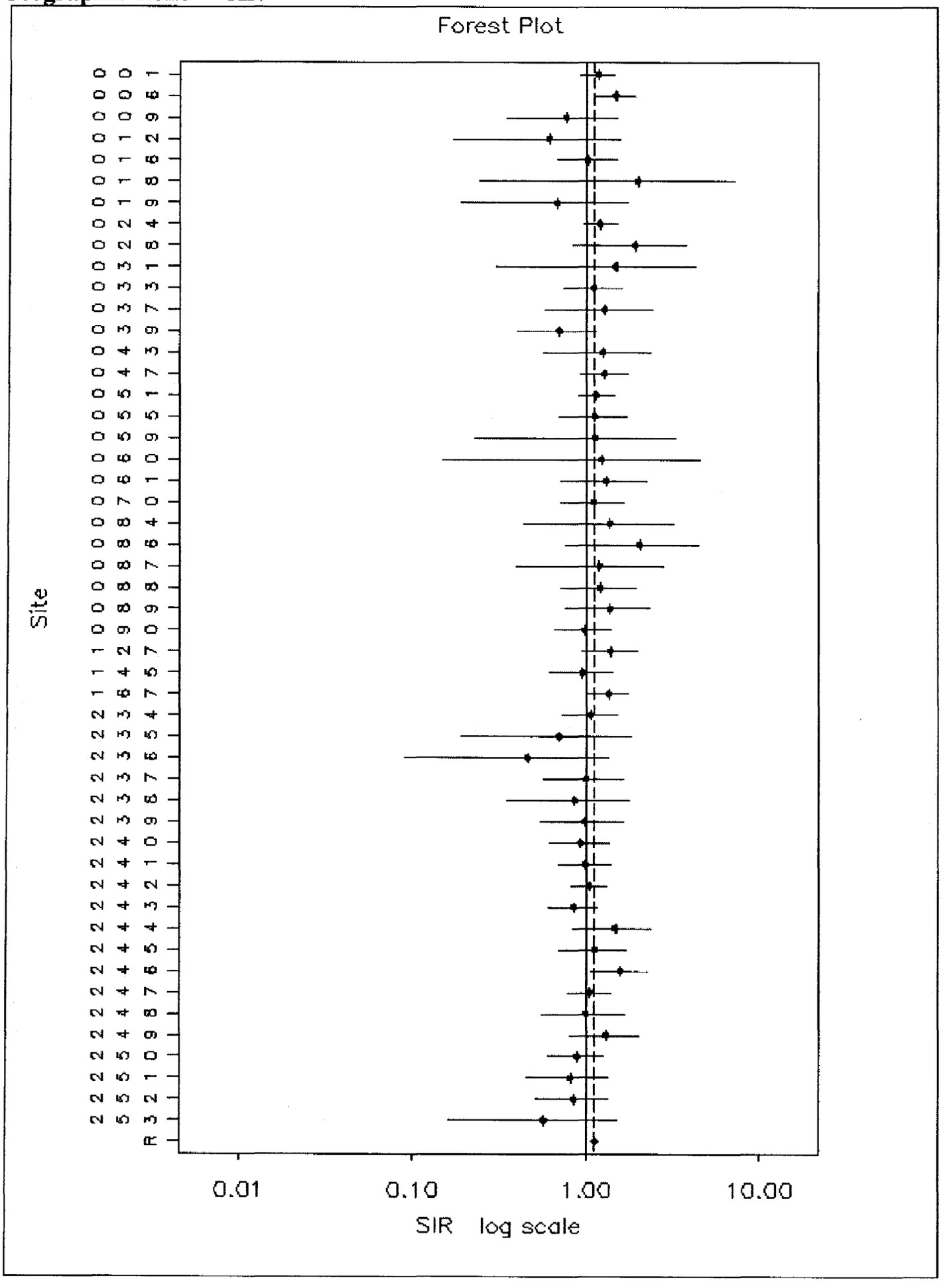
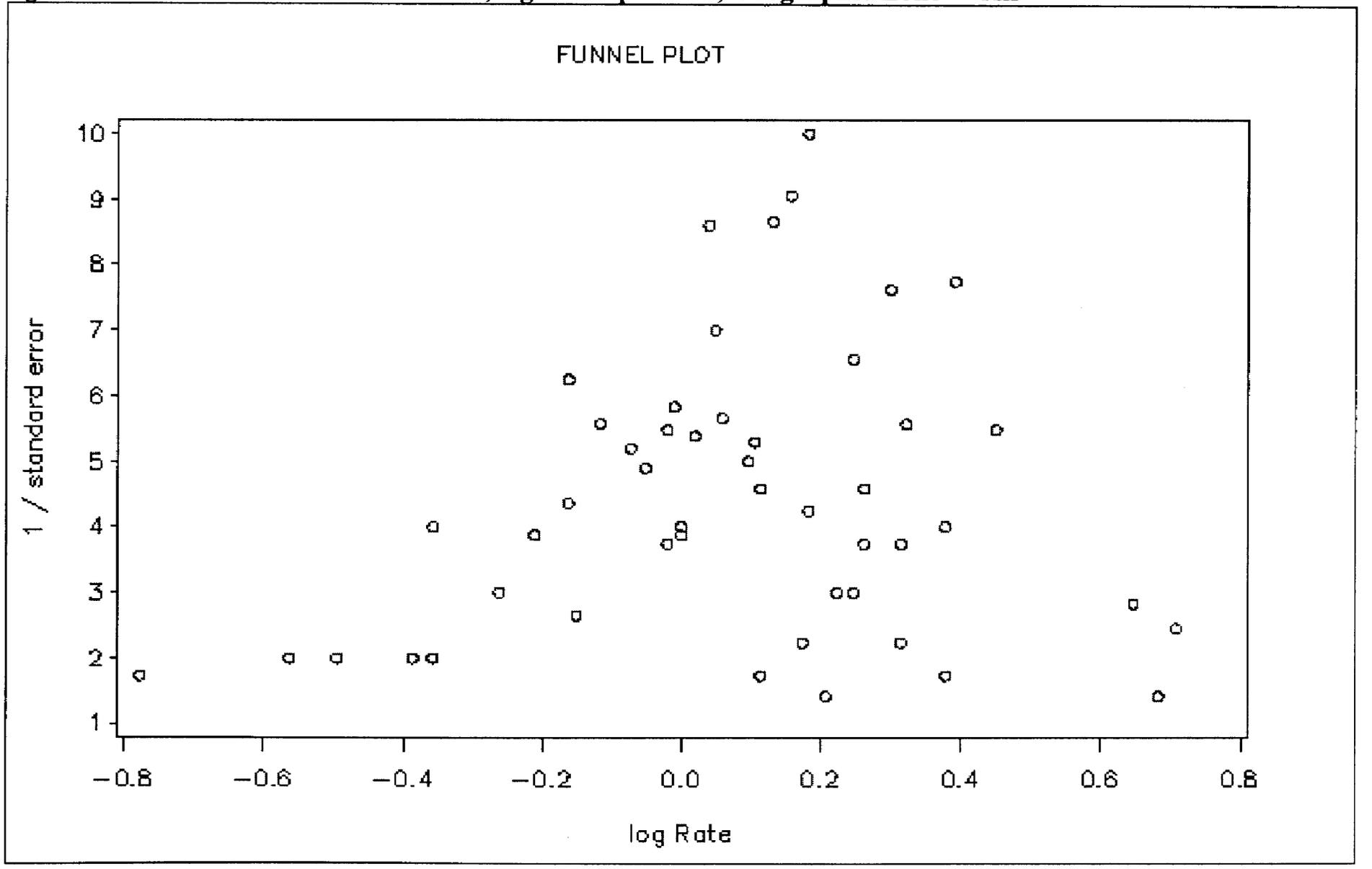


Figure 4.5.3 – Funnel Plot for Meta-SIR, Age Group = 0-25, Geographic Zone = 'All'



Analysis 6

Analysis 6 was restricted to the following conditions:

- SMR
- 0 - 25 age group
- All geographic zones

One hundred and fifteen sites from Great Britain, Canada, France, Japan, Spain, and United States met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.183, suggesting that the effect sizes are homogenous. However, the radial plot in Figure 4.6.1 indicates that sites 080, 124, 202, and 232 may be contributing to heterogeneity. Since sites 134, 128, 172 and 210 are located far from the y-axis, they may be contributing greatly to the meta-rate. Meta-rates are presented in Table 4.8.1 for all three models described in the methods section. Meta-rates are greater than one for all models but none are significant.

Table 4.8.1 – Meta-SMR, Age Group = 0-25, Geographic Zone = 'All'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.00	(0.96, 1.03)	1.02	(0.98, 1.06)	1.02	(0.98, 1.06)

The analysis was rerun without the sites that may be contributing to heterogeneity. There was no change in rates or confidence intervals for the three models (Table 4.8.2).

Table 4.8.2 – Meta-SMR, Age Group = 0-25, Geographic Zone = 'All', Excluding Sites that may be Contributing to Heterogeneity

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.00	(0.96, 1.04)	1.02	(0.98, 1.06)	1.02	(0.98, 1.06)

The Forest Plot (Figure 4.6.2) indicates that the site-specific rates scattered around one. The funnel plot (Figure 4.6.3) does not indicate evidence of publication bias.

Figure 4.6.1 – Radial Plot for Meta-SMR, Age Group = 0-25, Geographic Zone = 'All'

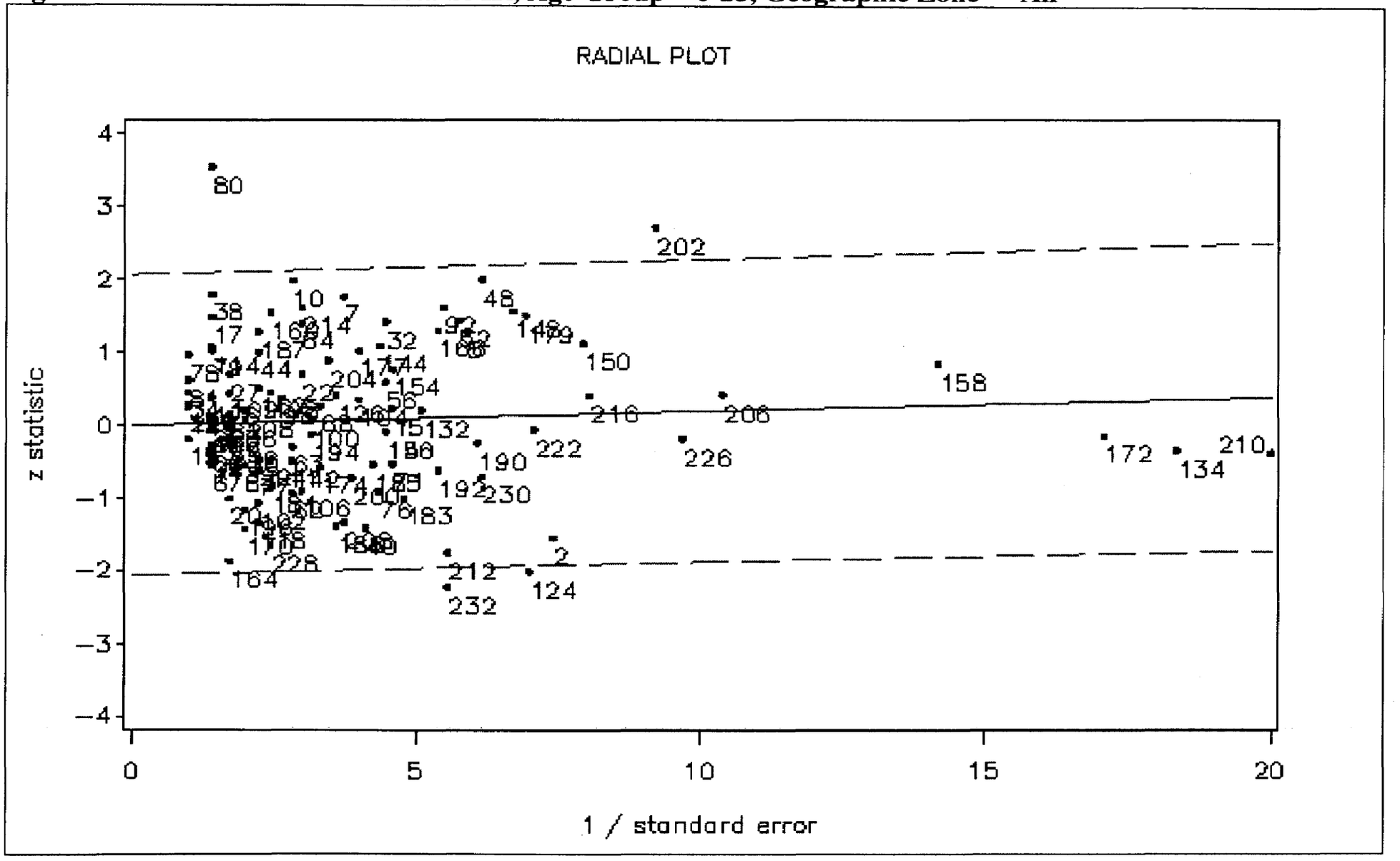


Figure 4.6.2 – Forest Plot for Random-Effects Meta-SMR, Age Group = 0-25, Geographic Zone = 'All'

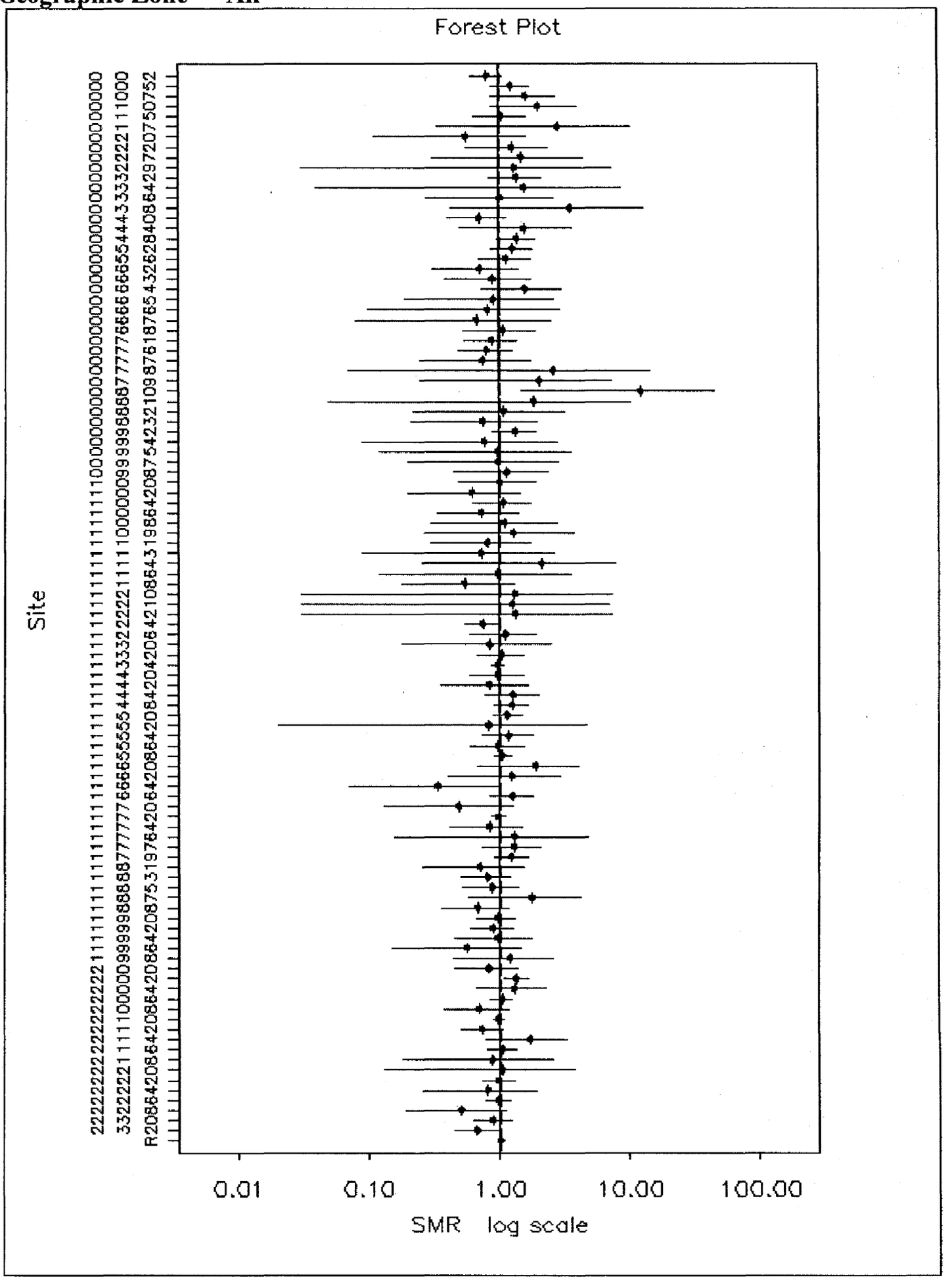
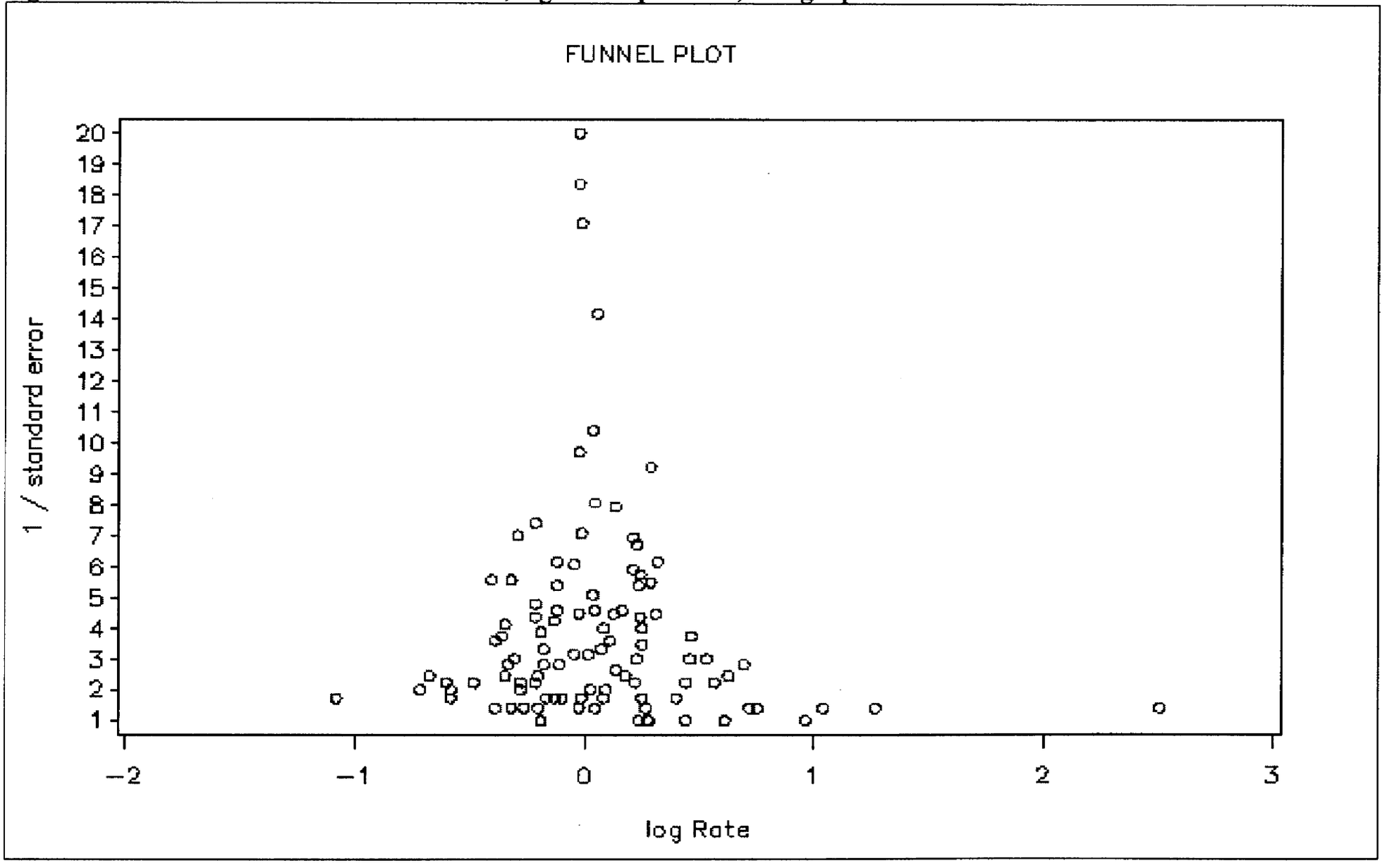


Figure 4.6.3 – Funnel Plot for Meta-SMR, Age Group = 0-25, Geographic Zone = 'All'



Analysis 7

Analysis 7 was restricted to the following conditions:

- SIR
- 0 - 25 age group
- < 16 km geographic zone

Forty-one sites from Great Britain, France, Scotland, West Germany, and East Germany met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.243, suggesting that the effect sizes are homogenous. However, the radial plot in Figure 4.7.1 indicates that sites 006 and 085 may be contributing to heterogeneity. Since sites 001, 006, and 242 are located far from the y-axis, they may be contributing greatly to the meta-rate. Meta-rates are presented in Table 4.9.1 for all three models described in the methods section. Meta-rates are significantly greater than one for all models.

Table 4.9.1 – Meta-SIR, Age Group = 0-25, Geographic Zone = '< 16 km'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.08	(1.01, 1.15)	1.11	(1.03, 1.18)	1.10	(1.03, 1.19)

The analysis was rerun without the sites that may be contributing to heterogeneity. Meta-rates remain greater than one but were no longer significant (Table 4.9.2).

Table 4.9.2 – Meta-SIR, Age Group = 0-25, Geographic Zone = '< 16 km', Excluding Sites that may be Contributing to Heterogeneity

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.05	(0.98, 1.13)	1.02	(0.98, 1.06)	1.07	(1.00, 1.15)

The Forest Plot (Figure 4.7.2) indicates that the site-specific rates scattered around one with many of the larger studies greater than one. The funnel plot (Figure 4.7.3) does not indicate evidence of publication bias.

Figure 4.7.1 – Radial Plot for Meta-SIR, Age Group = 0-25, Geographic Zone = '< 16 km'

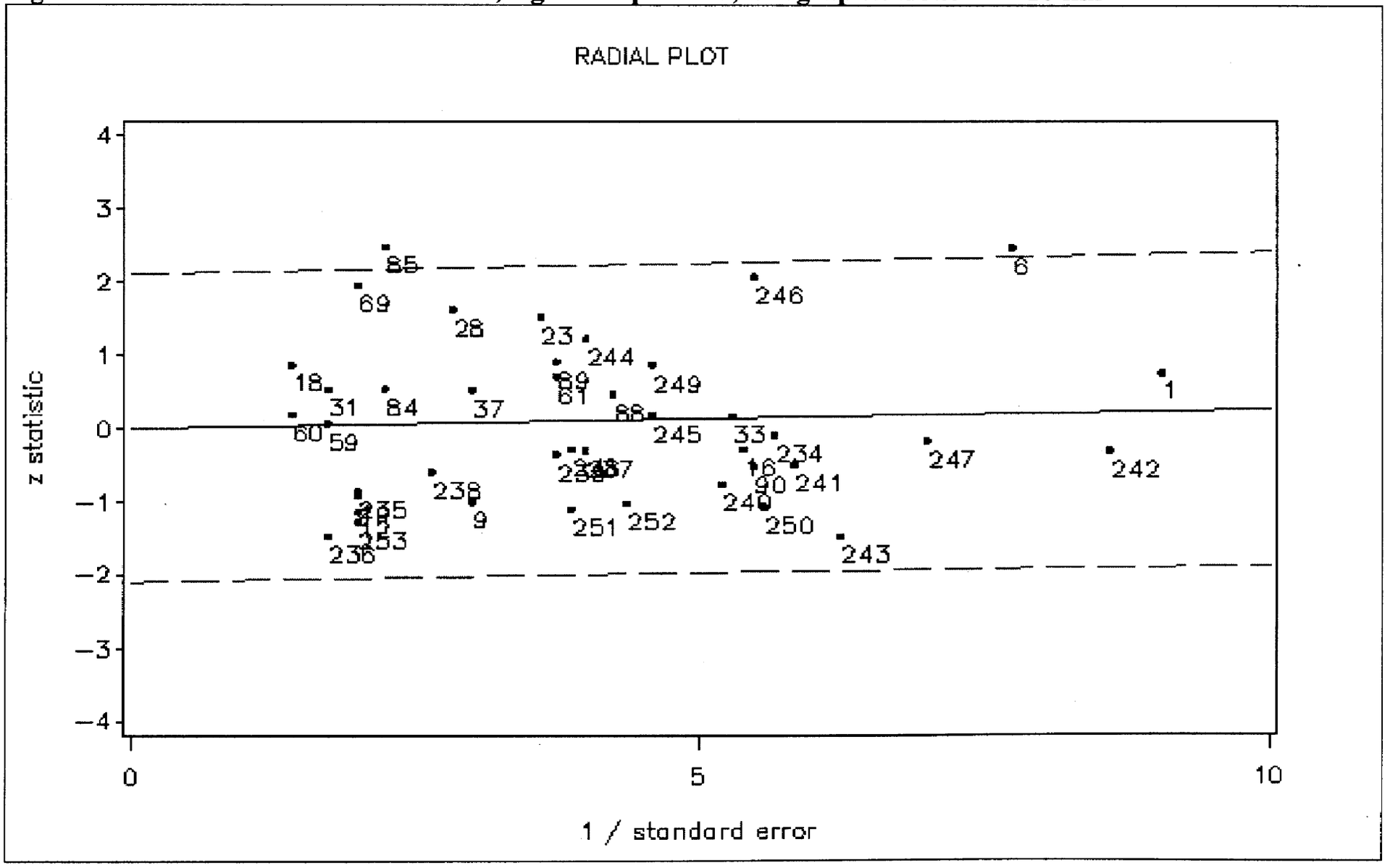


Figure 4.7.2 – Forest Plot for Random-Effects Meta-SIR, Age Group = 0-25, Geographic Zone = '< 16 km'

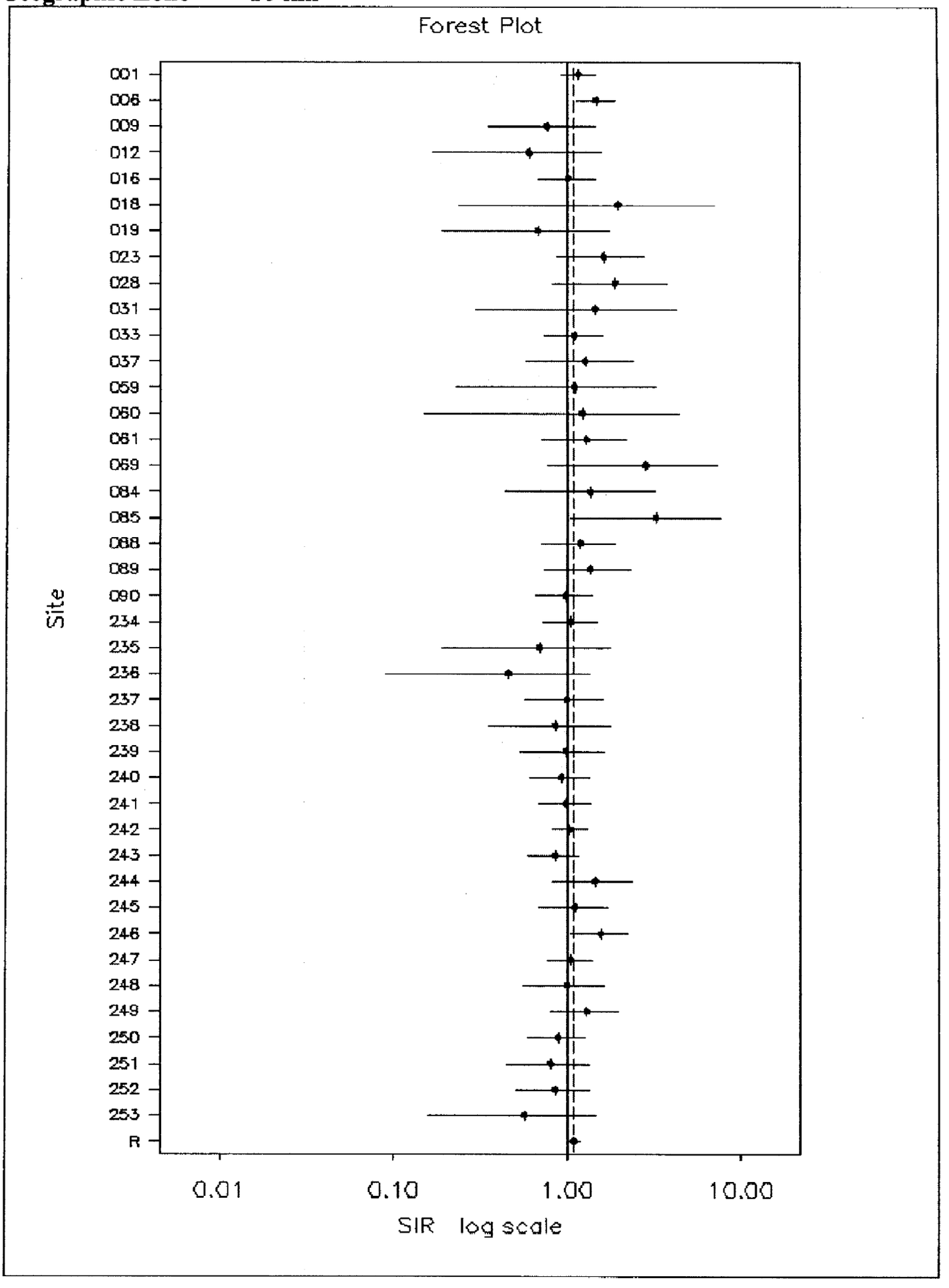
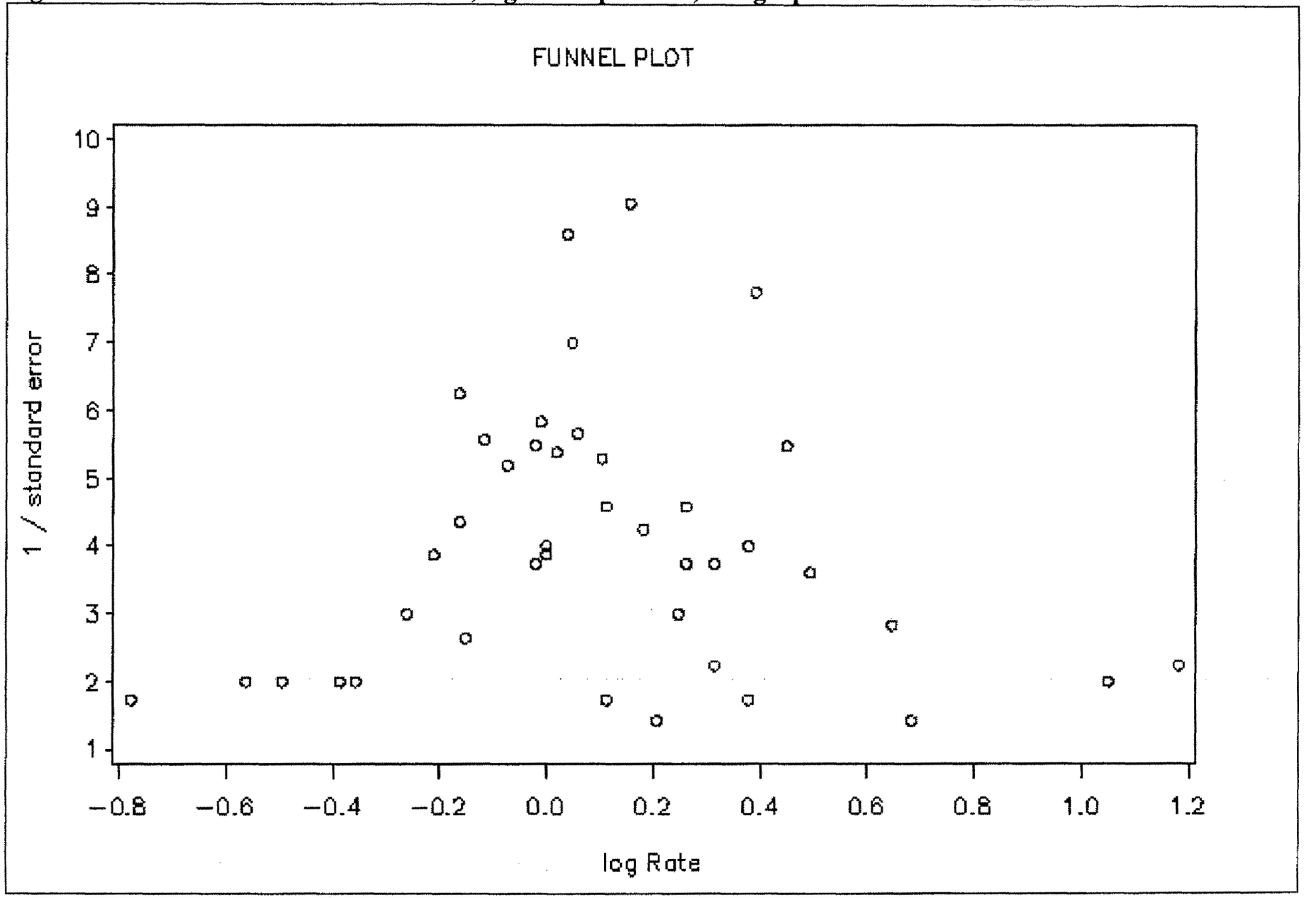


Figure 4.7.3 – Funnel Plot for Meta-SIR, Age Group = 0-25, Geographic Zone = '< 16 km'



Analysis 8

Analysis 8 was restricted to the following conditions:

- SMR
- 0 - 25 age group
- < 16 km geographic zone

Thirty-seven sites from Great Britain, France, Japan, and Spain met the criteria. Cochran Chi-Square Test for Homogeneity produced a p-value=0.440, suggesting that the effect sizes are homogenous. However, the radial plot in Figure 4.8.1 indicates that site 002 may be contributing to heterogeneity. Since site 002 is located far from the y-axis, the site with possible heterogeneity may be contributing greatly to the meta-rate. Meta-rates are presented in Table 4.10.1 for all three models described in the methods section. Meta-rates are greater than one for all models, but none are significant.

Table 4.10.1 – Meta-SMR, Age Group = 0-25, Geographic Zone = '< 16 km'

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.01	(0.90, 1.14)	1.09	(0.97, 1.23)	1.09	(0.97, 1.23)

The analysis was rerun without the sites that may be contributing to heterogeneity. Meta-rates increased and fixed effects and random effects models were now statistically significant (Table 4.10.2).

Table 4.10.2 – Meta-SMR, Age Group = 0-25, Geographic Zone = '< 16 km', Excluding Sites that may be Contributing to Heterogeneity

Unadjusted		Fixed Effects		Random Effects	
Rate	95% CI	Rate	95% CI	Rate	95% CI
1.08	(0.94, 1.23)	1.18	(1.03, 1.34)	1.18	(1.03, 1.34)

The Forest Plot (Figure 4.8.2) indicates that the site-specific rates scattered around one. The funnel plot (Figure 4.8.3) does not indicate evidence of publication bias.

Figure 4.8.1 – Radial Plot for Meta-SMR, Age Group = 0-25, Geographic Zone = '< 16 km'

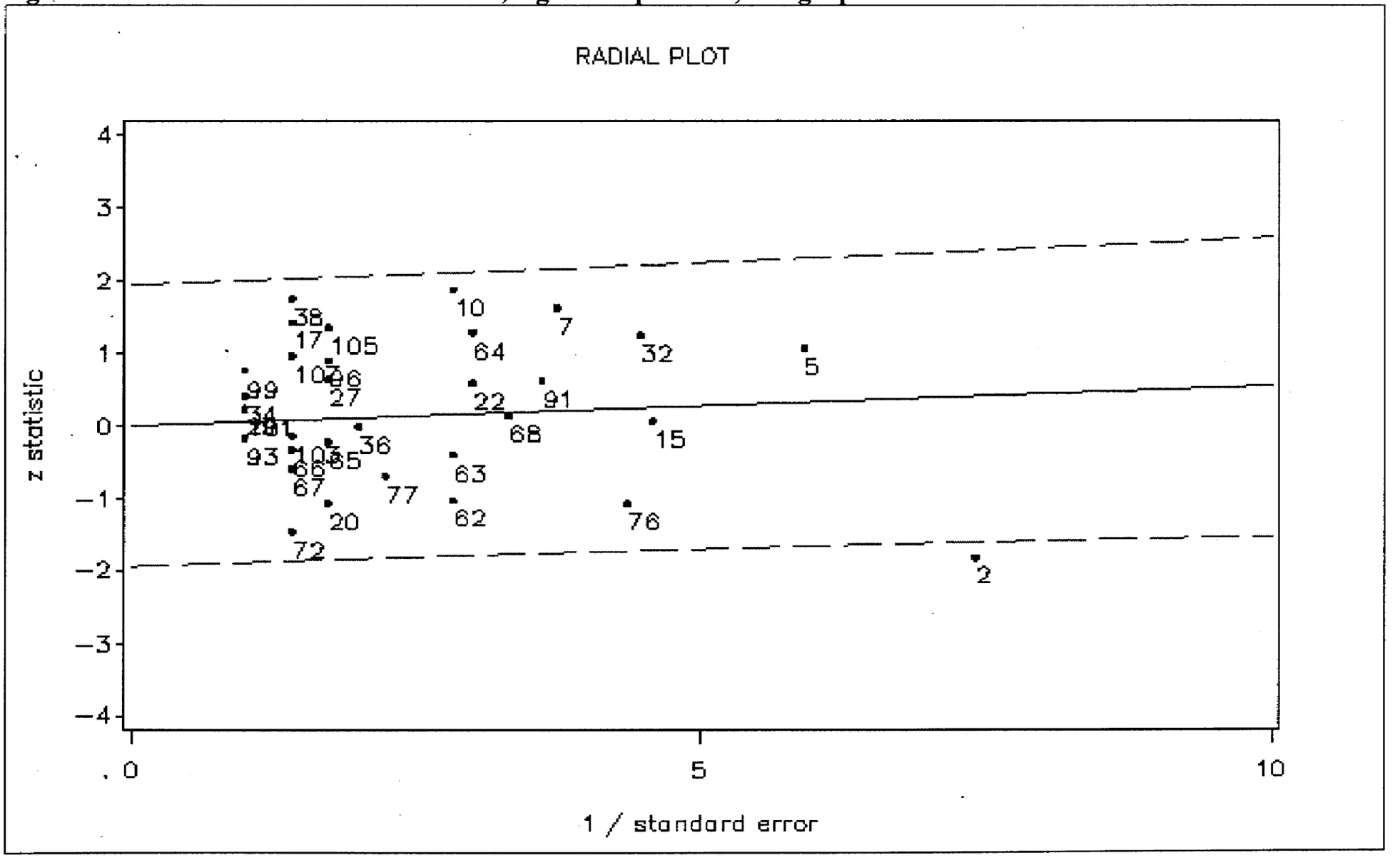


Figure 4.8.2 – Forest Plot for Random-Effects Meta-SMR, Age Group = 0-25, Geographic Zone = '< 16 km'

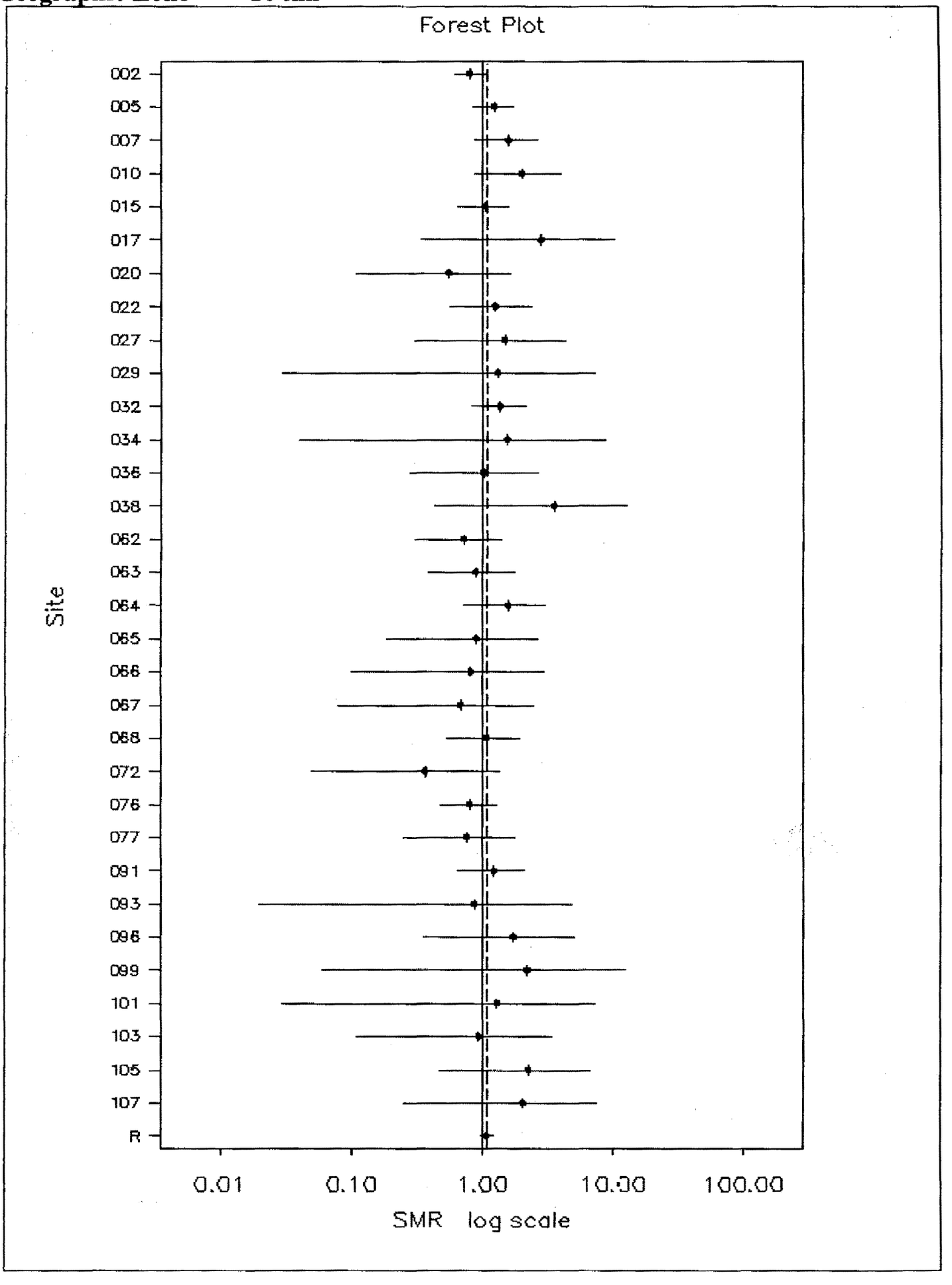
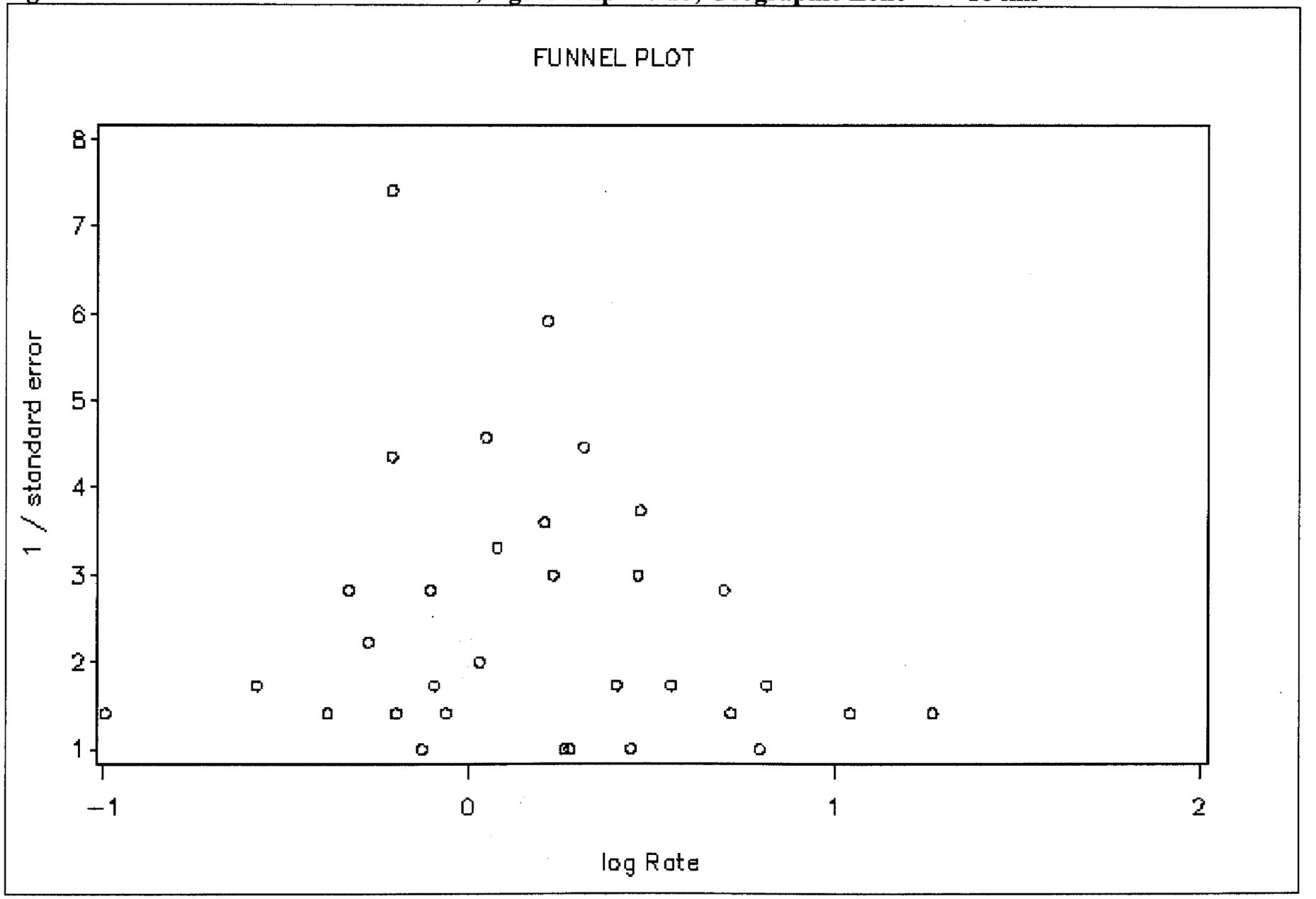


Figure 4.8.3 – Funnel Plot for Meta-SMR, Age Group = 0-25, Geographic Zone = '< 16 km'



Additional Analyses

When determining whether a study within the "< 16 km" zone captured cases that truly lie within 16 kilometers or whether only some part of the census boundary lay within 16 kilometers was not generally specified. For that reason, a study met the criteria as long as some part of the census boundary was within the zone. For Aldermaston, the algorithm led us to use data from a study that has at least one-third of the population within 10 miles (16 km) of the site. It is possible that the majority of the population resided outside the zone. However, data was also available that had at least two-thirds of the population within 8 miles (13 km) of the site. Using observed and expected as an indicator of population size, the disparity in population between the above analyses is evident (Table 4.11). For example, the 10-mile region expects an eight-fold increase in the number of cases, as compared to the 8-mile region. While the SIR for the 8-mile region is slightly larger than the 10-mile region, the 10-mile region may have a greater influence when calculating the meta-SIR due to the size of the population.

Table 4.11 – Study Population Comparison for Aldermaston

Region	Age Group	Obs	Exp	SIR
1/3 population within 10 miles	0-9	51	42.15	1.21
	0-25	82	70.09	1.17
2/3 population within 8 miles	0-9	8	5.49	1.46
	0-25	14	8.81	1.59

Therefore, SIR analyses for both age groups in geographic zone = '< 16 km' were reanalyzed by substituting the 8-mile for the 10-mile region (Table 4.12). There was no change is significance for the 0-9 age group. In the 0-25 age group, the lower confidence interval is below one changing all models from significant to nonsignificant.

Table 4.12 – 1/3 pop within 10 miles of Aldermaston to 2/3 pop within 8 miles

		Unadjusted		Fixed Effects		Random Effects	
Age Group	Geographic Zone	Rate	95% CI	Rate	95% CI	Rate	95% CI
0-9	< 16 km	1.19	(1.02, 1.38)	1.24	(1.07, 1.44)	1.23	(1.04, 1.44)
0-25	< 16 km	1.04	(0.97, 1.12)	1.07	(0.99, 1.15)	1.07	(0.99, 1.15)

Spatial and Temporal Analysis Near Pickering Nuclear Generator

Temporal Analysis

Overall SIR and smoothed moving SIR graphs were produced for 0-4 and 0-14 age groups at the census division level. The analysis was also performed at the census subdivision level for 0-14 age group. However, the smaller population and fewer cases did not allow for smoothed moving SIRs for 0-4 age group to be studied at the census subdivision level. The smoothing consisted of five-year intervals, moved in two, three, four, and five-year increments.

The overall SIR for the four census subdivision areas, ages 0-14 are shown in Table 4.13. Pickering/Ajax, in which Pickering Nuclear Generator (PNG) resides, had no increase in the overall SIR. Of the control areas, Stoney Creek/Grimsby had an SIR

below one, Vaughan had a statistically non-significant SIR greater than one, and Niagara Falls/Welland/Thorold had a statistically significant rate, SIR=2.68.

Table 4.13 – Overall SIR by Census Subdivision 1971-2000 – Age 0-14

Census Subdivsion Group	Obs	Exp	SIR	95% CI
Pickering/Ajax	37	37.48	0.99	(0.70, 1.36)
Vaughan	29	26.30	1.10	(0.74, 1.58)
Stoney Creek/Grimsby	9	19.15	0.47	(0.21, 0.89)
Niagara Falls/Welland/Thorold	37	13.81	2.68	(1.89, 3.69)

Table 4.14 shows the overall SIR for the four census division areas, ages 0-14. Also included is Essex, a border census division similar to Niagara in that they are near populated cities in the U.S. Essex was added *a posteriori* for comparison to Niagara because the census divisions share many of the same characteristics. The census division of Durham contains PNG. Although Durham, York, and Niagara have SIRs greater than one, none are statistically significant. Hamilton-Wentworth and Essex have SIRs below one.

Table 4.14 – Overall SIR by Census Division 1971-2000 – Age 0-14

Census Divsion	Obs	Exp	SIR	95% CI
Durham	141	128.82	1.09	(0.86, 1.40)
York	156	136.34	1.14	(0.90, 1.45)
Hamilton-Wentworth	119	133.18	0.89	(0.69, 1.15)
Niagara	123	117.00	1.05	(0.81, 1.37)
Essex	98	106.62	0.92	(0.69, 1.22)

The overall SIR for the four census division areas, age group 0-4 is shown in Table 4.15. All SIRs are near one and none are statistically significant.

Table 4.15 – Overall SIR by Census Division 1971-2000 – Age 0-4

Census Division	Obs	Exp	SIR	95% CI
Durham	78	70.78	1.10	(0.87, 1.38)
York	77	73.24	1.05	(0.83, 1.31)
Hamilton-Wentworth	70	71.97	0.97	(0.76, 1.23)
Niagara	68	61.33	1.11	(0.86, 1.41)
Essex	60	56.93	1.05	(0.80, 1.36)

Smoothed Moving SIR for Census Subdivisions Pickering and Ajax: 0-14 Age Group

Pickering and Ajax are the census subdivisions that are most likely at the highest risk of radiation exposure from PNG. The overall SIR for childhood leukemia from 1971-2000 was 0.99 (95% CI= 0.70, 1.36). Smoothed moving windows with five year intervals were created and moved in two, three, four, and five-year increments (Figures 4.9.1-4, respectively). Moving the window in two-year increments offer the least amount of smoothing and five-year increments generates the greatest amount of smoothing. All four increments indicate SIRs below one with upper confidence bands above one until approximately 1980; and from 1980-2000 the SIR consistently remained near one with nonsignificant confidence bands.

Figure 4.9.1 – Census Subdivision Pickering and Ajax, Age 0-14 (2 Year Increments)

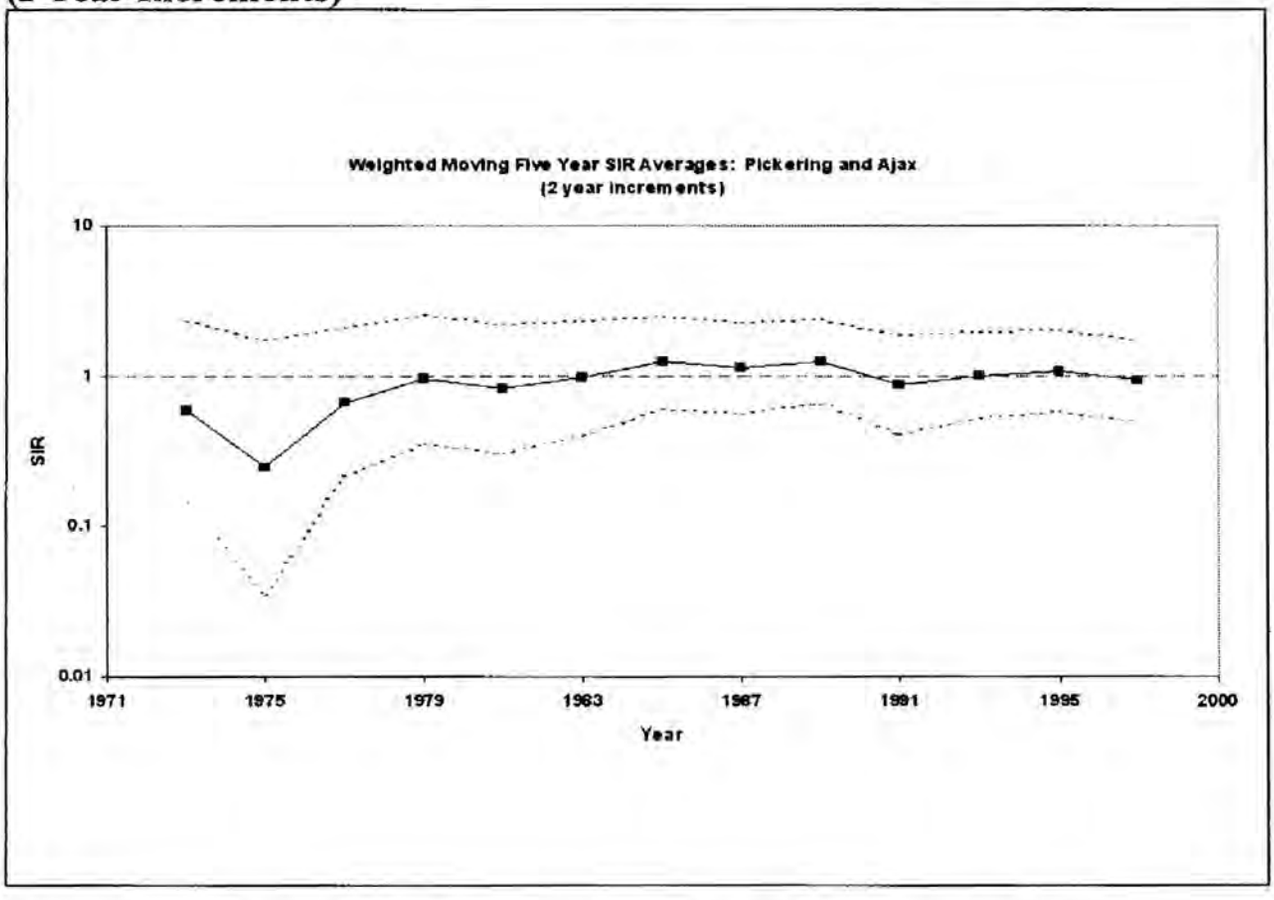


Figure 4.9.2 – Census Subdivision Pickering and Ajax, Age 0-14 (3 Year Increments)

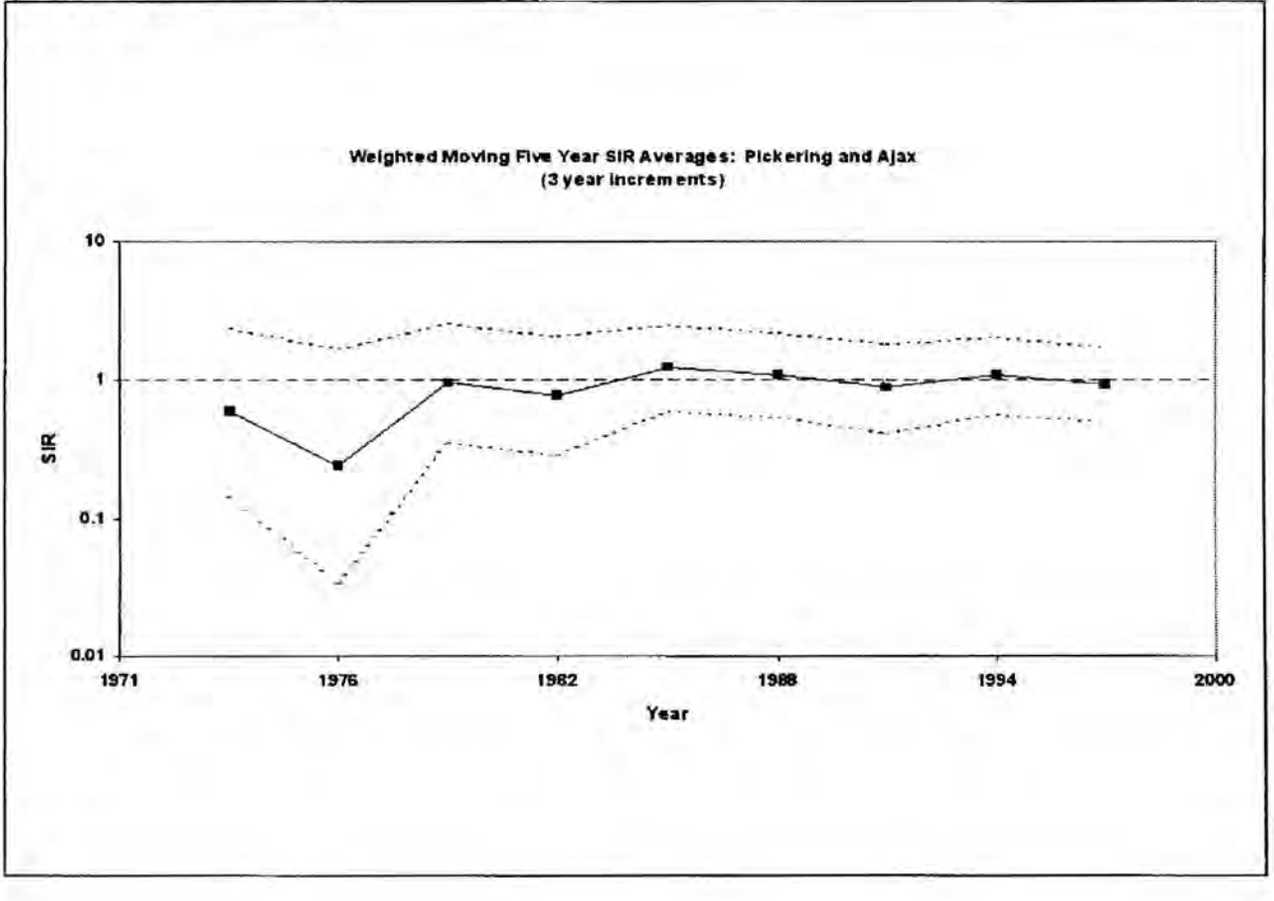


Figure 4.9.3 – Census Subdivision Pickering and Ajax, Age 0-14 (4 Year Increments)

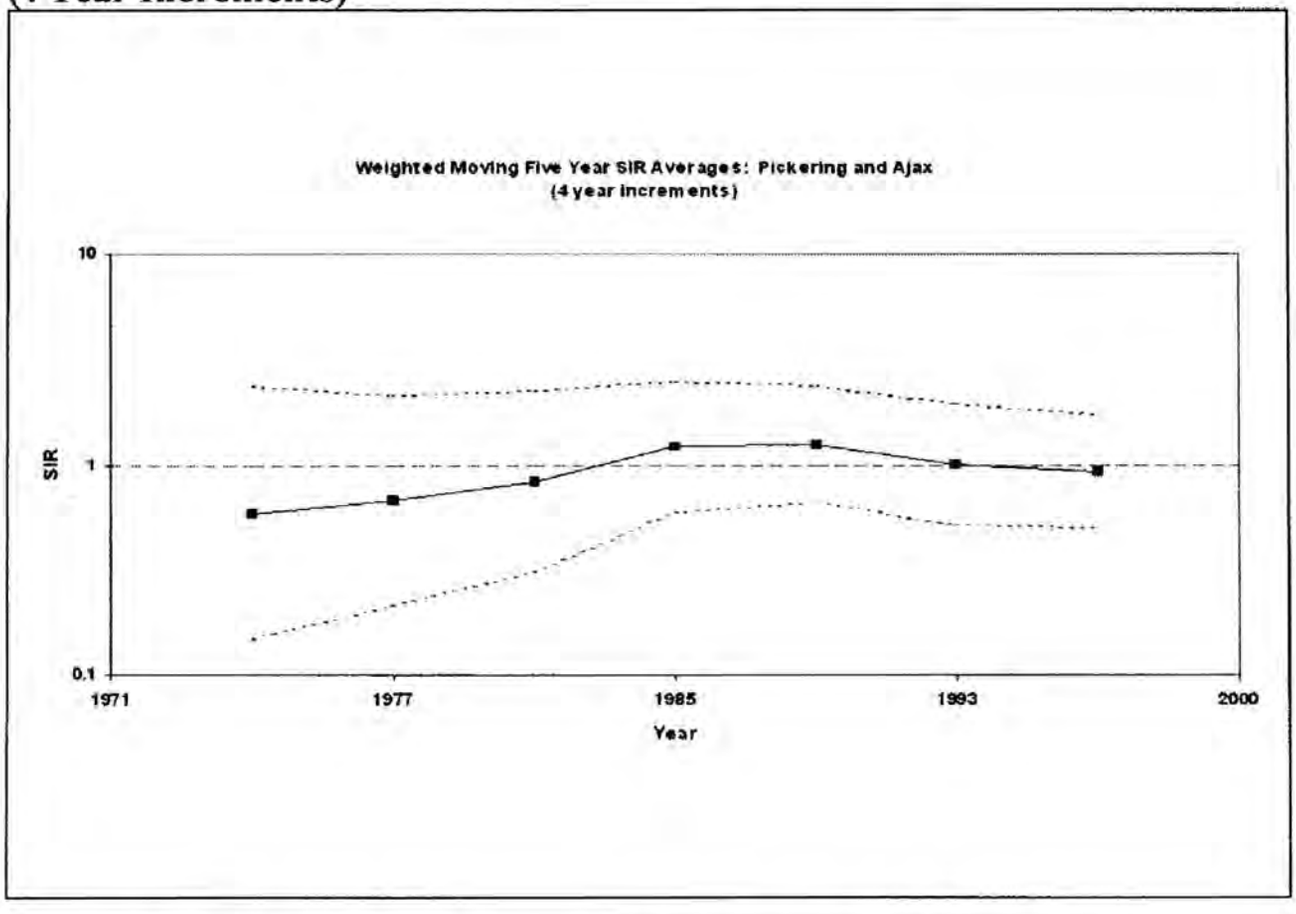
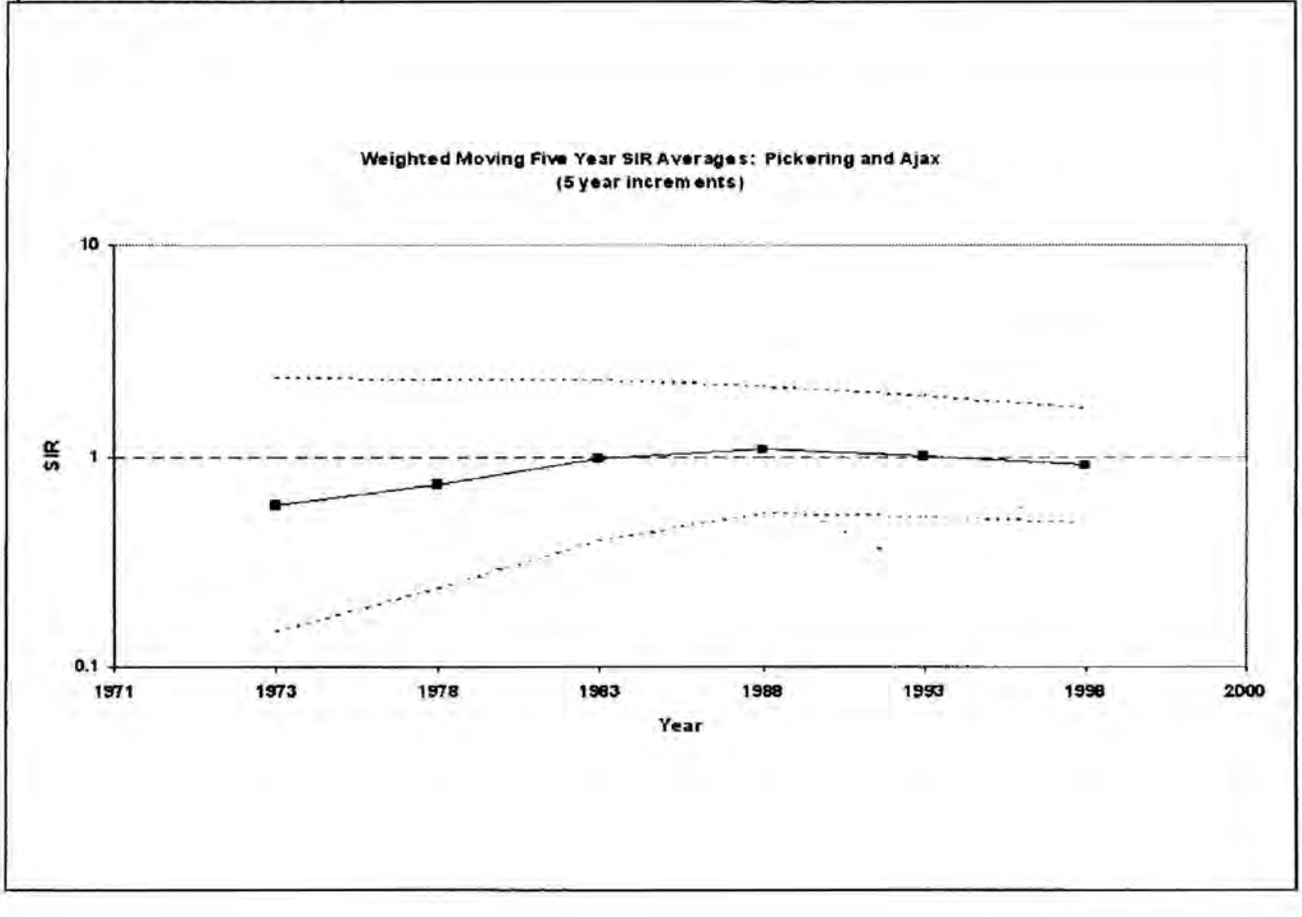


Figure 4.9.4 – Census Subdivision Pickering and Ajax, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Subdivision Vaughan: 0-14 Age Group

The overall SIR for childhood leukemia from 1971-2000 was 1.10 (95% CI= 0.74, 1.58). The smoothed moving windows are shown in Figures 4.10.1-4. Vaughan experienced excess cases of childhood leukemia in the 1970's and early 1980's, achieving significance around 1980. Throughout the 1980s and 1990s, the two-year and three-year increments show the smoothed SIR oscillating around one. However the four-year and five-year increments suggest a downward trend during that same time period. The early excess cases are most likely what account for the overall SIR being greater than one.

Figure 4.10.1 – Census Subdivision Vaughan, Age 0-14 (2 Year Increments)

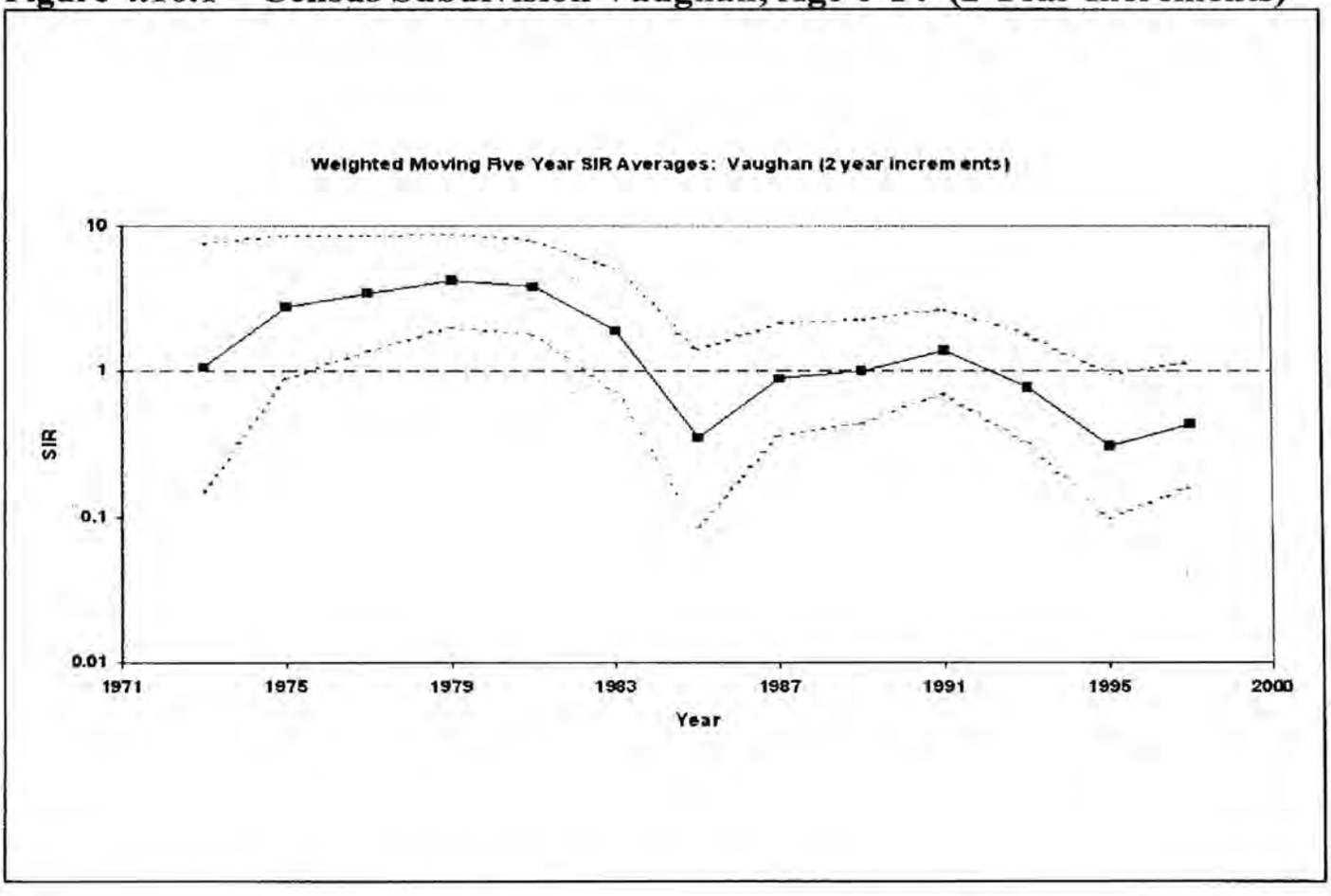


Figure 4.10.2 – Census Subdivision Vaughan, Age 0-14 (3 Year Increments)

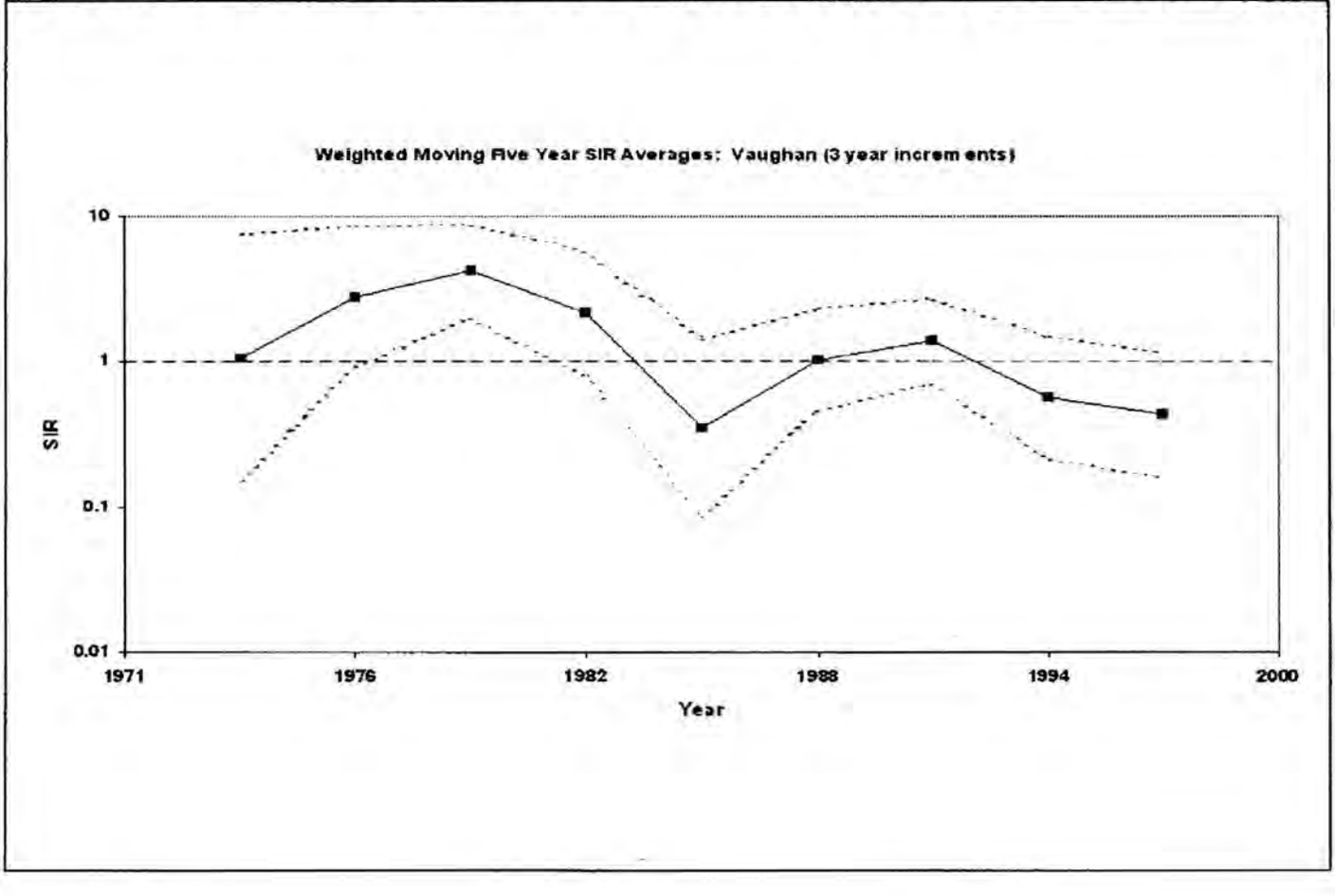


Figure 4.10.3 – Census Subdivision Vaughan, Age 0-14 (4 Year Increments)

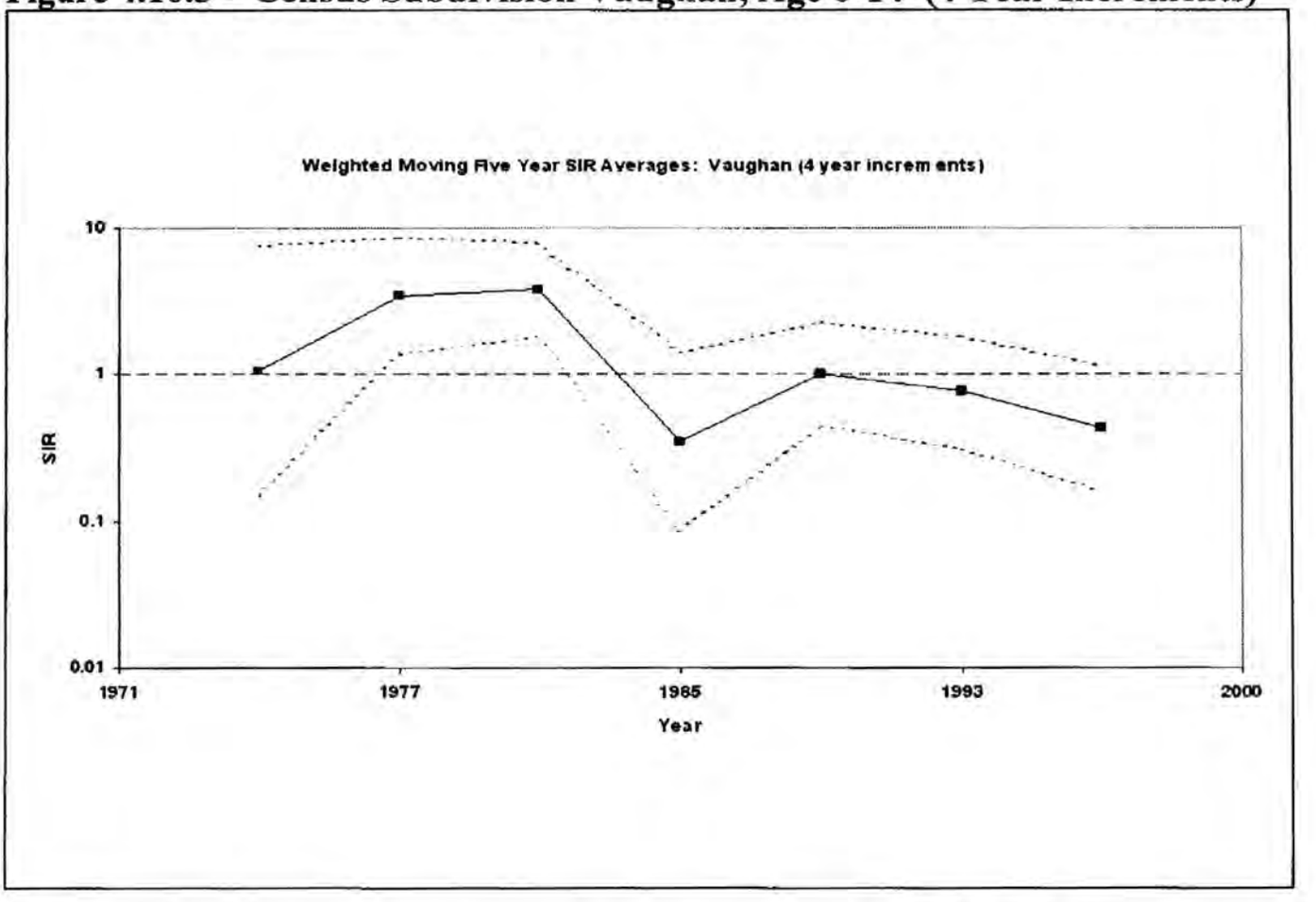
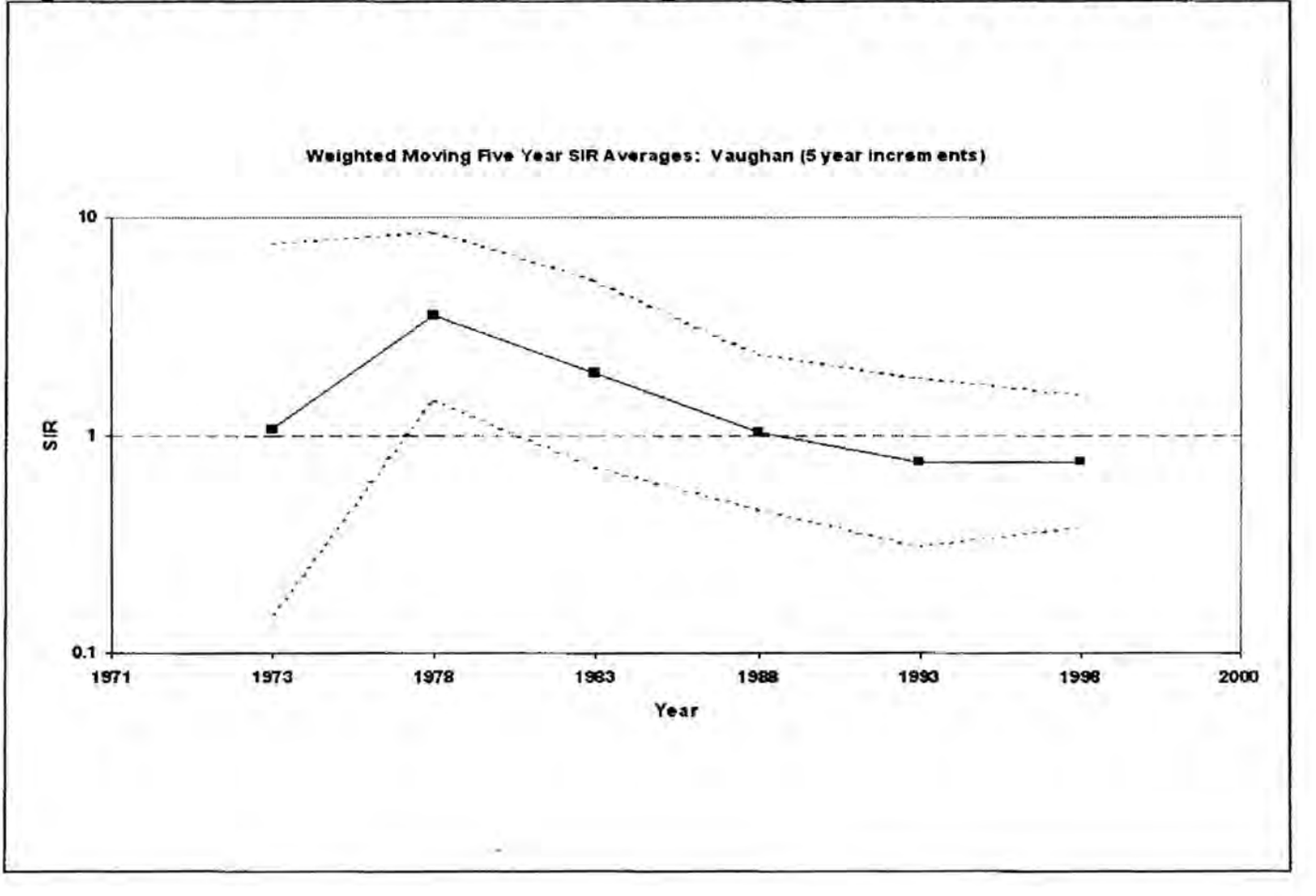


Figure 4.10.4 – Census Subdivision Vaughan, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Subdivisions Stoney Creek and Grimsby: 0-14 Age Group

The overall SIR for childhood leukemia from 1971-2000 was 0.47 (95% CI= 0.21, 0.89). The smoothed moving windows are shown in Figures 4.11.1-4. The smoothed SIR remained consistently below one for the entire study period. Although the smoothed SIRs failed to achieve significance, the overall SIR was significant.

Figure 4.11.1 – Census Subdivisions Stoney Creek and Grimsby, Age 0-14 (2 Year Increments)

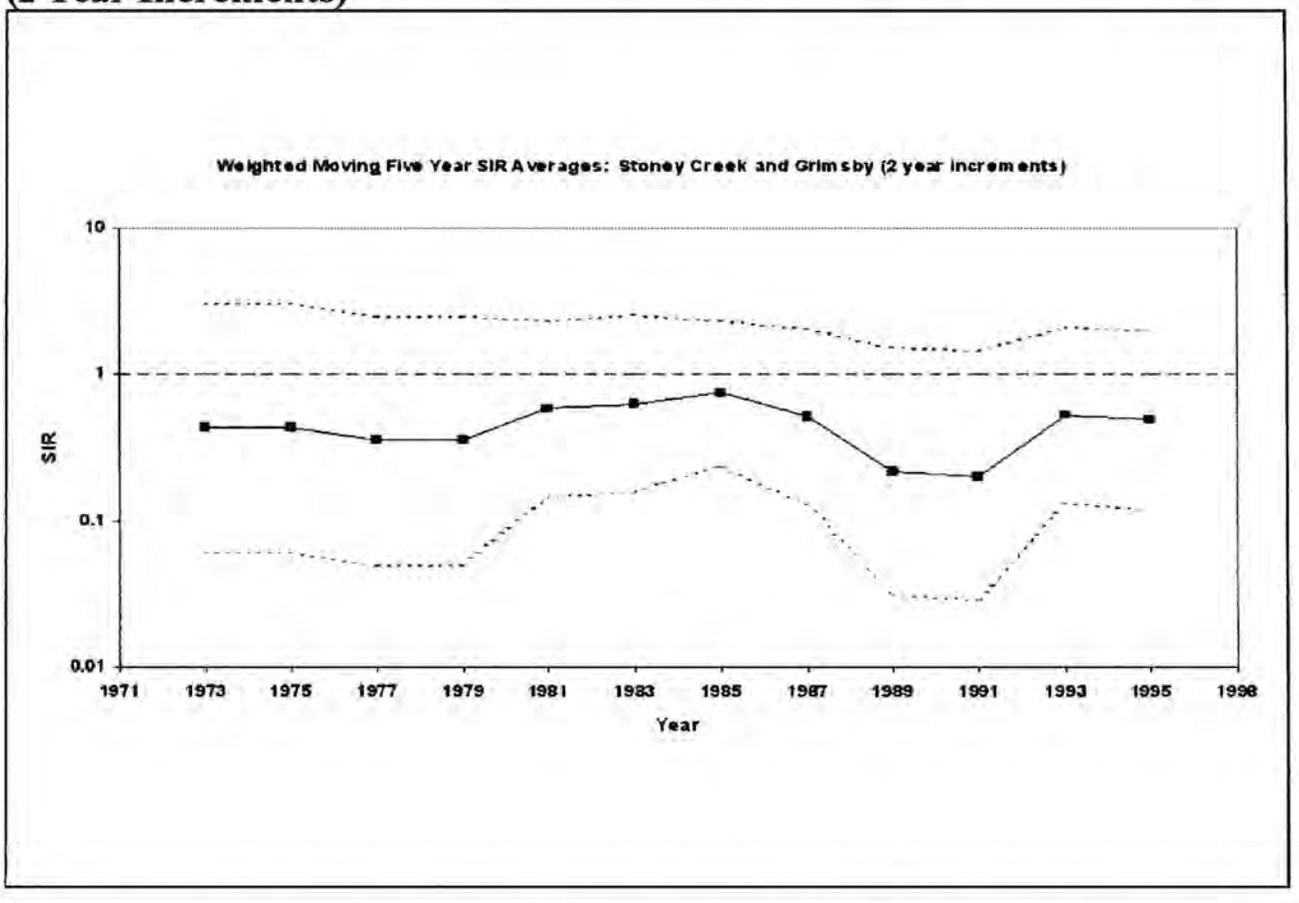


Figure 4.11.2 – Census Subdivisions Stoney Creek and Grimsby, Age 0-14 (3 Year Increments)

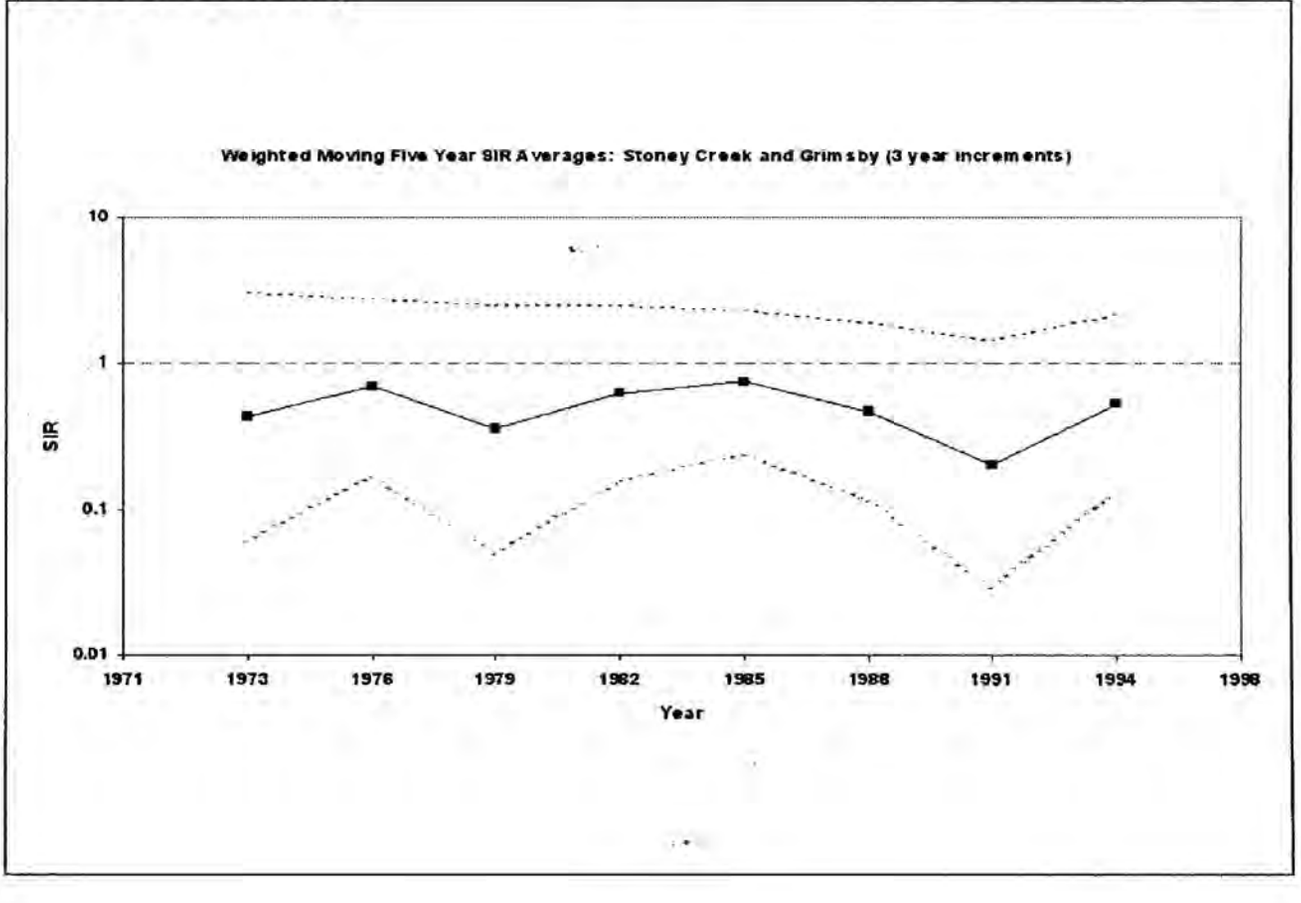


Figure 4.11.3 – Census Subdivisions Stoney Creek and Grimsby, Age 0-14 (4 Year Increments)

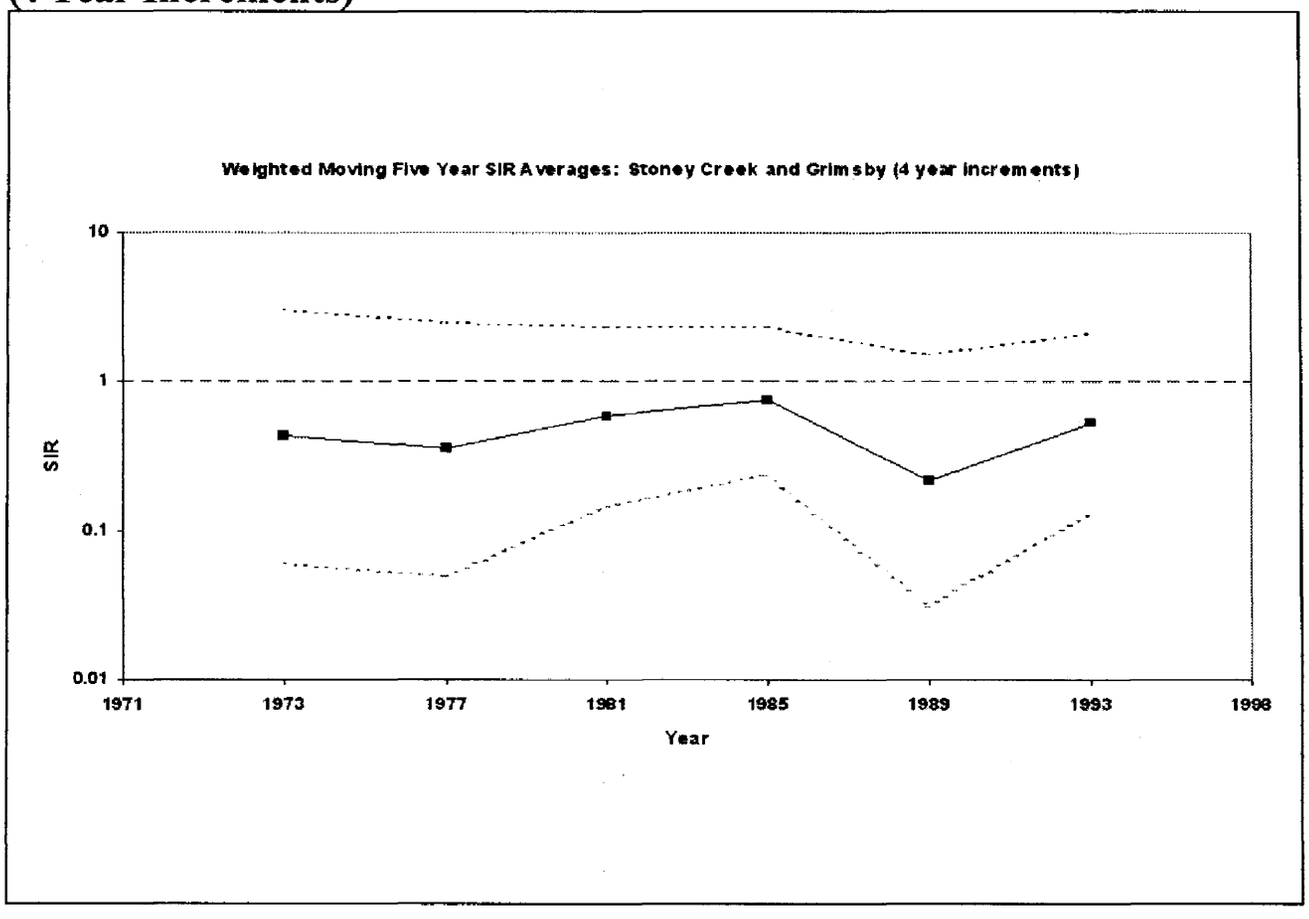
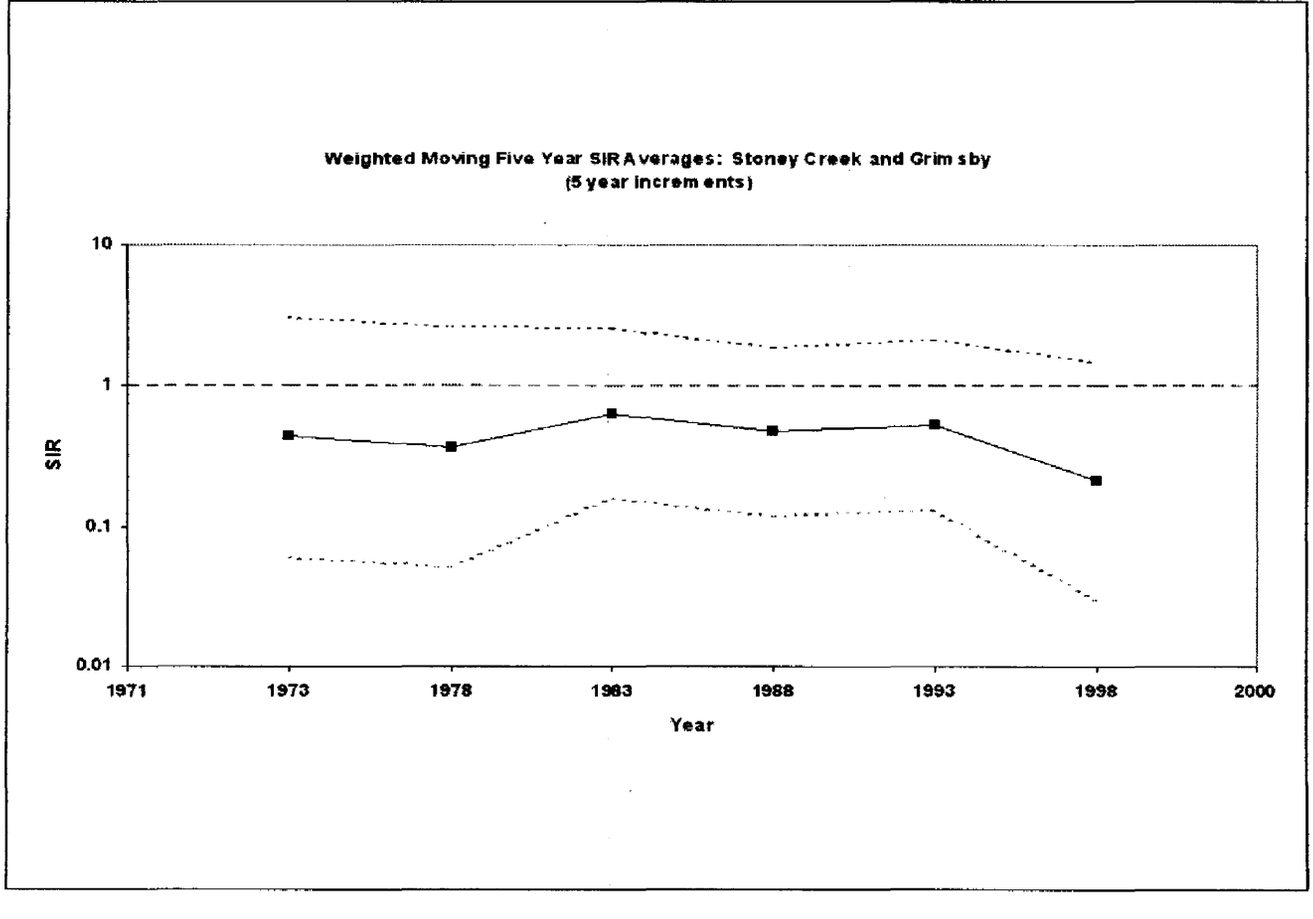


Figure 4.11.4 – Census Subdivisions Stoney Creek and Grimsby, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Subdivisions Niagara Falls, Welland, and Thorold: 0-14 Age Group

The overall SIR for childhood leukemia from 1971-2000 was 2.68 (95% CI= 1.89, 3.69). The smoothed moving windows are shown in Figures 4.12.1-4. Except for one point in the last 1970s, the smoothed SIRs remained consistent and above one, often achieving significance.

Figure 4.12.1 – Census Subdivisions Niagara Falls, Welland, and Thorold, Age 0-14 (2 Year Increments)

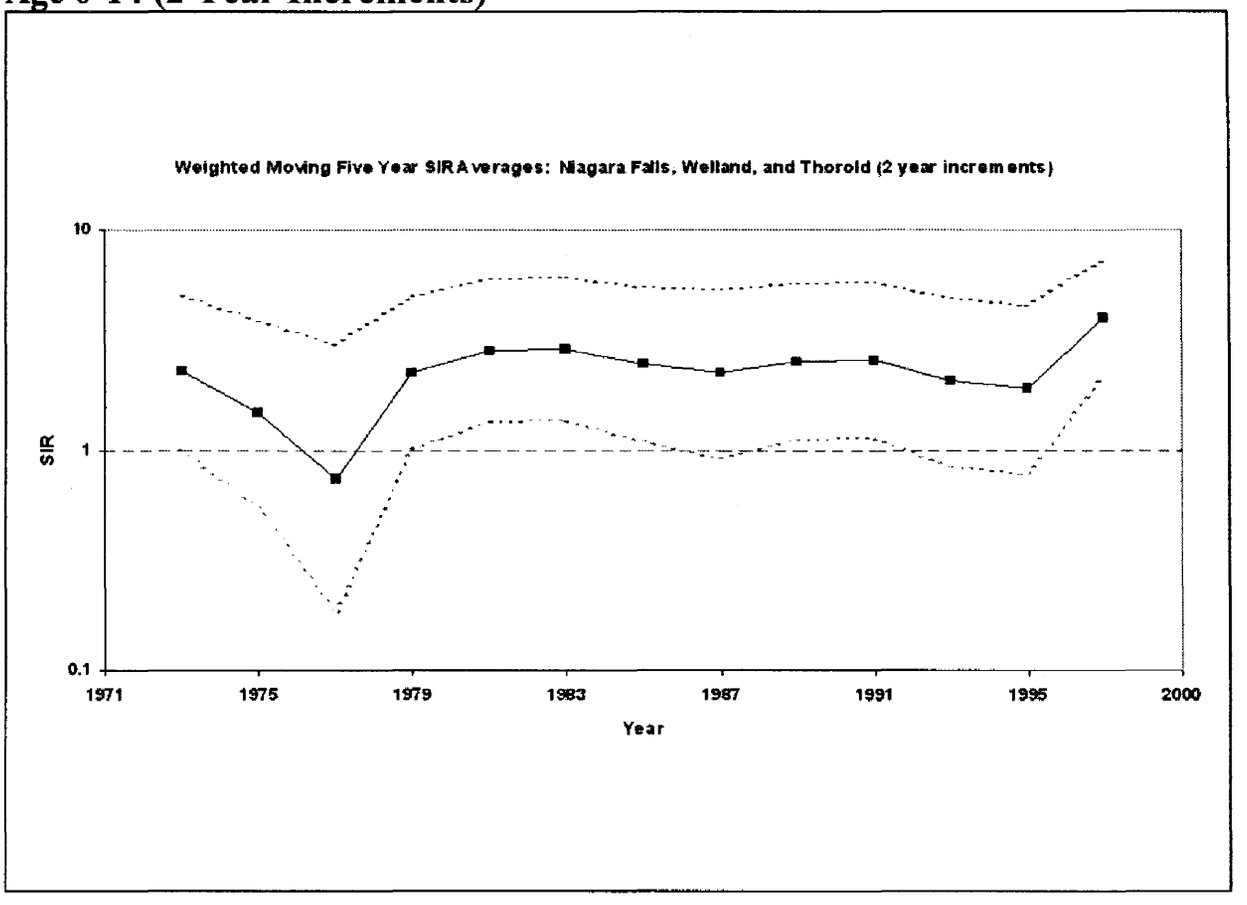


Figure 4.12.2 – Census Subdivisions Niagara Falls, Welland, and Thorold, Age 0-14 (3 Year Increments)

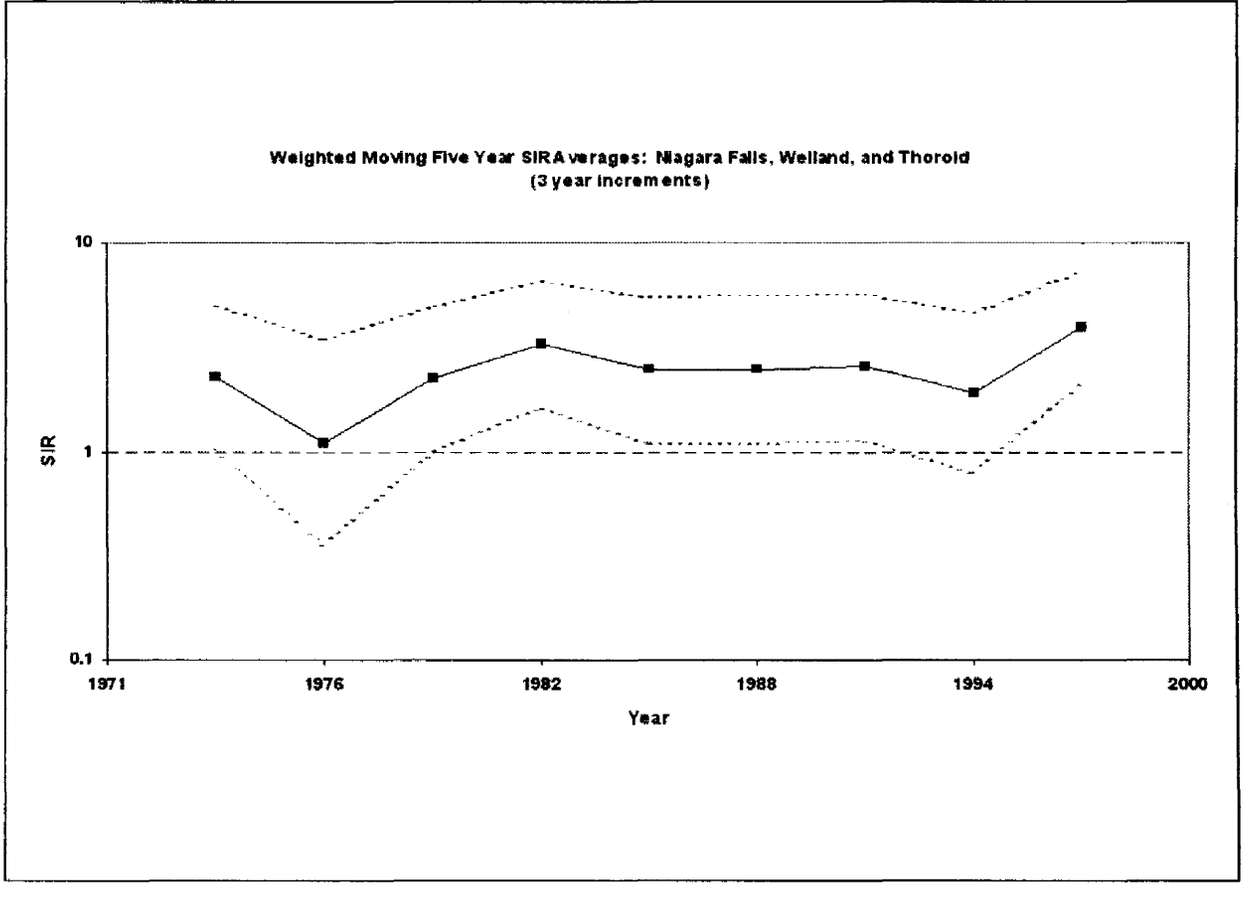


Figure 4.12.3 – Census Subdivisions Niagara Falls, Welland, and Thorold, Age 0-14 (4 Year Increments)

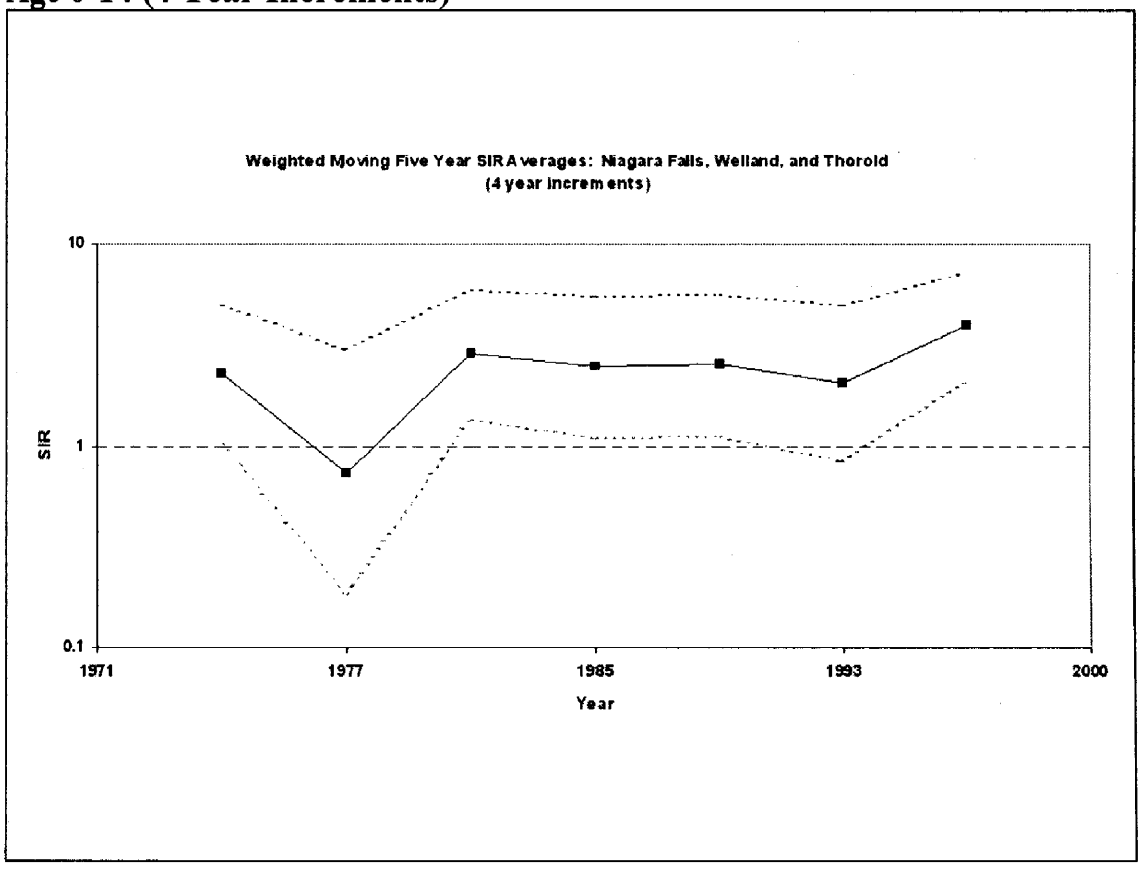
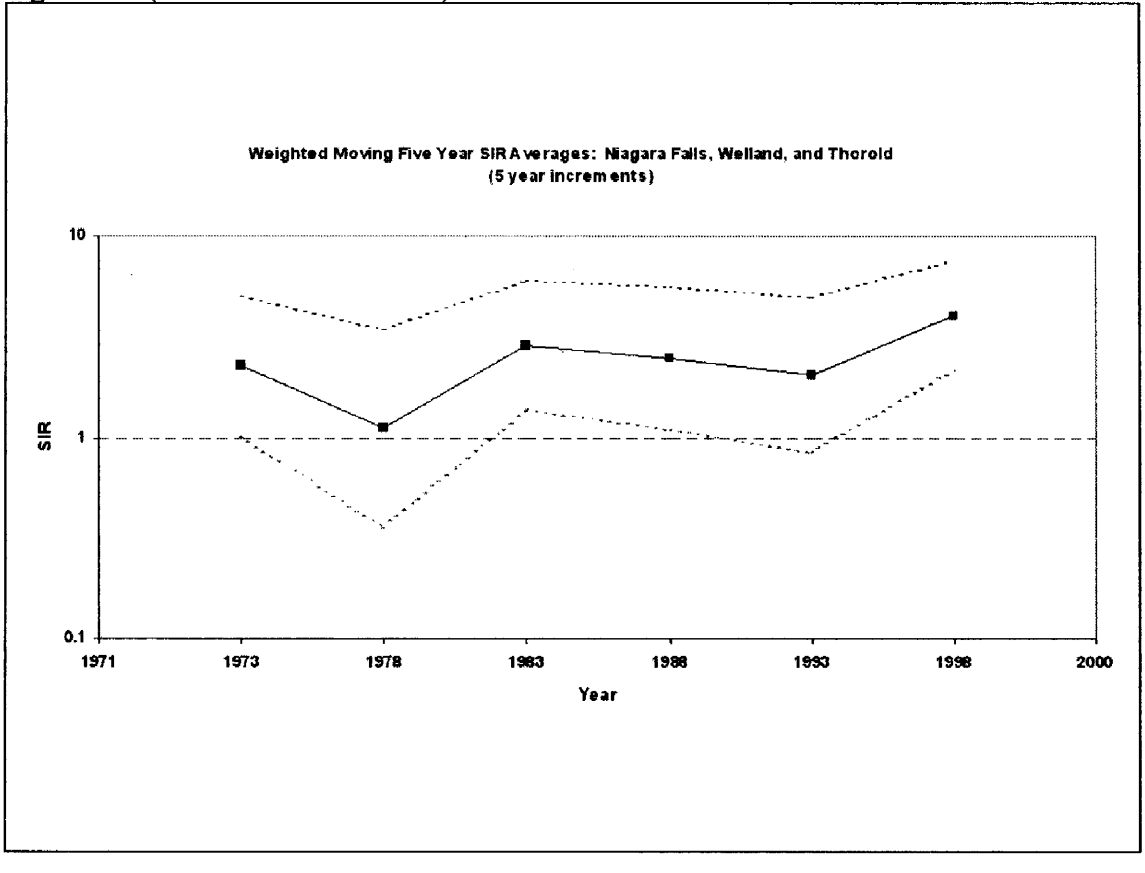


Figure 4.12.4 – Census Subdivisions Niagara Falls, Welland, and Thorold, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Division Durham: 0-14 Age Group

The census division of Durham contains the census subdivisions of Pickering and Ajax, and consequently PNG. The overall SIR for childhood leukemia from 1971-2000 was 1.09 (95% CI= 0.86, 1.40). The smoothed moving windows are shown in Figures 4.13.1-4. The smoothed SIRs always remained near one for the study period never achieving statistical significance.

Figure 4.13.1 – Census Division Durham, Age 0-14 (2 Year Increments)

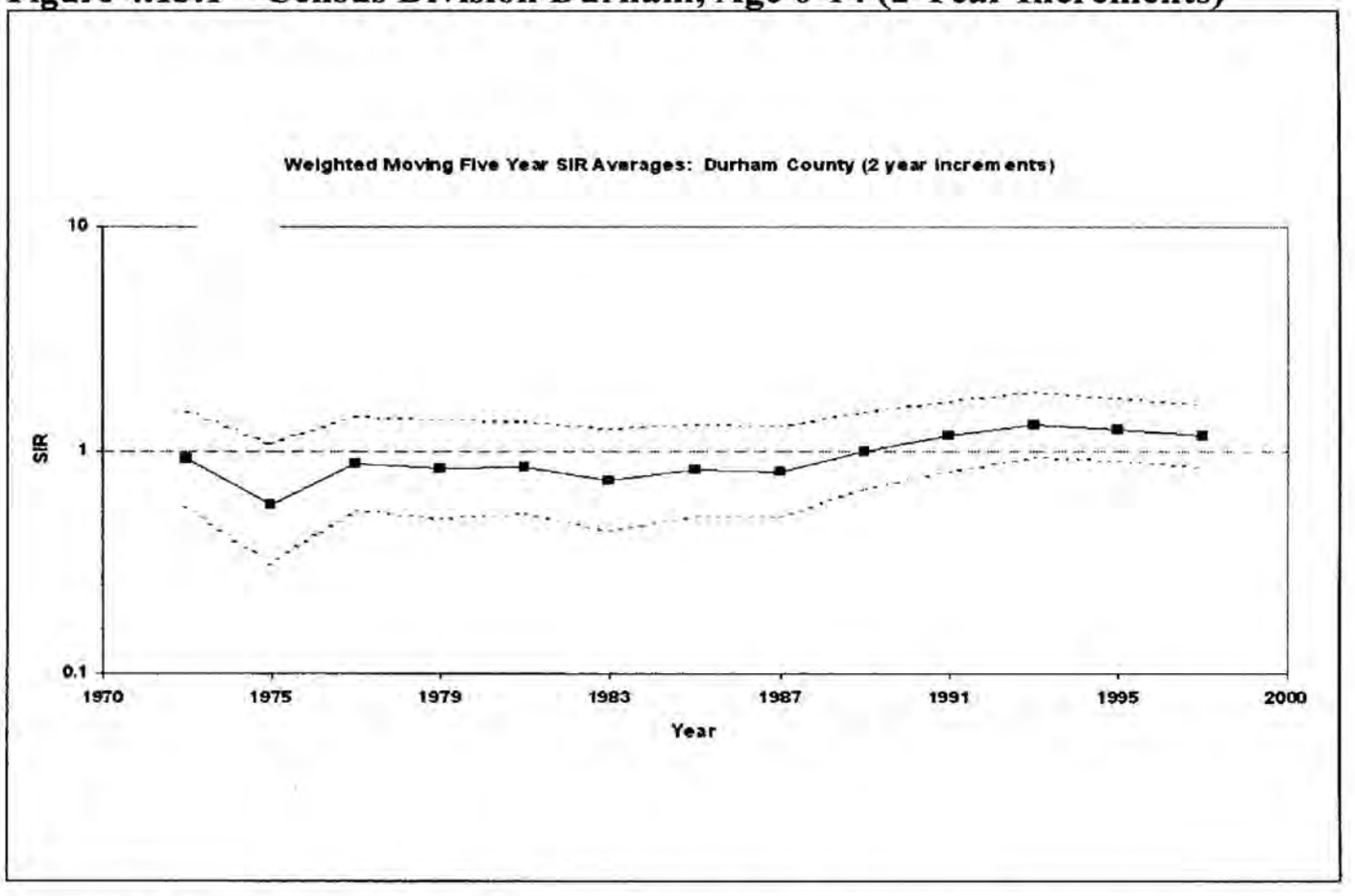


Figure 4.13.2 – Census Division Durham, Age 0-14 (3 Year Increments)

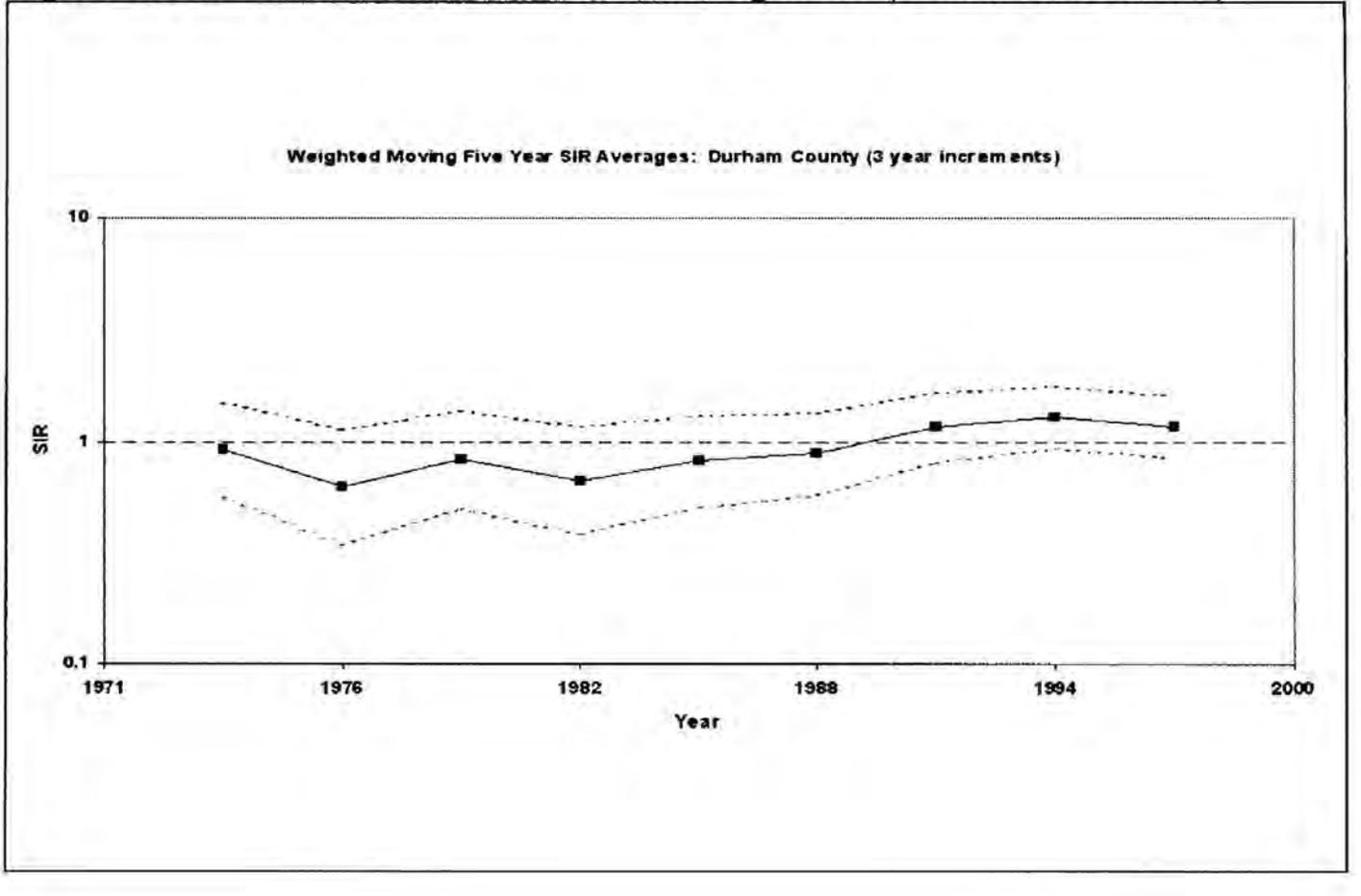


Figure 4.13.3 – Census Division Durham, Age 0-14 (4 Year Increments)

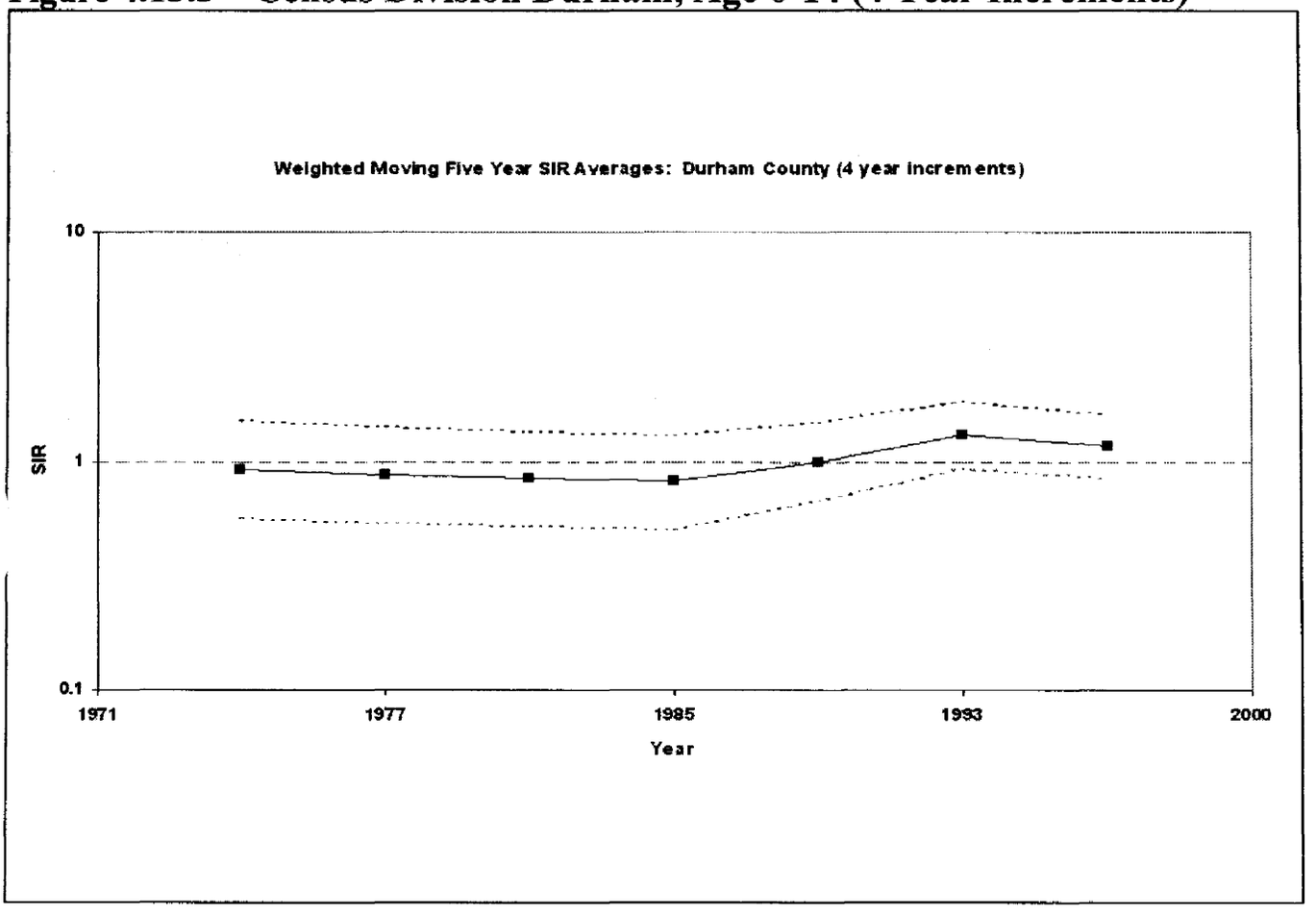
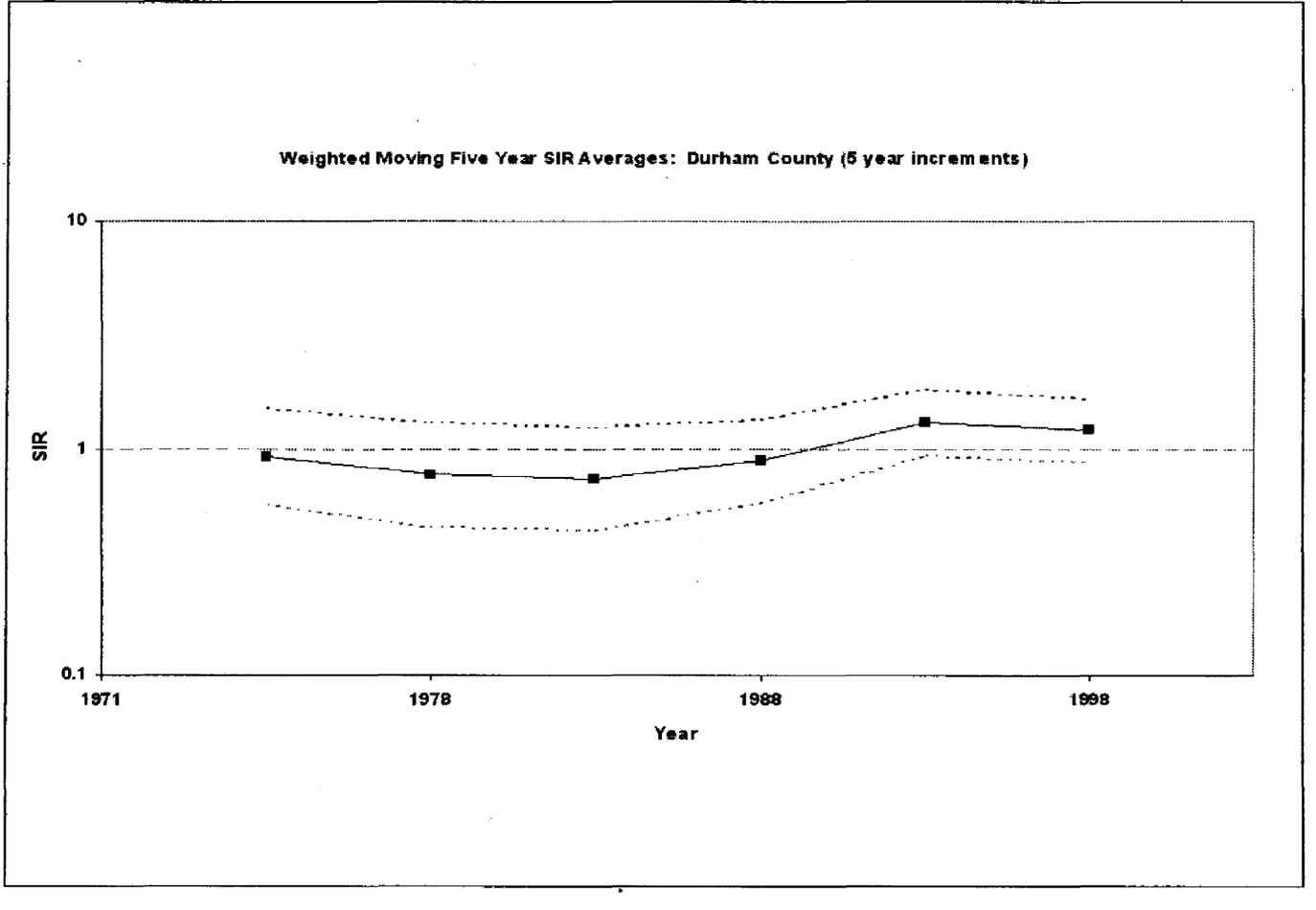


Figure 4.13.4 – Census Division Durham, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Division Durham: 0-4 Age Group

Census divisions have large enough populations to also produce smoothed moving SIRs for the 0-4 age group. The overall SIR for childhood leukemia from 1971-2000 was 1.10 (95% CI= 0.87, 1.38). The smoothed moving windows are shown in Figures 4.14.1-4. The smoothed SIRs for the 0-4 age group followed the same pattern as the 0-14 age group, consistently remaining near one and never achieving significance.

Figure 4.14.1 – Census Division Durham, Age 0-4 (2 Year Increments)

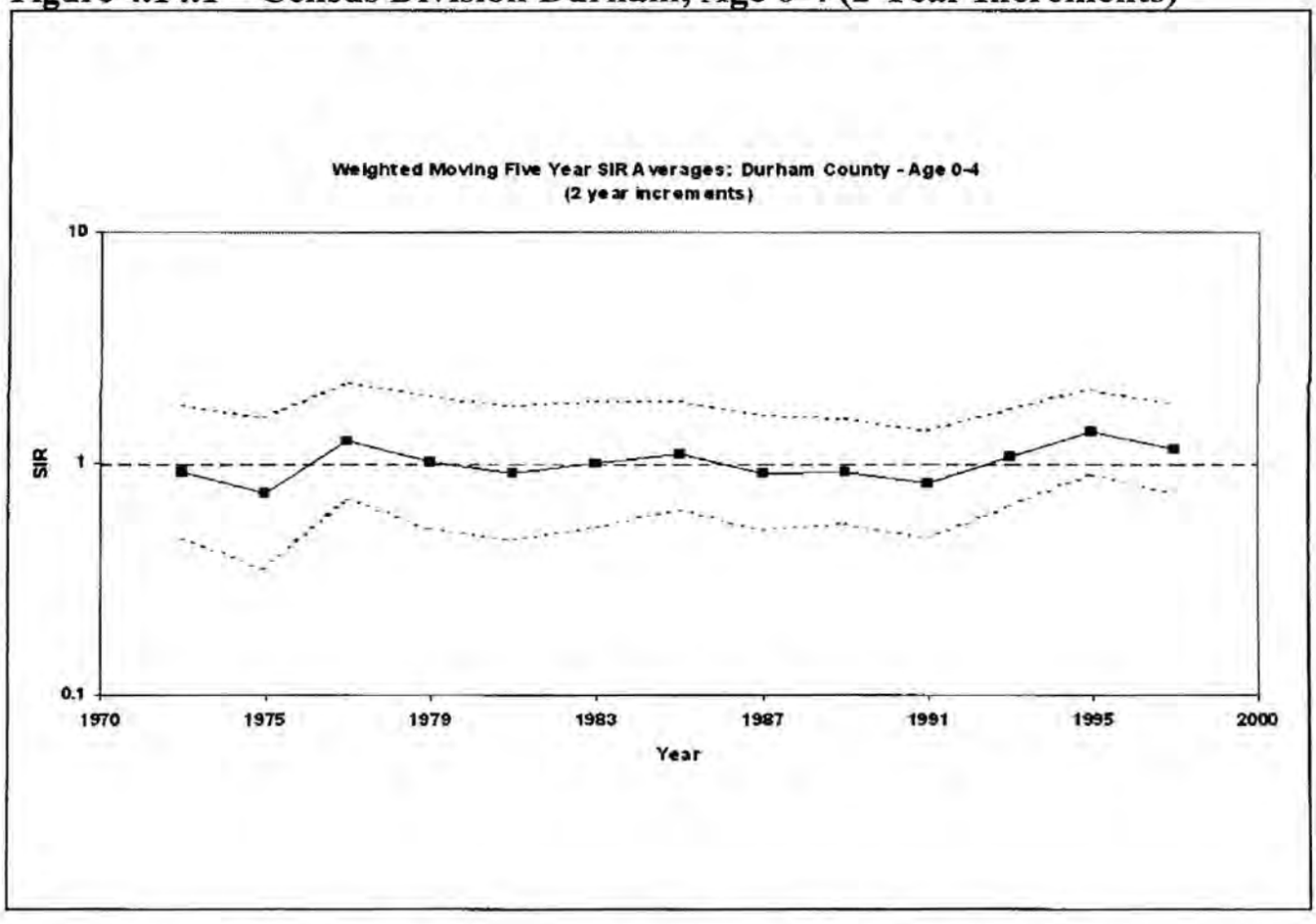


Figure 4.14.2 – Census Division Durham, Age 0-4 (3 Year Increments)

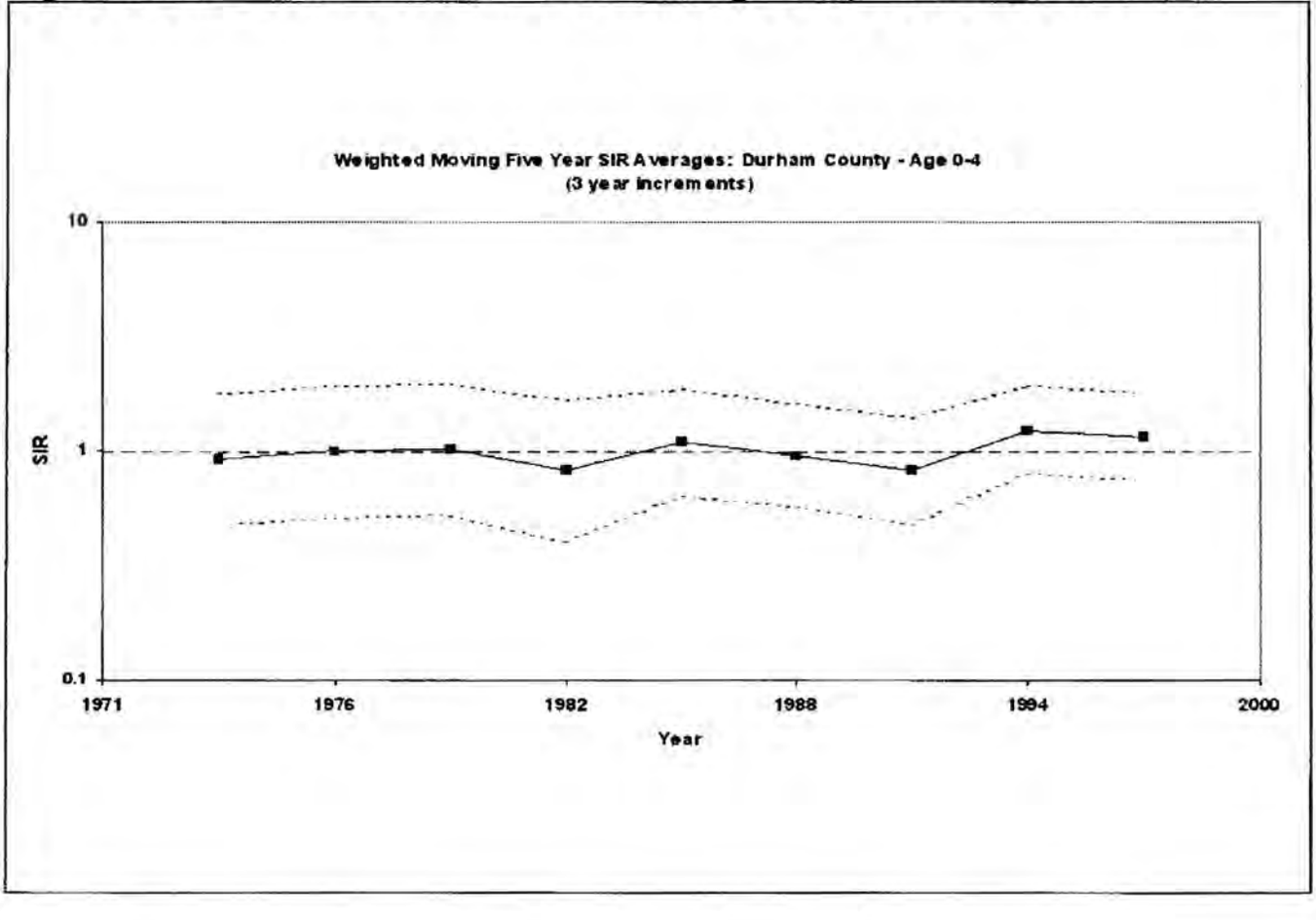


Figure 4.14.3 – Census Division Durham, Age 0-4 (4 Year Increments)

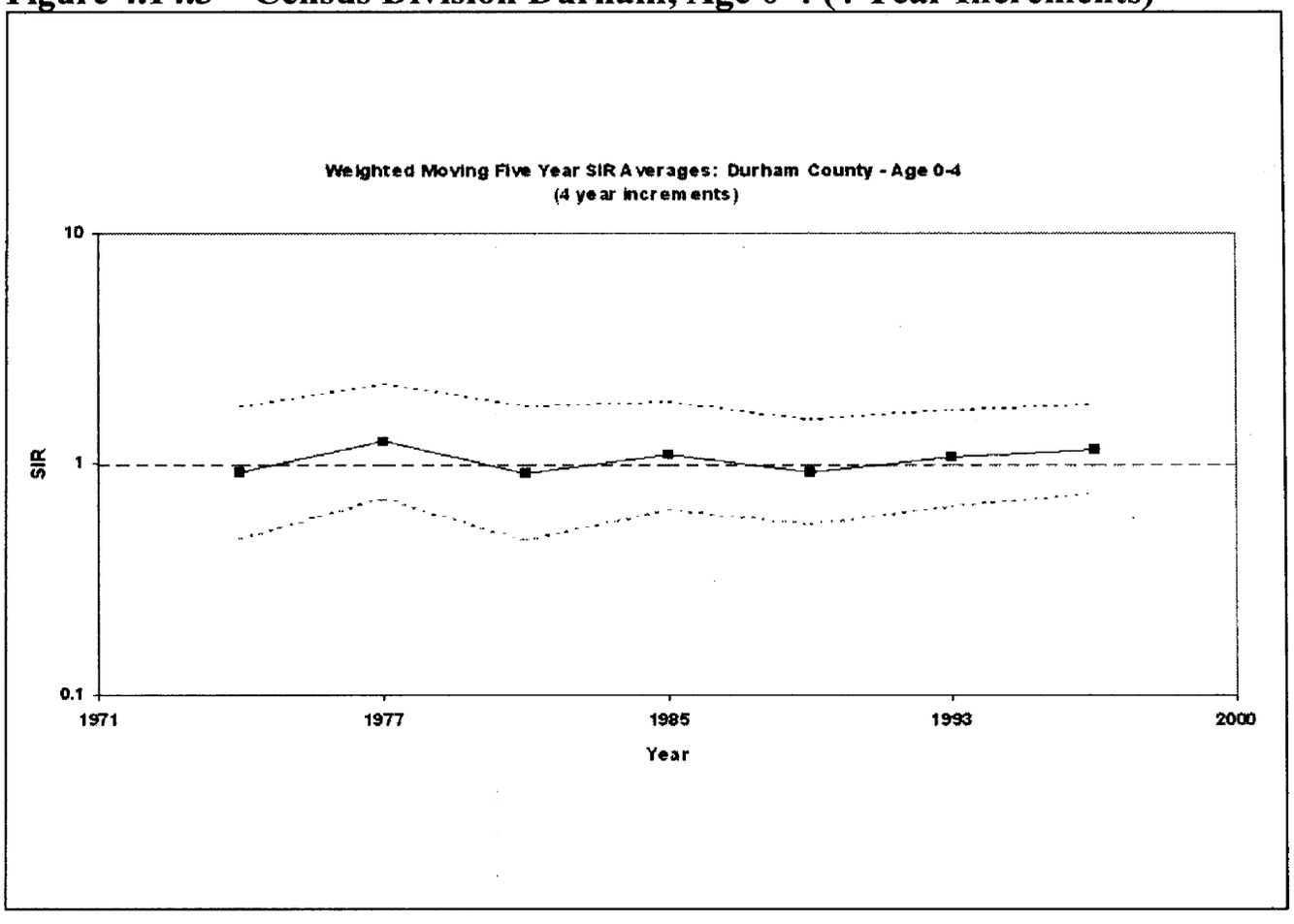
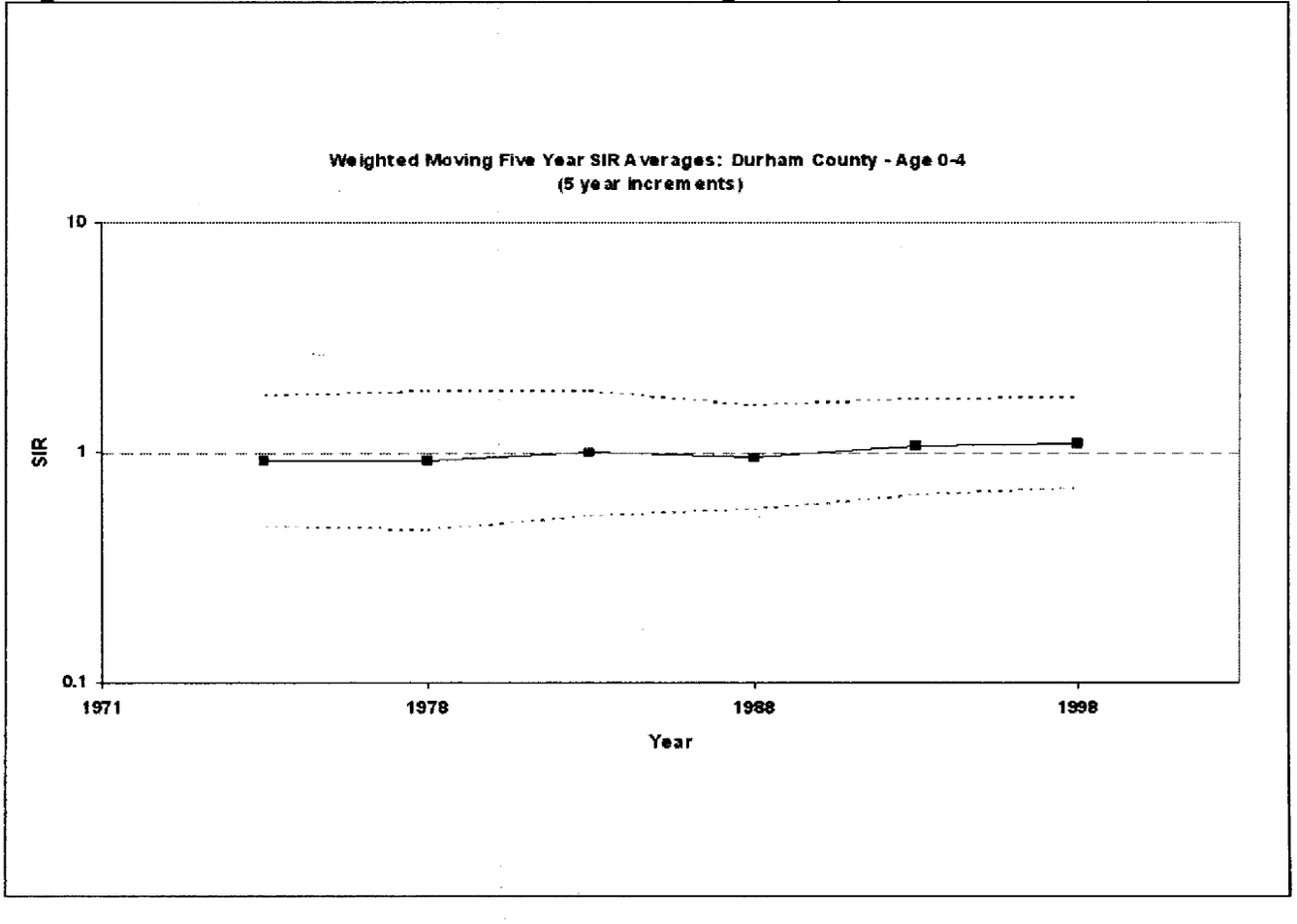


Figure 4.14.4 – Census Division Durham, Age 0-4 (5 Year Increments)



Smoothed Moving SIR for Census Division York: 0-14 Age Group

The census division of York contains the census subdivision of Vaughan. The overall SIR for childhood leukemia from 1971-2000 was 1.14 (95% CI= 0.90, 1.45). The smoothed moving windows are shown in Figures 4.15.1-4. The smoothed SIRs follow the same pattern as Vaughan with elevated rates in the late 1970s and early 1980s sometimes achieving statistical significance. During the remainder of the study period, rates consistently stayed near one.

Figure 4.15.1 – Census Division York, Age 0-14 (2 Year Increments)

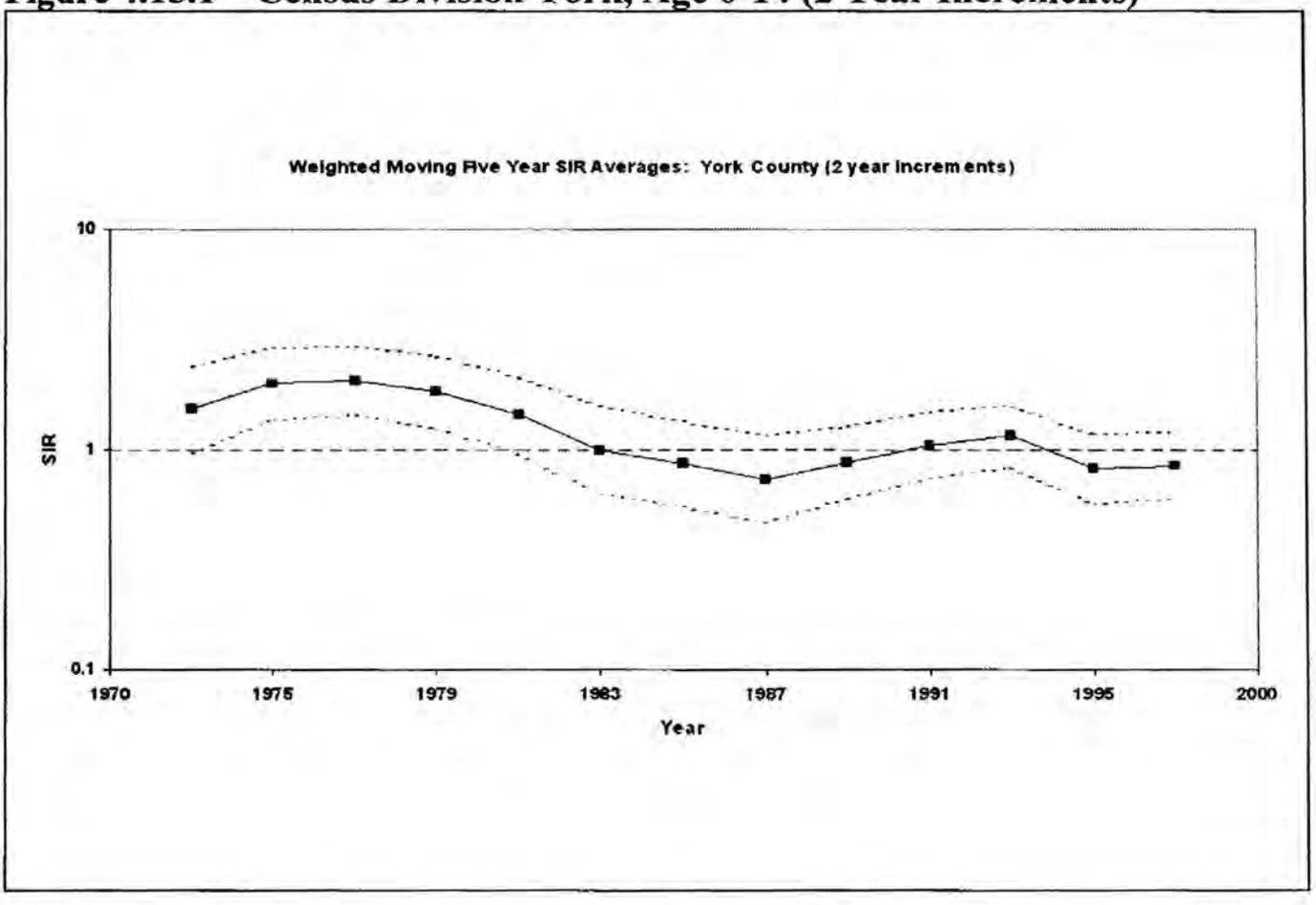


Figure 4.15.2 – Census Division York, Age 0-14 (3 Year Increments)

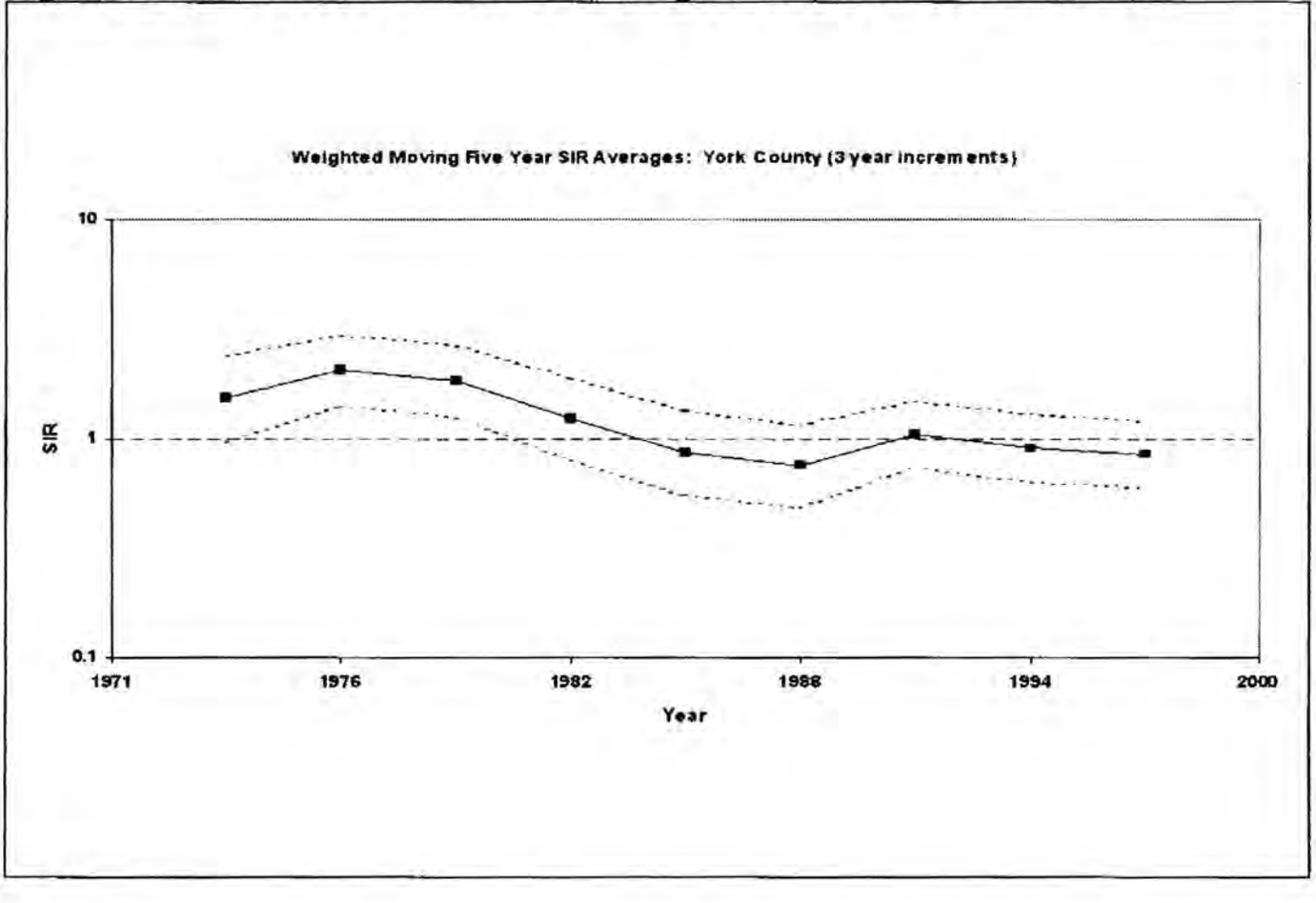


Figure 4.15.3 – Census Division York, Age 0-14 (4 Year Increments)

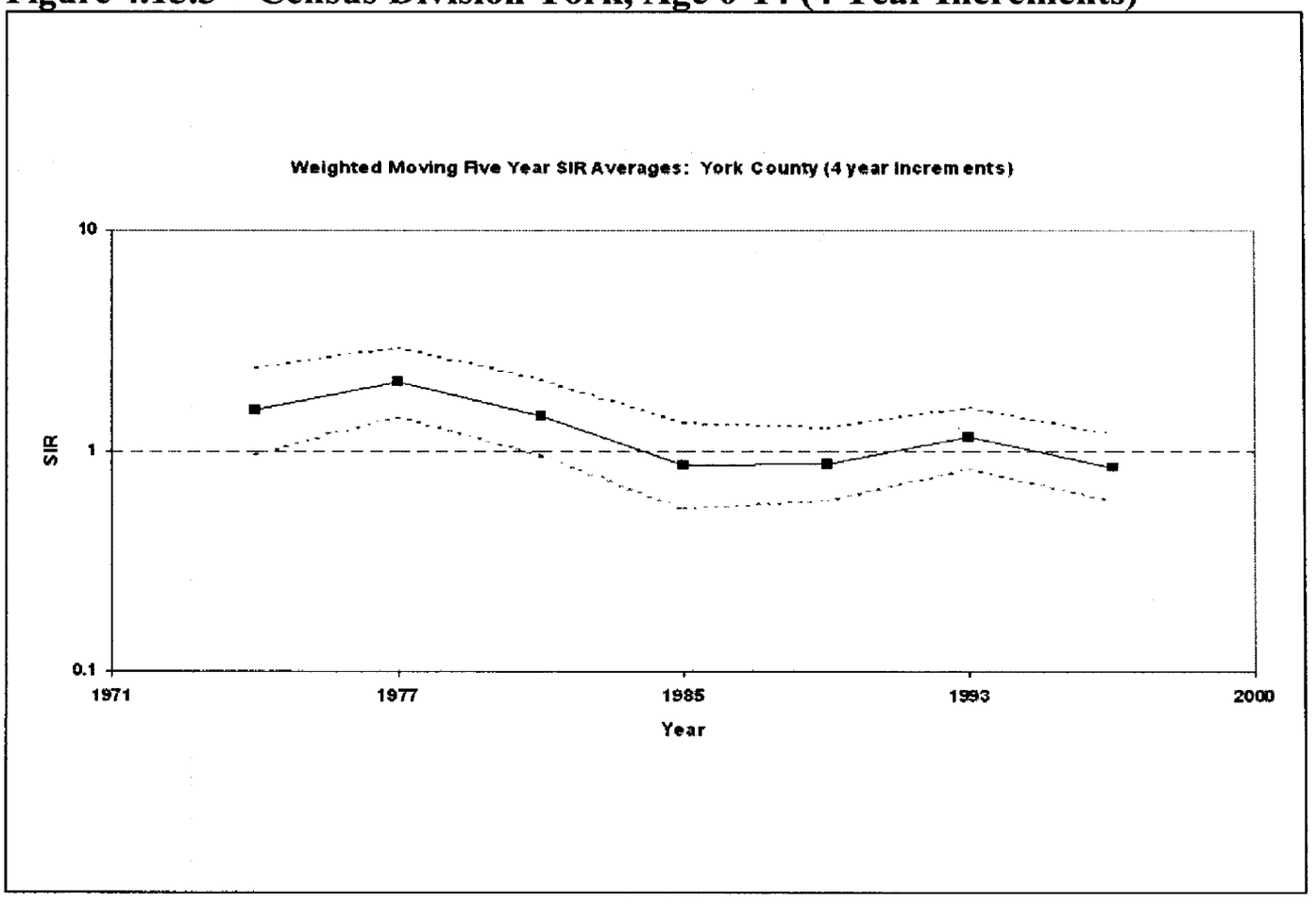
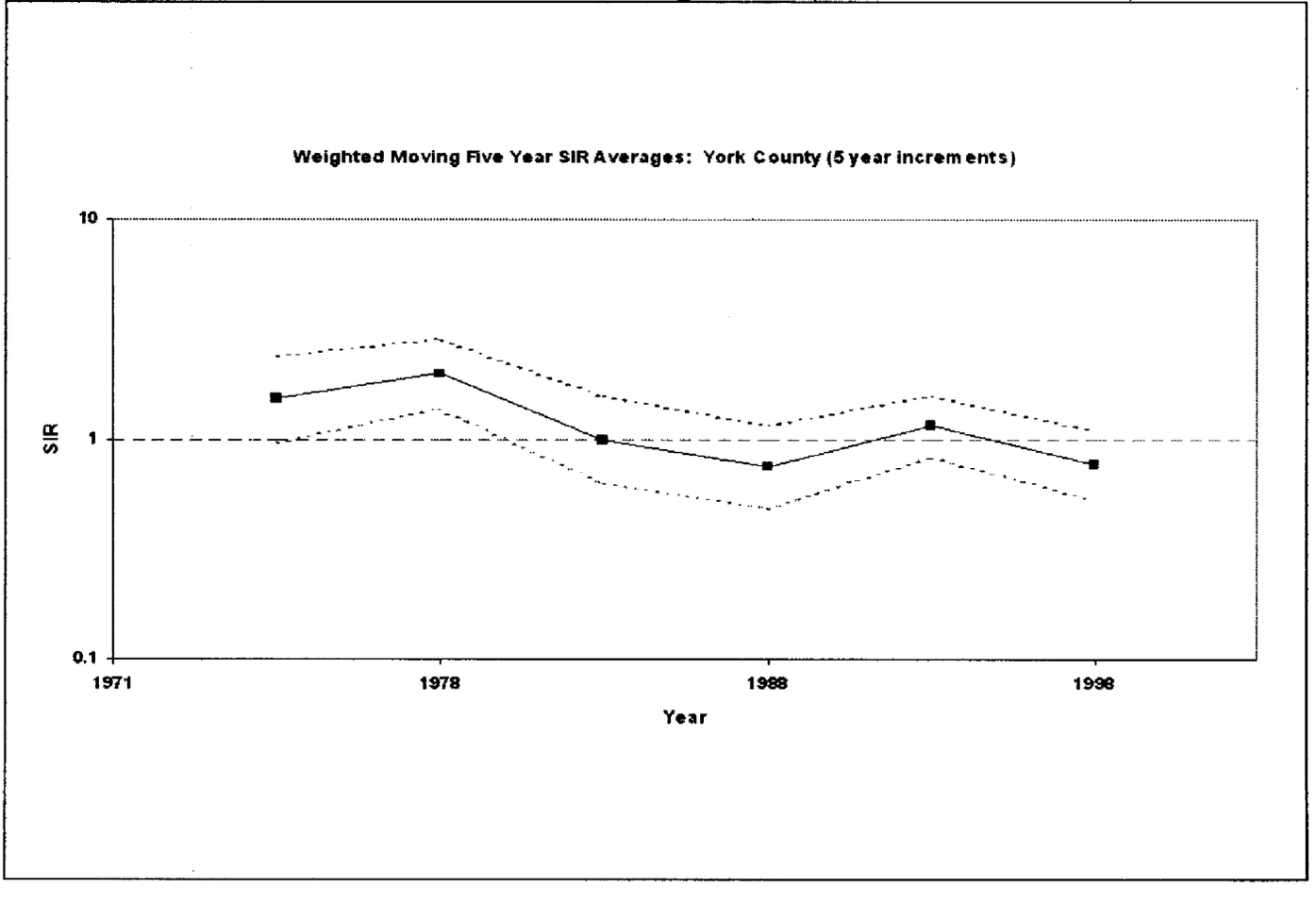


Figure 4.15.4 – Census Division York, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Division York: 0-4 Age Group

The overall SIR for childhood leukemia from 1971-2000 was 1.05 (95% CI= 0.83, 1.31), slightly lower than the SIR of 1.10 experience for the 0-14 age group. The smoothed moving windows are shown in Figures 4.16.1-4. The trend is the same as the 0-14 age group, with elevated rates (sometimes significant) in the late 1970s and early 1980s and remaining near one for the rest of the study period.

Figure 4.16.1 – Census Division York, Age 0-4 (2 Year Increments)

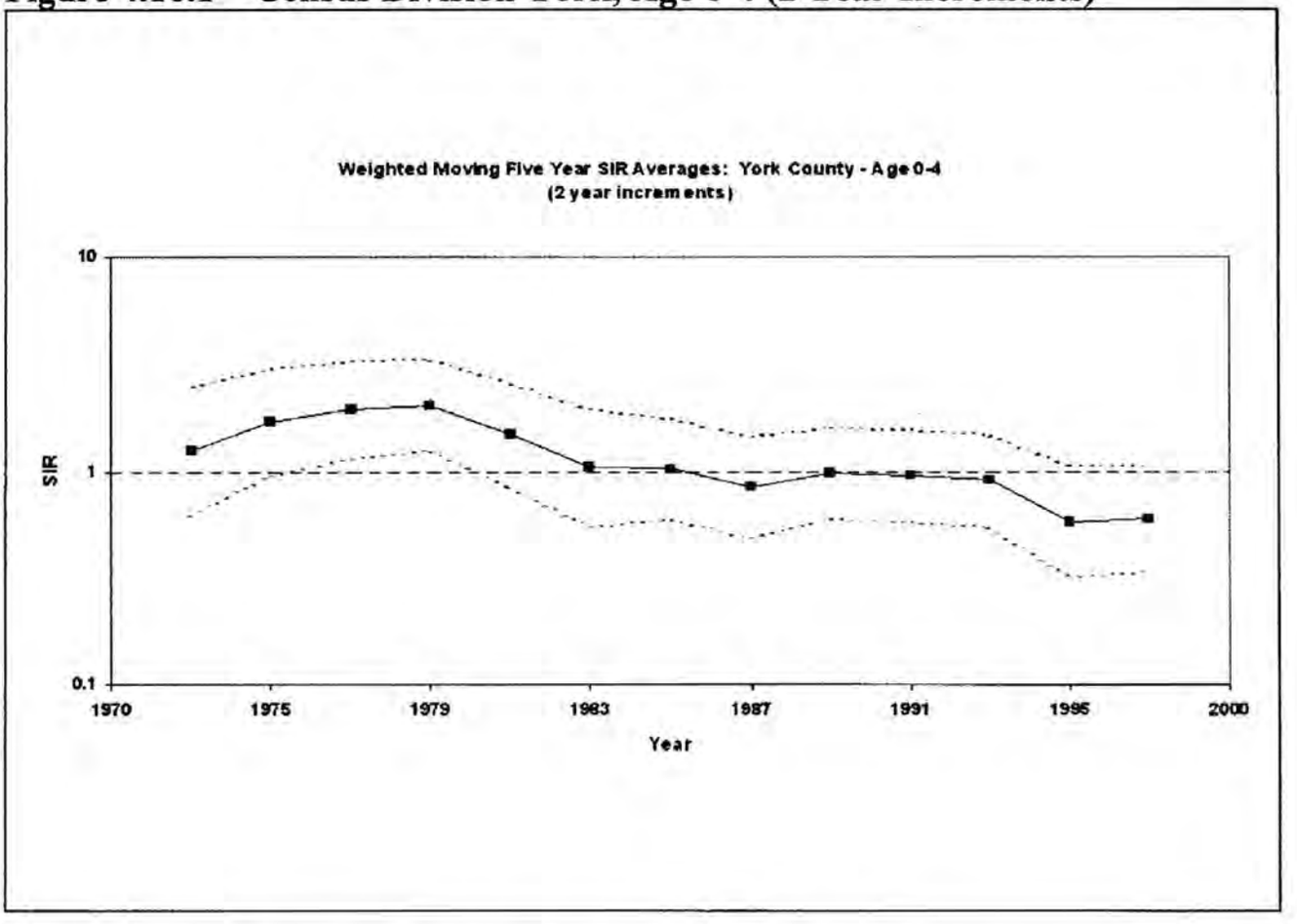


Figure 4.16.2 – Census Division York, Age 0-4 (3 Year Increments)

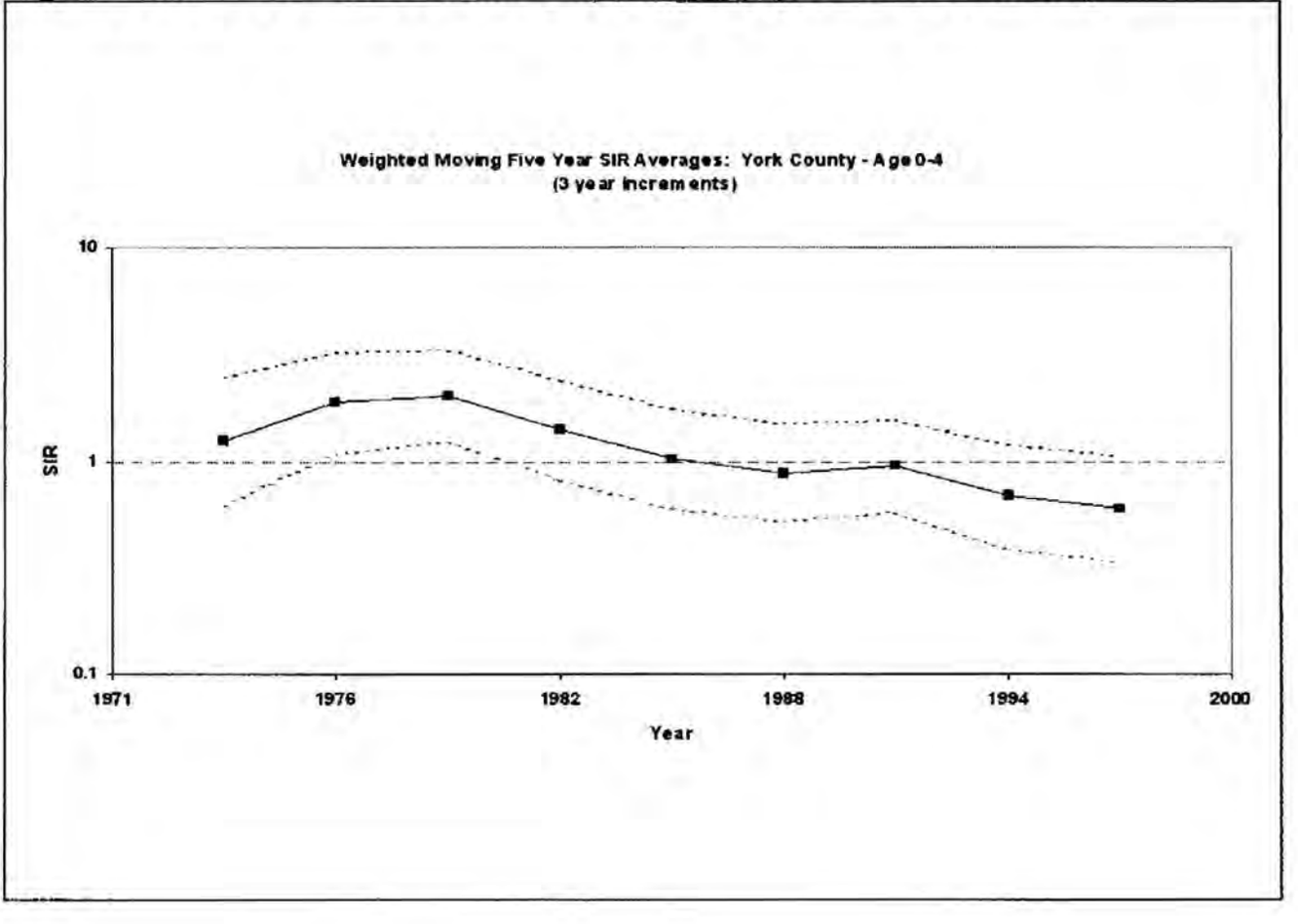


Figure 4.16.3 – Census Division York, Age 0-4 (4 Year Increments)

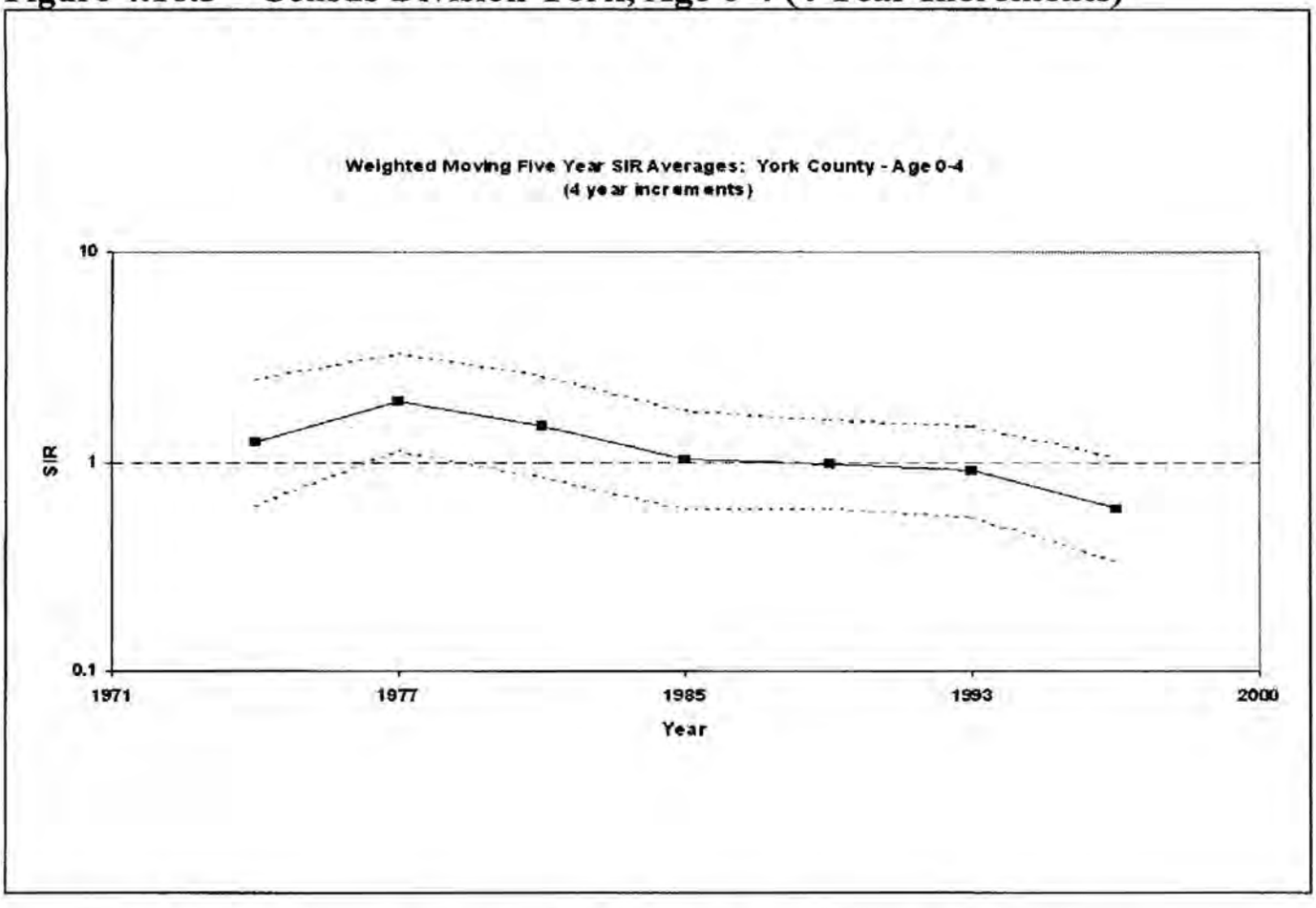
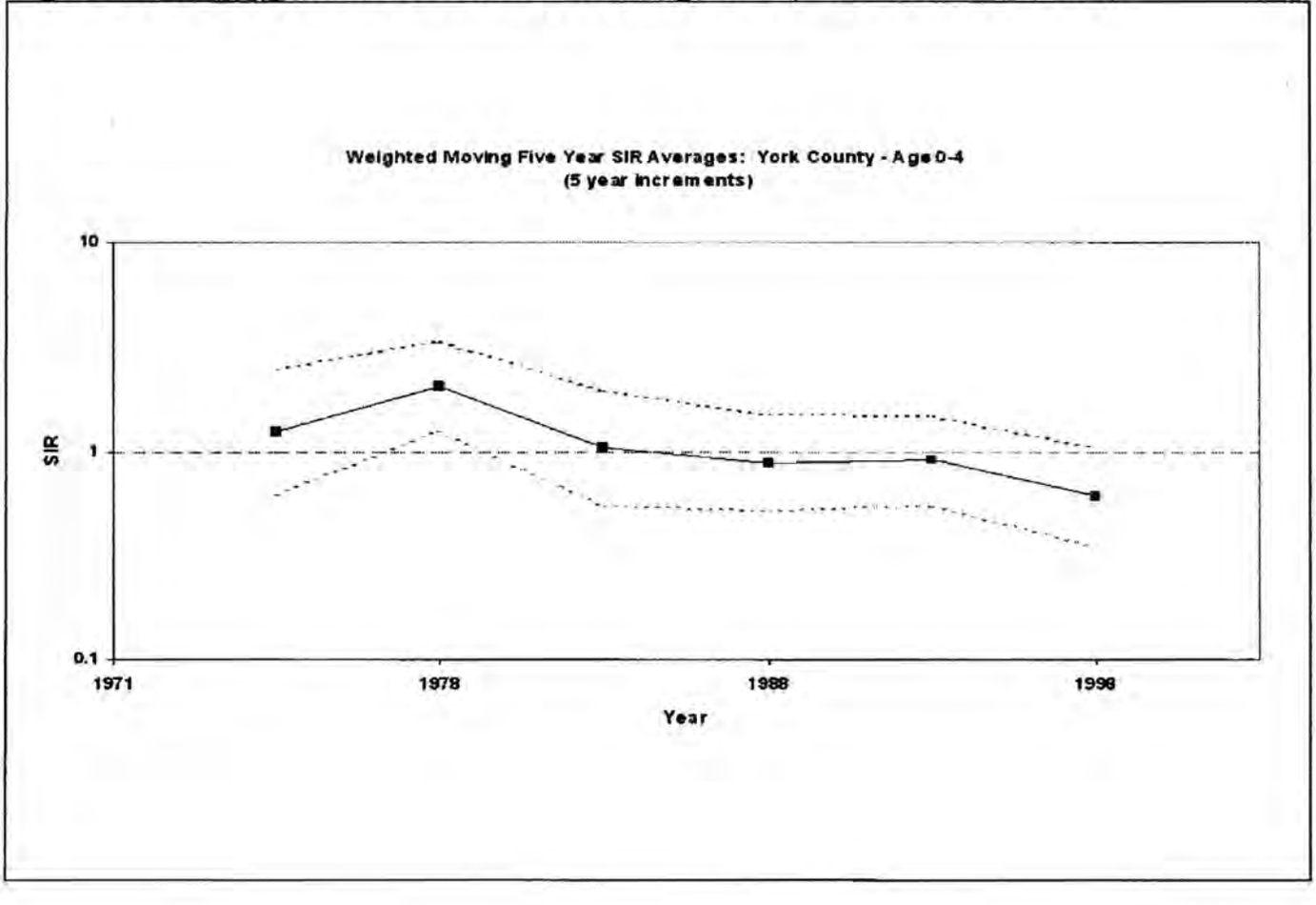


Figure 4.16.4 – Census Division York, Age 0-4 (5 Year Increments)



Smoothed Moving SIR for Census Division Hamilton-Wentworth: 0-14 Age Group

The census division of Hamilton-Wentworth contains the census subdivisions of Stoney Creek and Grimsby. The overall SIR for childhood leukemia from 1971-2000 was 0.89 (95% CI= 0.69, 1.15). Although higher than the overall SIR of 0.47 for Stoney Creek and Grimsby, the rate is still well below one. The smoothed moving windows are shown in Figures 4.17.1-4. The smoothed SIRs generally remained below one. For a brief period in the mid 1980s the rates were slightly statistically significantly below one for all increments except the 5-year increment.

Figure 4.17.1 – Census Division Hamilton-Wentworth, Age 0-14 (2 Year Increments)

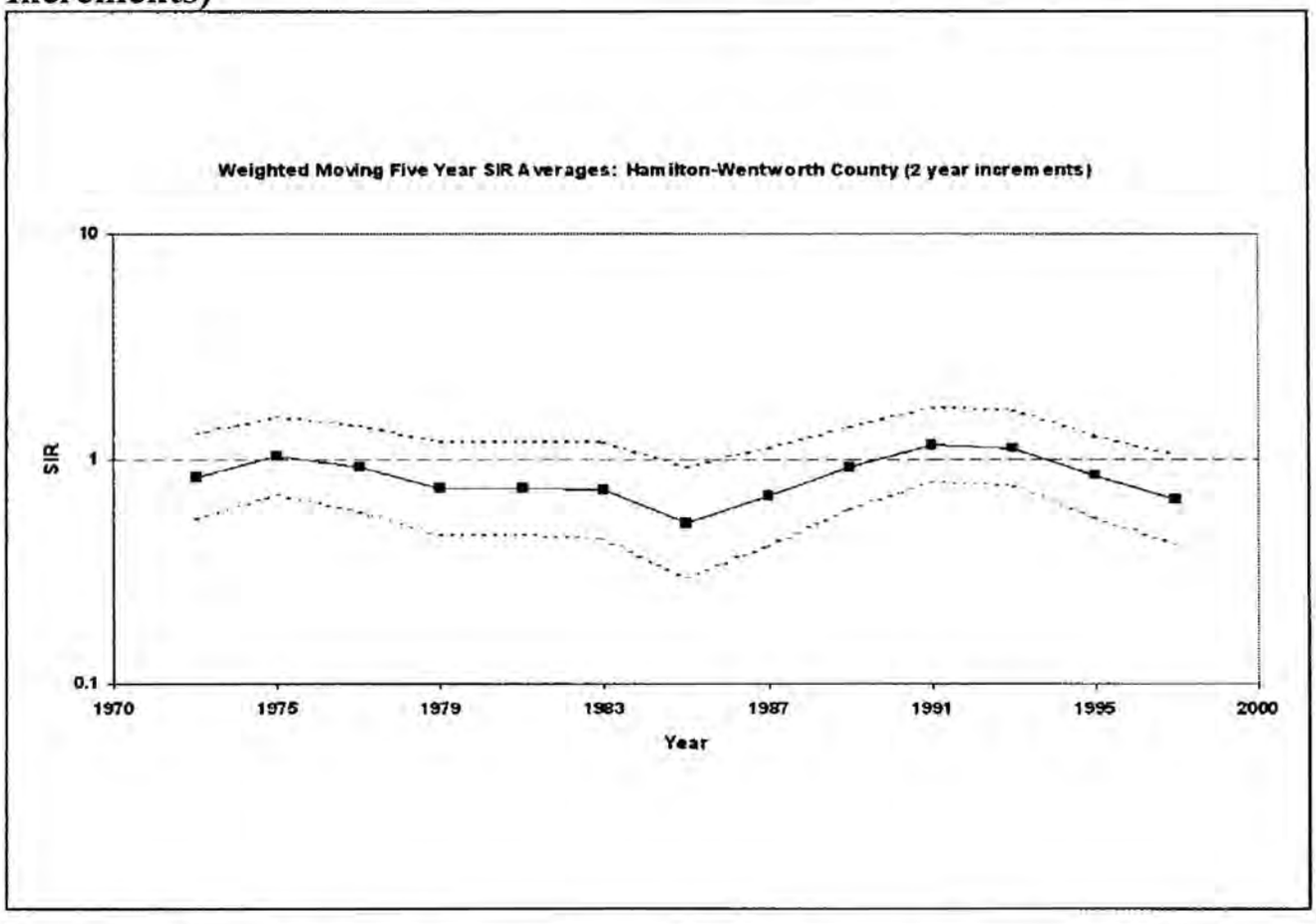


Figure 4.17.2 – Census Division Hamilton-Wentworth, Age 0-14 (3 Year Increments)

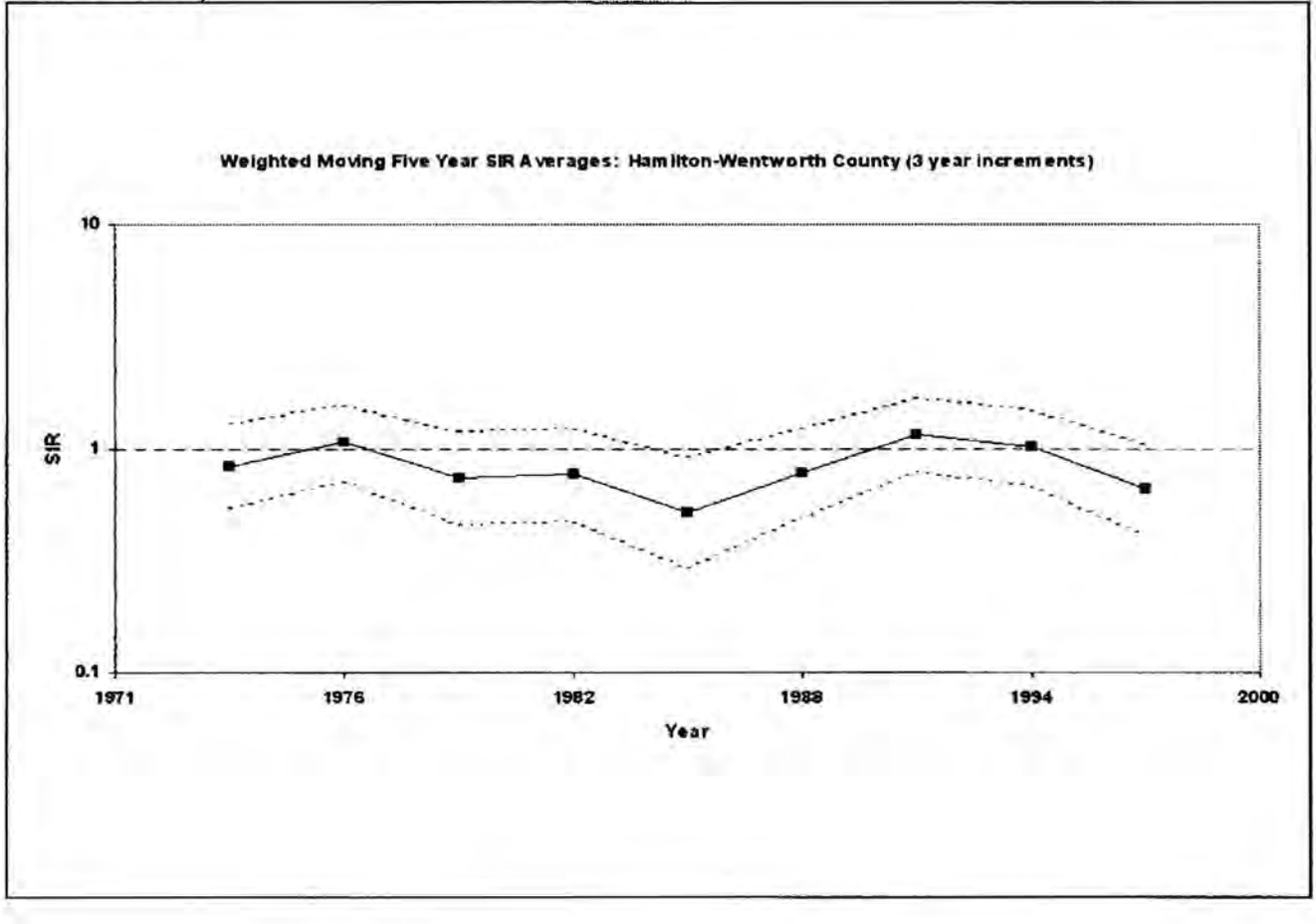


Figure 4.17.3 – Census Division Hamilton-Wentworth, Age 0-14 (4 Year Increments)

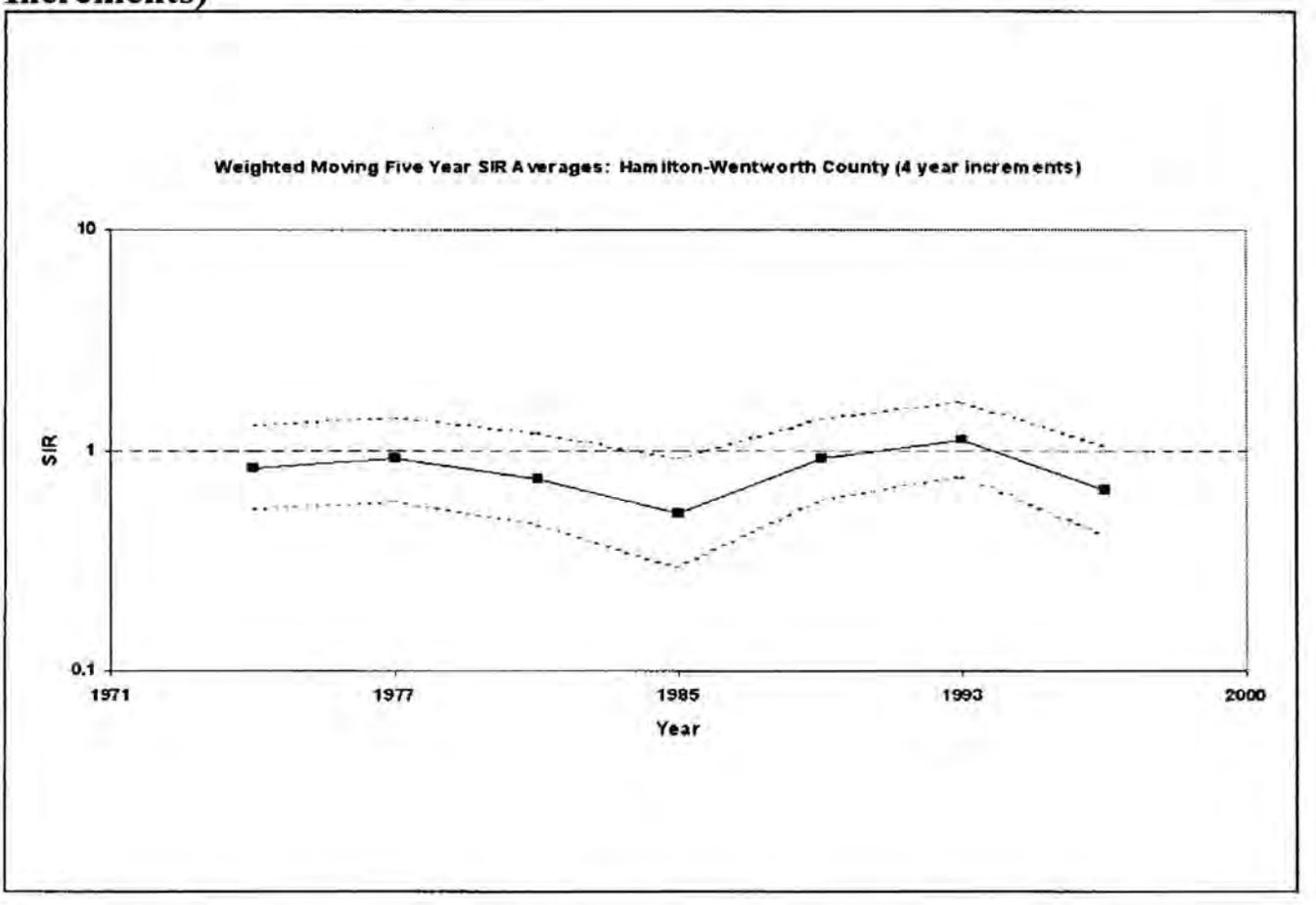
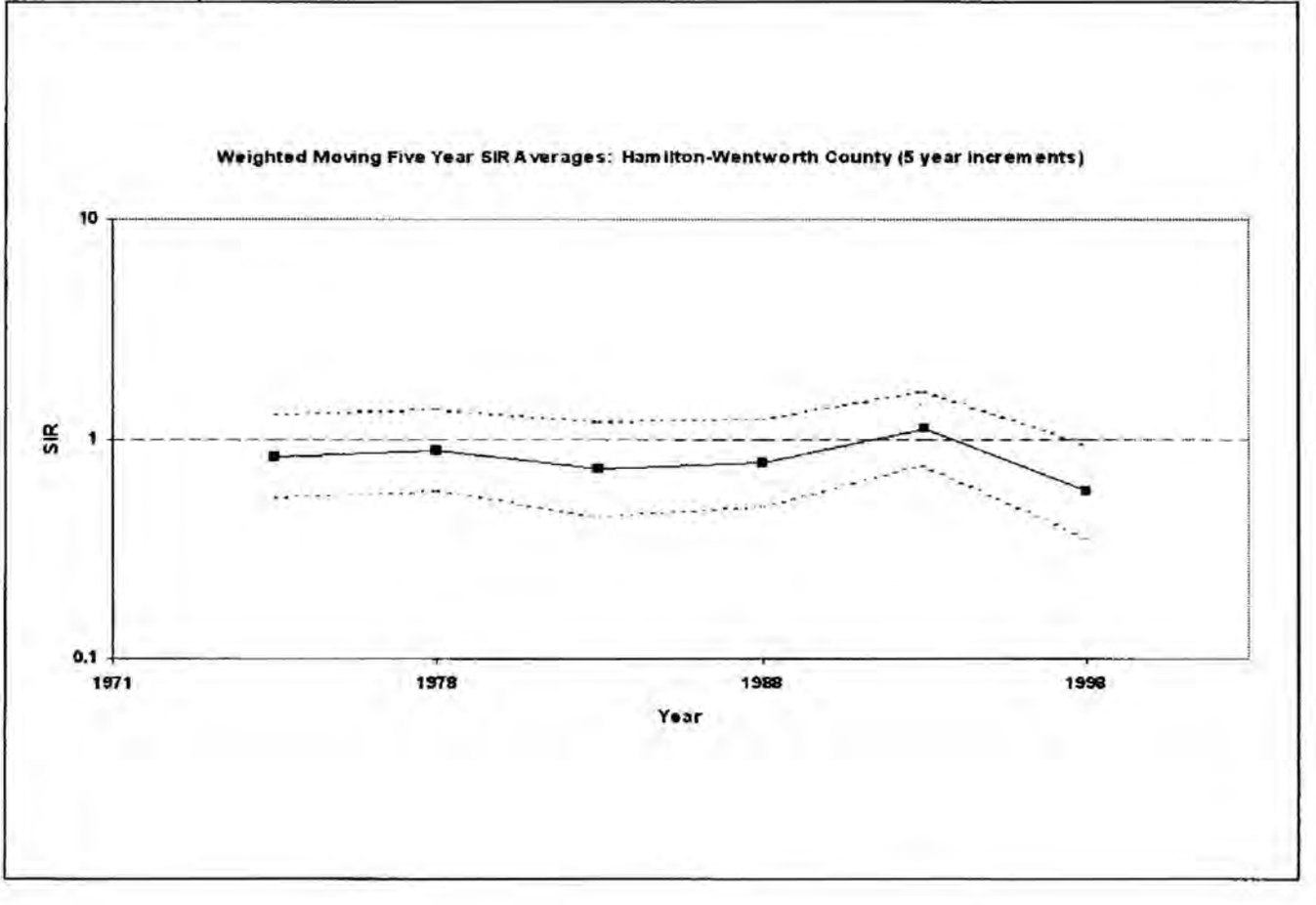


Figure 4.17.4 – Census Division Hamilton-Wentworth, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Division Hamilton-Wentworth: 0-4 Age Group

The overall SIR for childhood leukemia from 1971-2000 was 0.97 (95% CI= 0.76, 1.23). Although higher than the overall SIR of 0.89 for the 0-14 age group, the rate is still slightly below one. The smoothed moving windows are shown in Figures 4.18.1-4. The smoothed SIRs remained near one until the mid 1980s when the rates dropped well below one. For a brief period in the mid 1990s the smoothed SIRs were greater than one. However, statistical significance was never achieved.

Figure 4.18.1 – Census Division Hamilton-Wentworth, Age 0-4 (2 Year Increments)

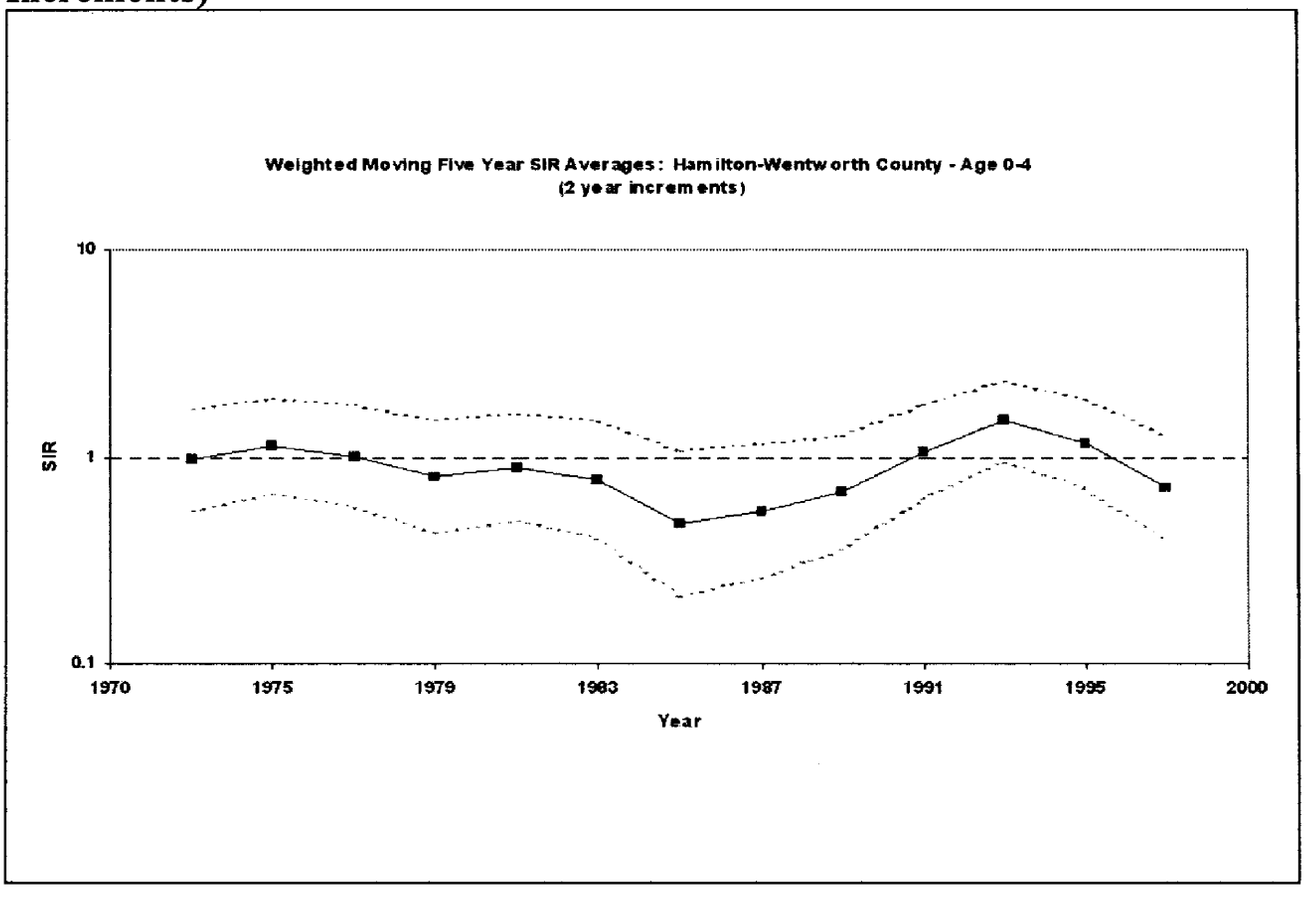


Figure 4.18.2 – Census Division Hamilton-Wentworth, Age 0-4 (3 Year Increments)

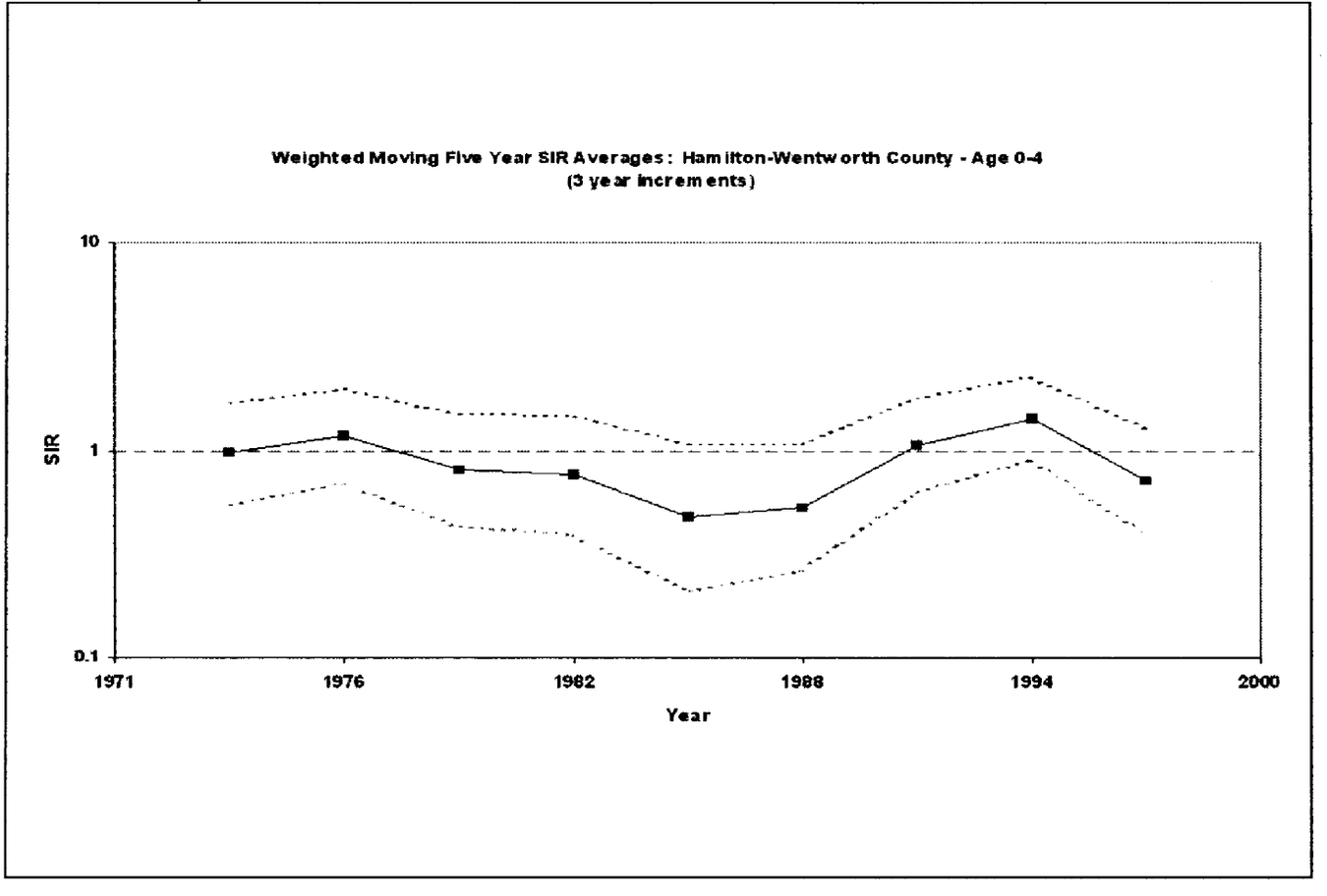


Figure 4.18.3 – Census Division Hamilton-Wentworth, Age 0-4 (4 Year Increments)

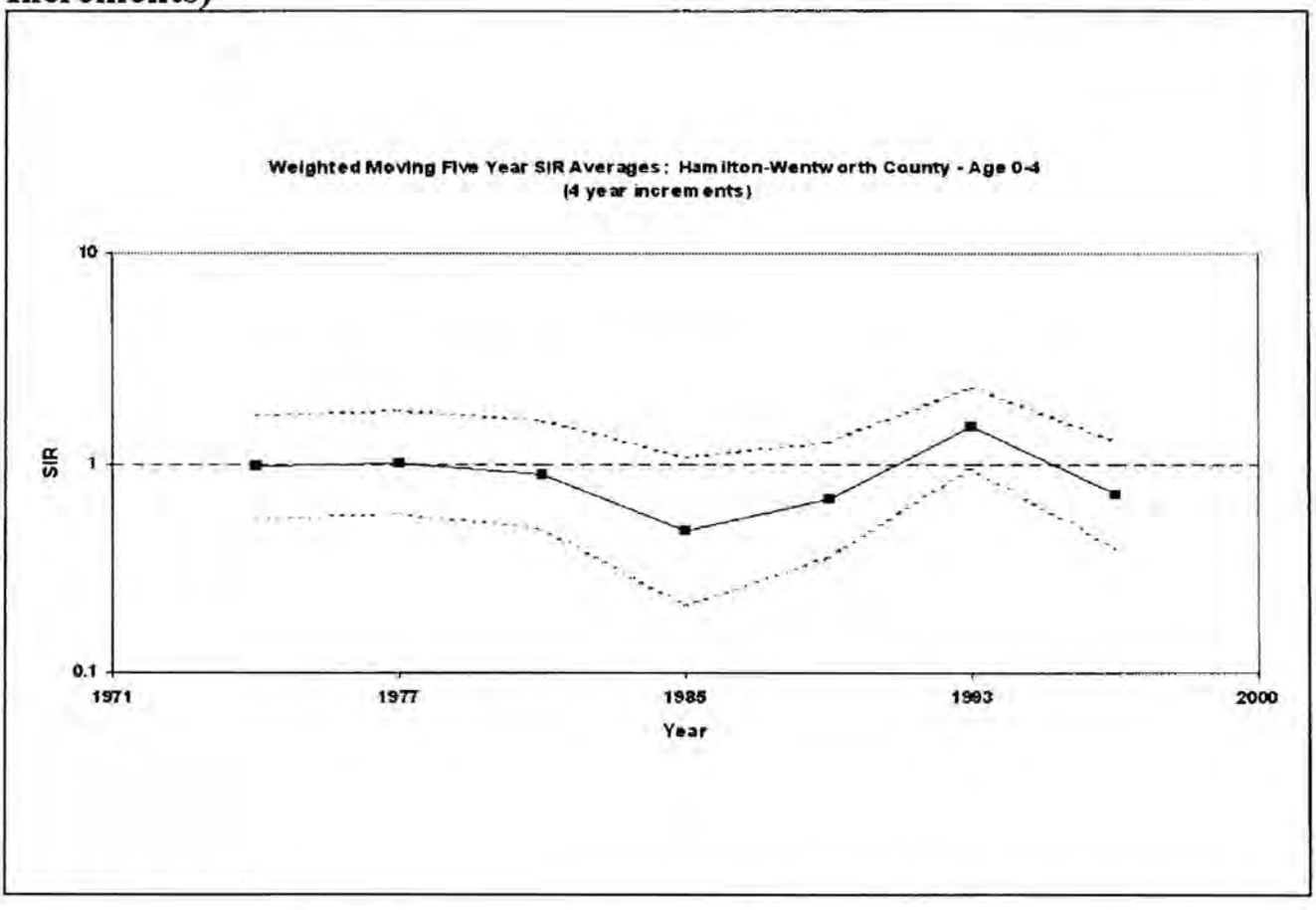
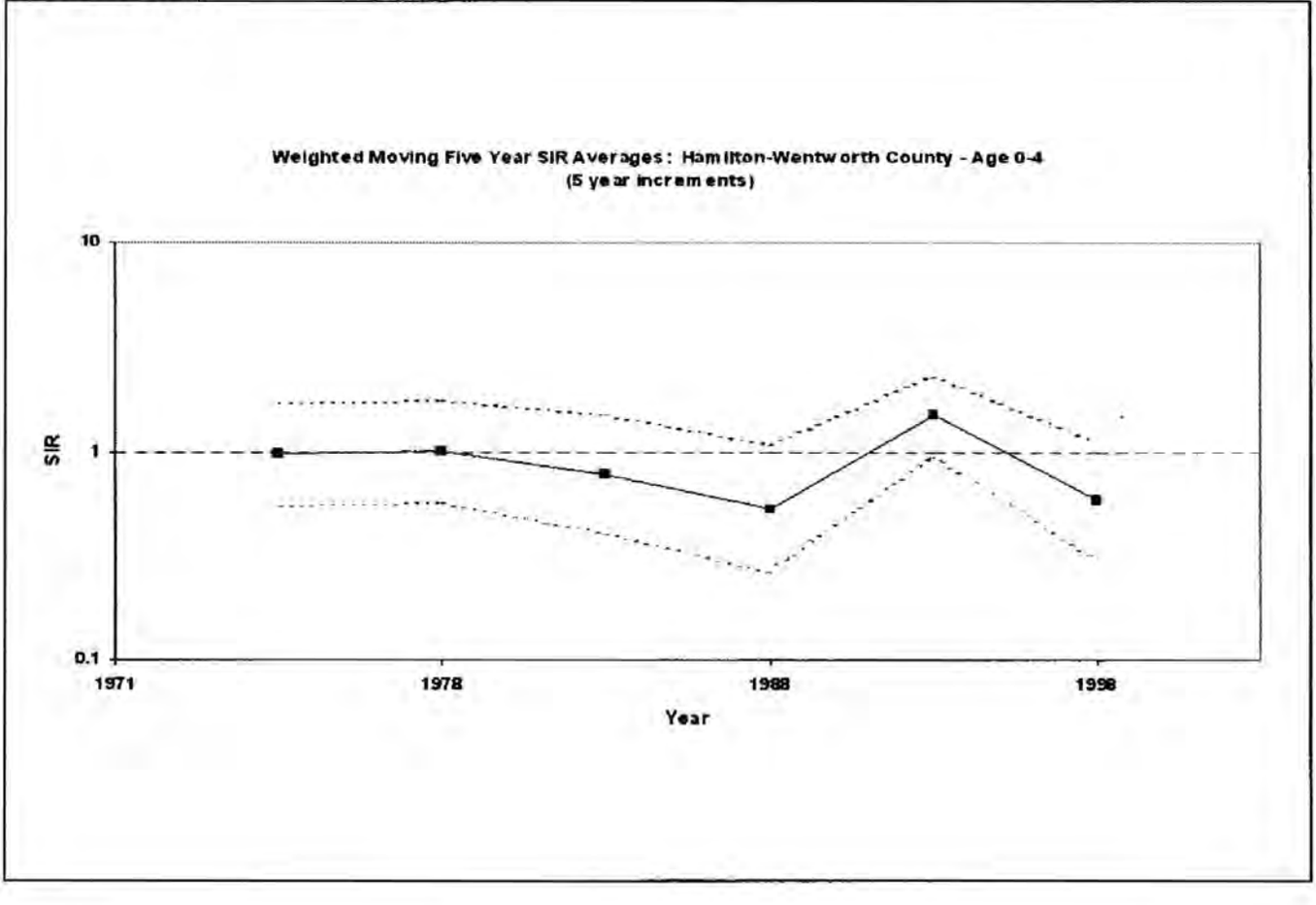


Figure 4.18.4 – Census Division Hamilton-Wentworth, Age 0-4 (5 Year Increments)



Smoothed Moving SIR for Census Division Niagara: 0-14 Age Group

The census division of Niagara contains the census subdivisions of Niagara Falls, Welland, and Thorold. The overall SIR for childhood leukemia from 1971-2000 was 1.05 (95% CI= 0.81, 1.37), well below the statistically significant overall SIR of 2.68 experienced by the census subdivisions. The smoothed moving windows are shown in Figures 4.19.1-4. Unlike the census subdivision smoothed SIRs that were above one for the entire study period, the census division smoothed SIRs stayed consistently near one.

Figure 4.19.1 – Census Division Niagara, Age 0-14 (2 Year Increments)

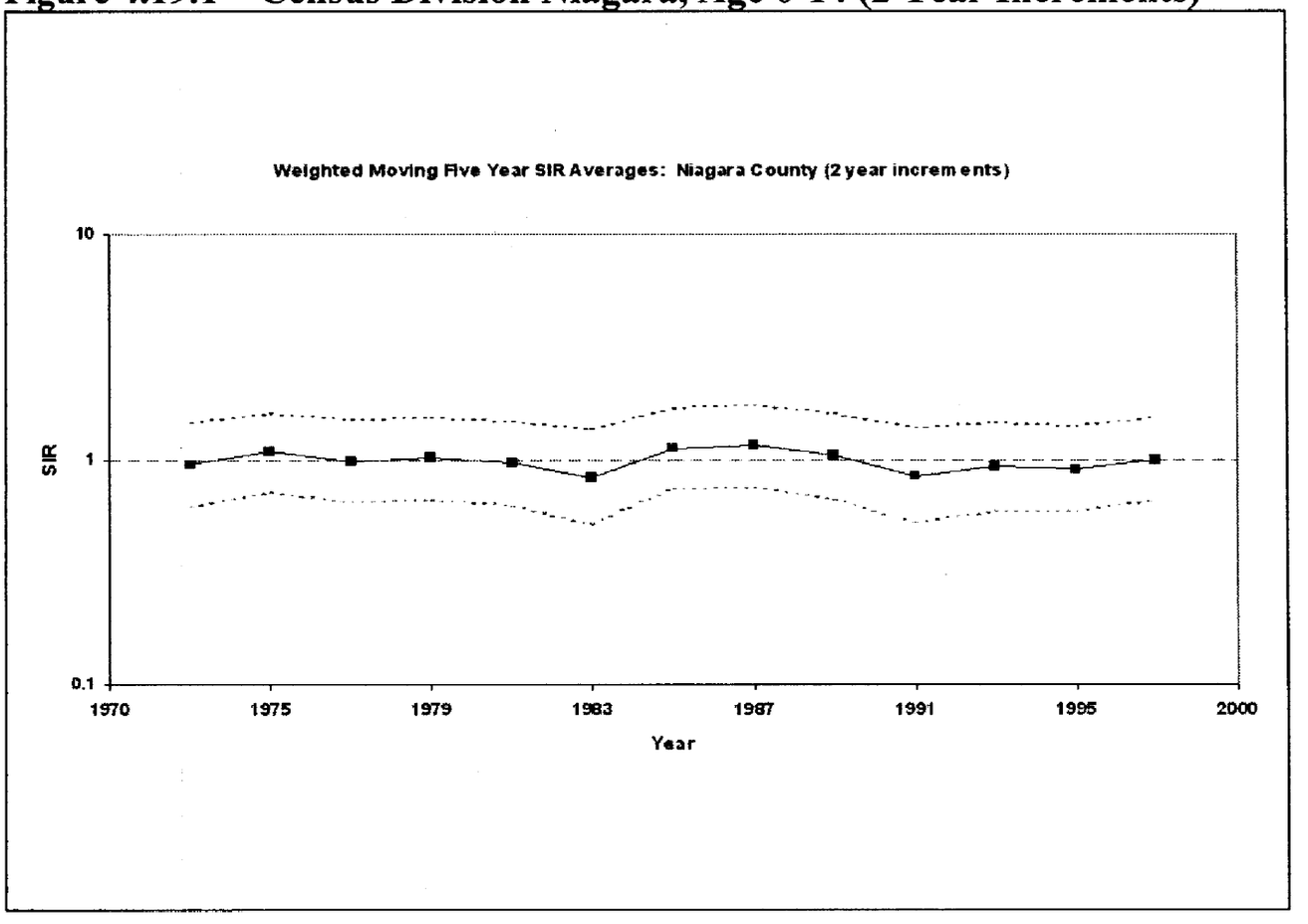


Figure 4.19.2 – Census Division Niagara, Age 0-14 (3 Year Increments)

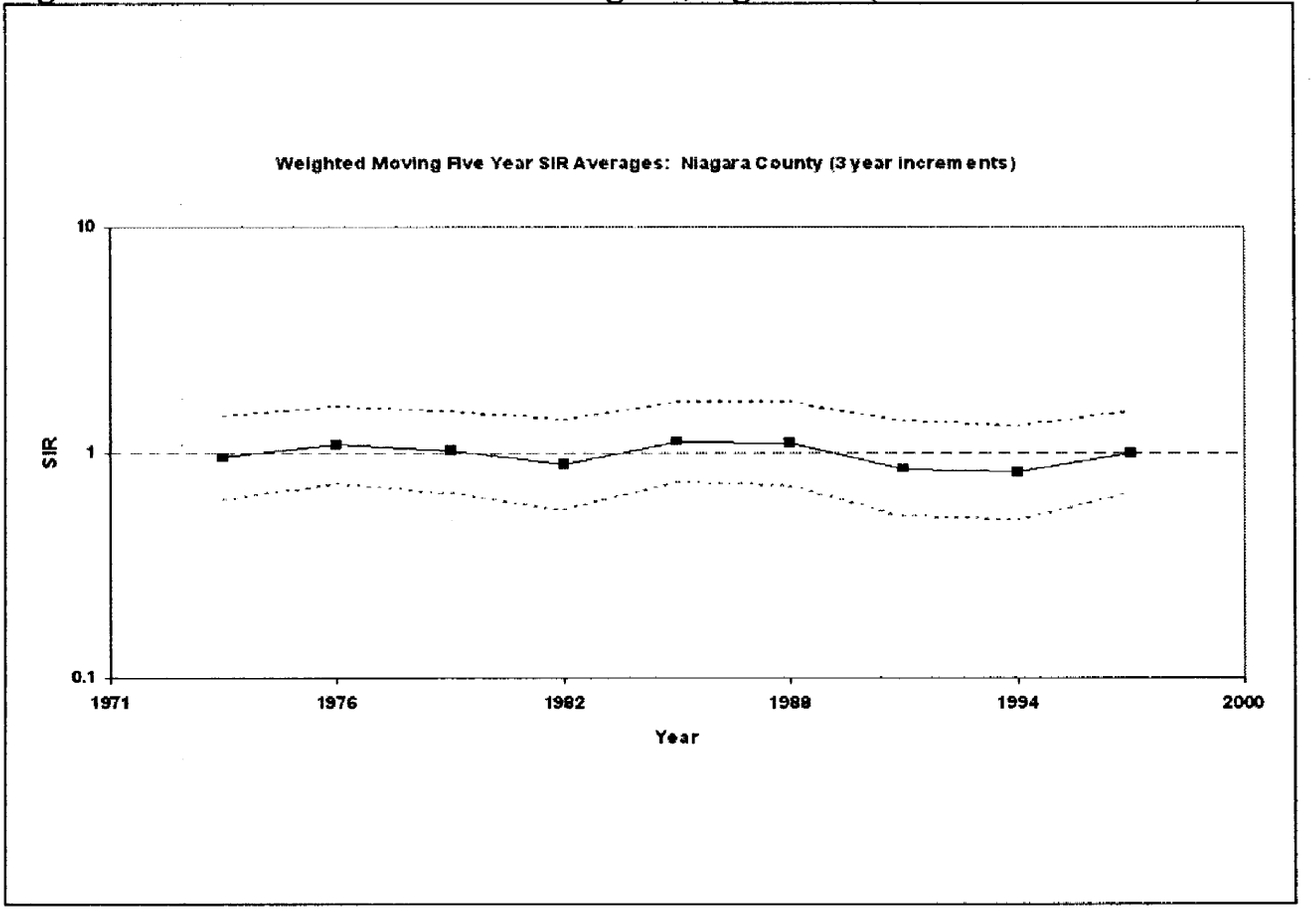


Figure 4.19.3 – Census Division Niagara, Age 0-14 (4 Year Increments)

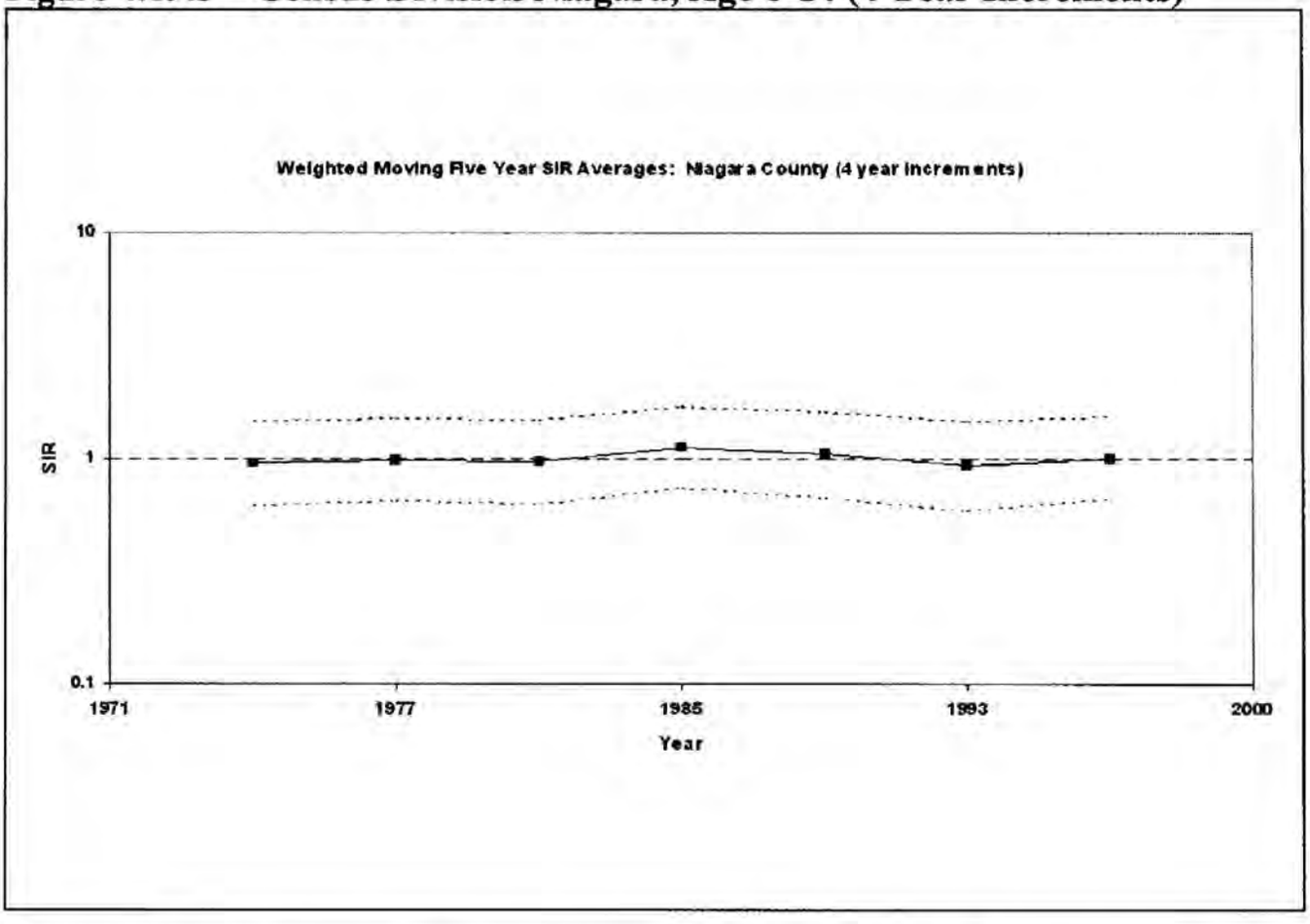
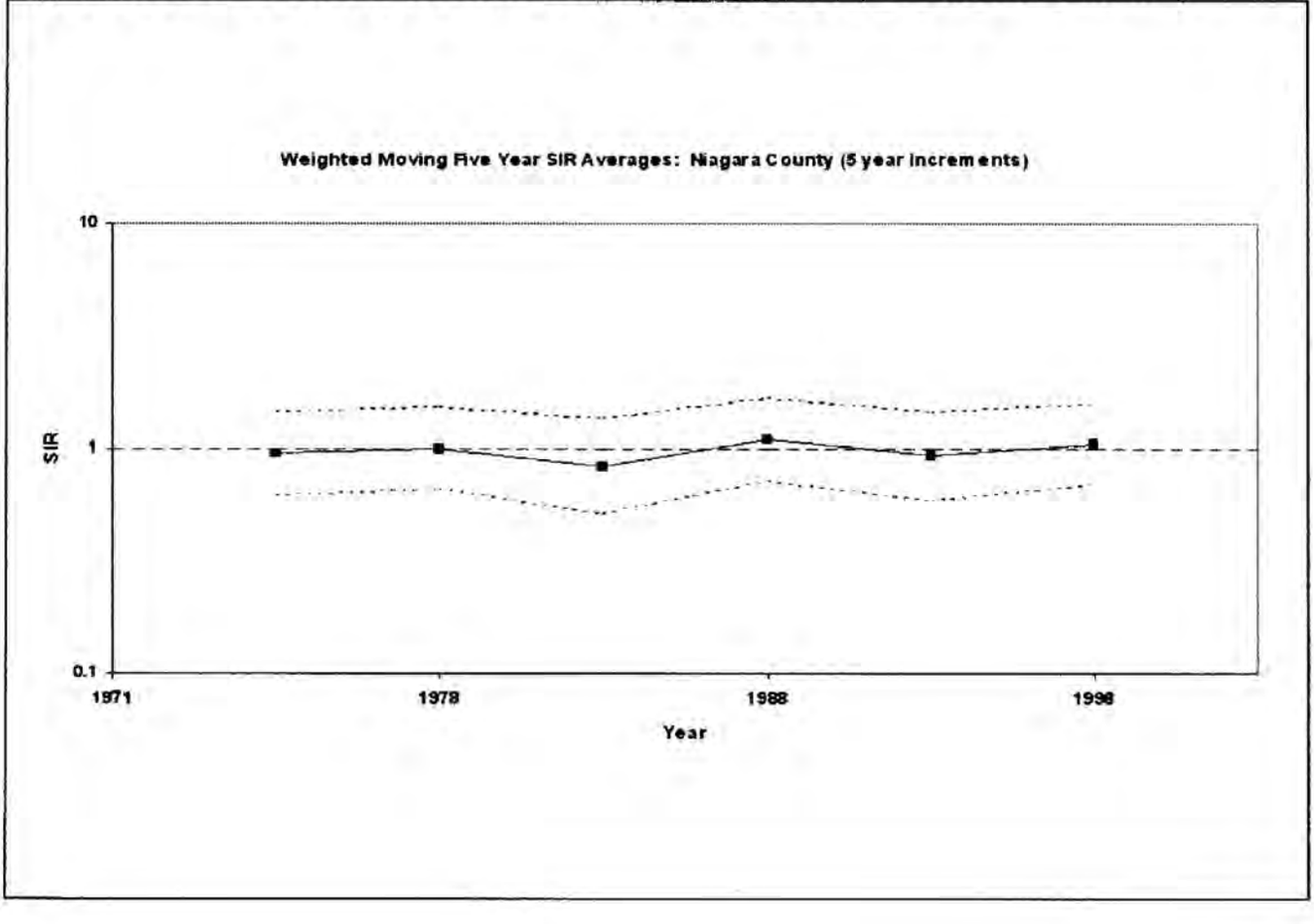


Figure 4.19.4 – Census Division Niagara, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Division Niagara: 0-4 Age Group

The overall SIR for childhood leukemia from 1971-2000 was 1.11 (95% CI= 0.86, 1.41), slightly higher than the overall SIR for the 0-14 age group. The smoothed moving windows are shown in Figures 4.20.1-4. The smoothed SIRs remained near one for most of the study period. Increased rates were experienced in the late 1980s, but not significantly so.

Figure 4.20.1 – Census Division Niagara, Age 0-4 (2 Year Increments)

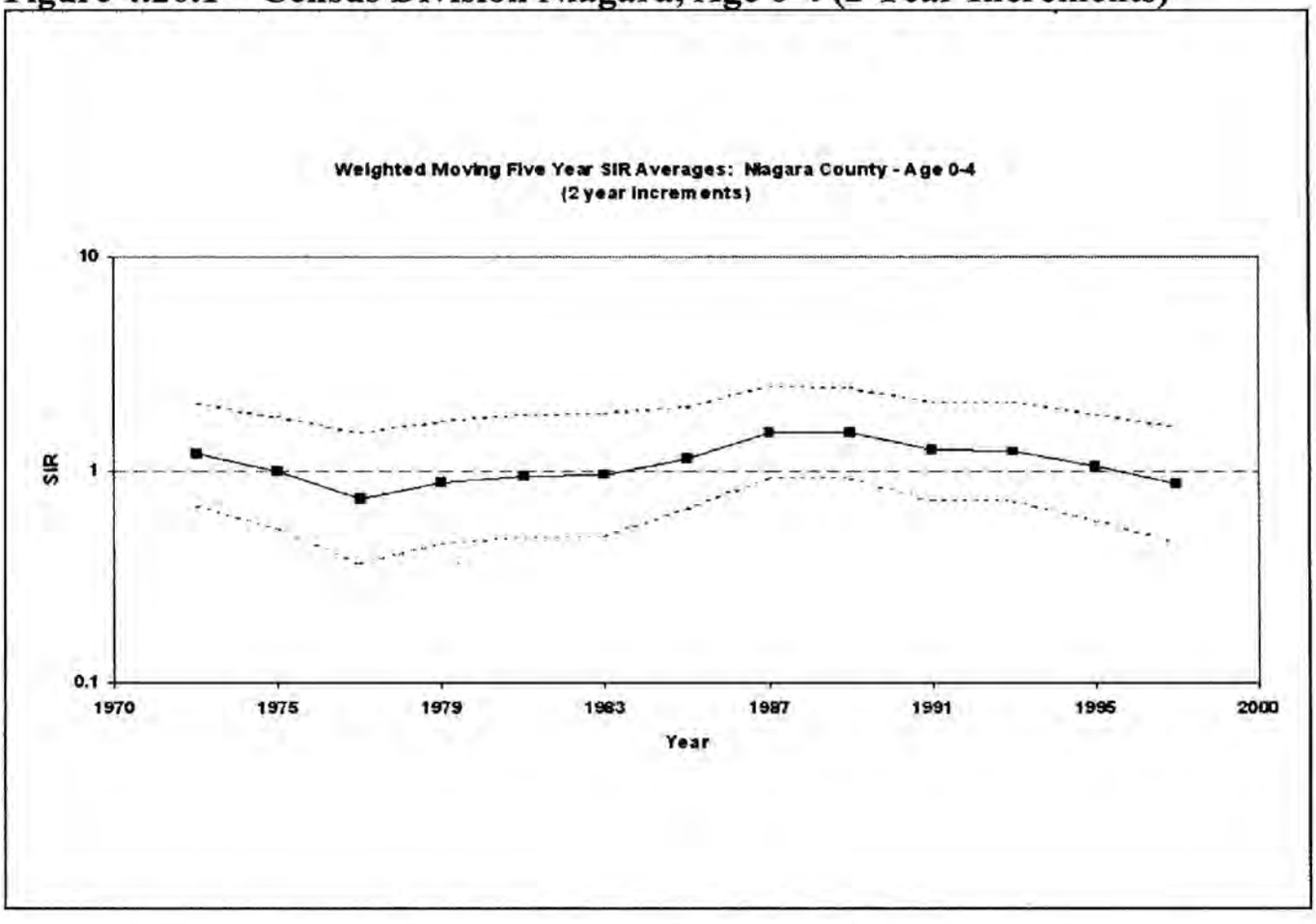


Figure 4.20.2 – Census Division Niagara, Age 0-4 (3 Year Increments)

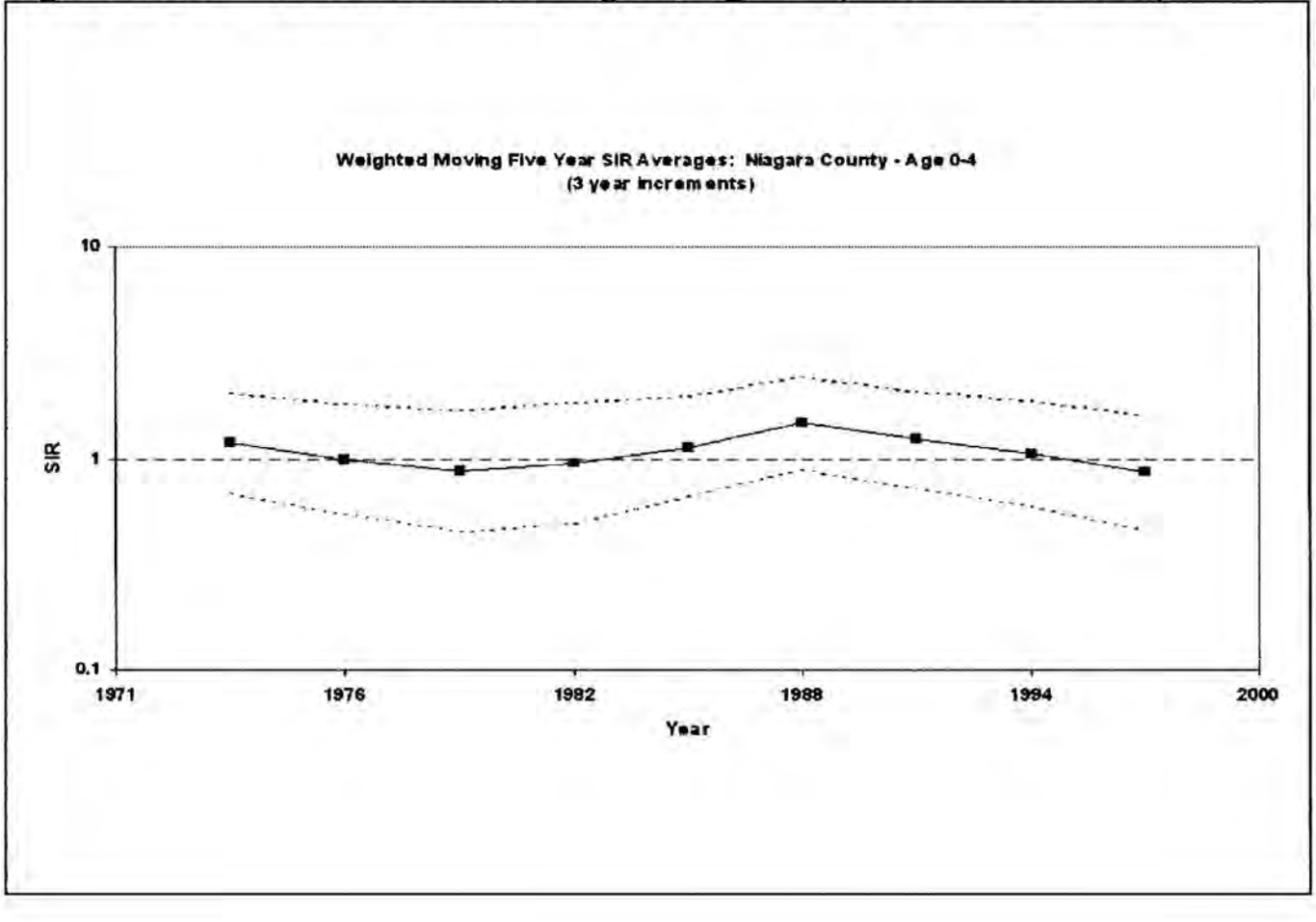


Figure 4.20.3 – Census Division Niagara, Age 0-4 (4 Year Increments)

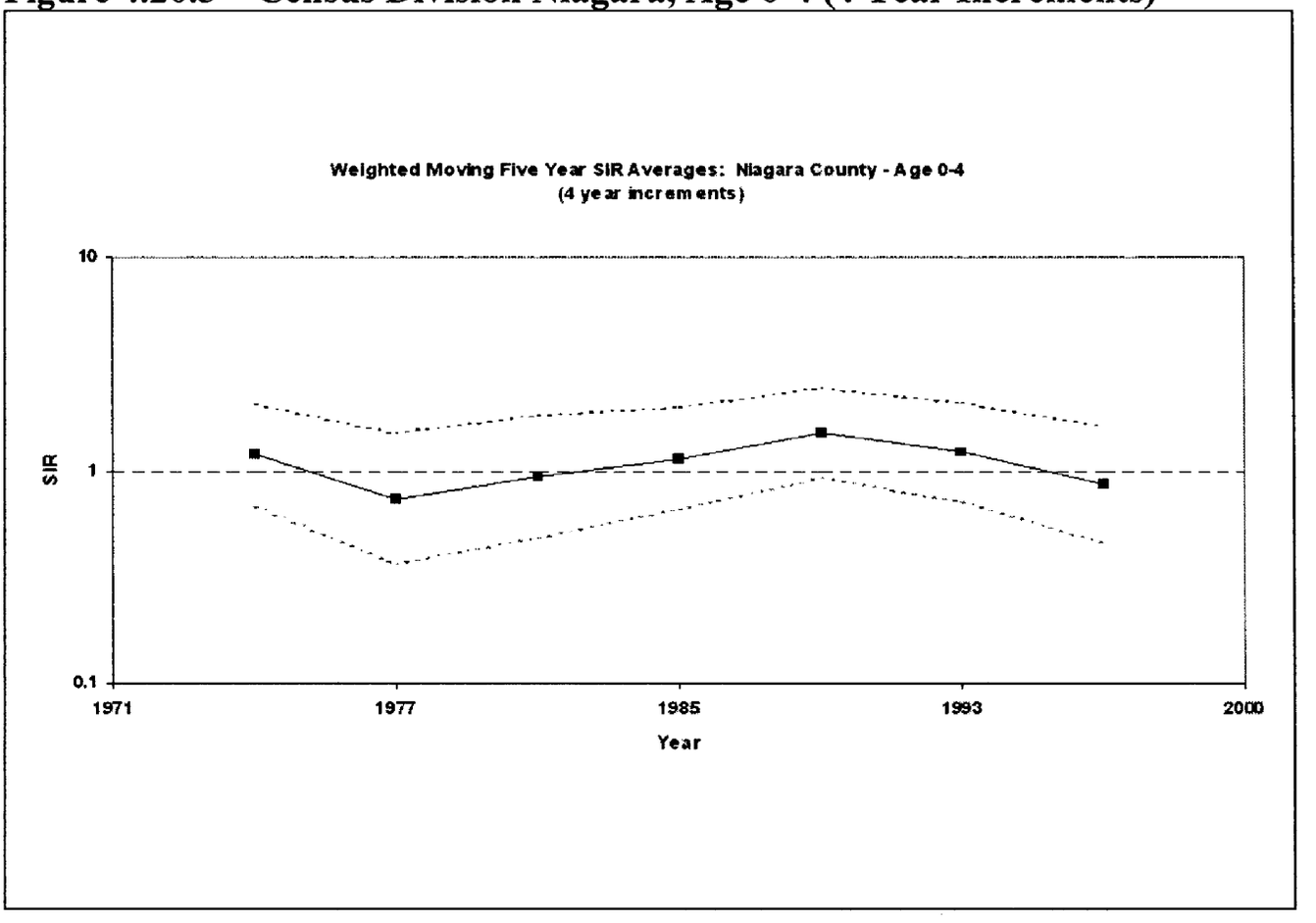
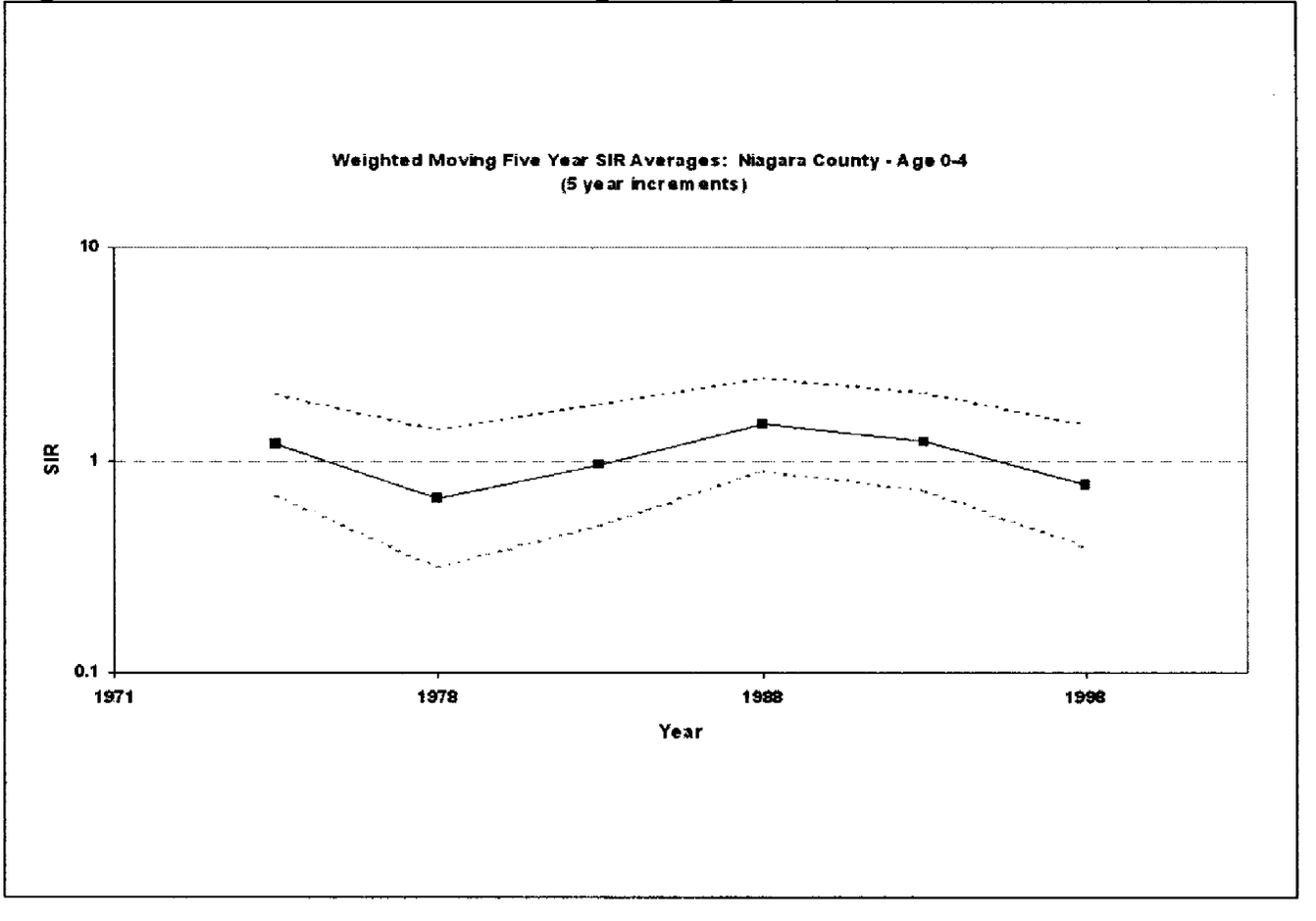


Figure 4.20.4 – Census Division Niagara, Age 0-4 (5 Year Increments)



Smoothed Moving SIR for Census Division Essex: 0-14 Age Group

Essex was added *a posteriori* for comparison to Niagara because the census divisions share many of the same characteristics. In particular, both census divisions are similarly populated and near populated cities in the U.S. Although it would have been preferable to include census subdivisions within Essex, since it was the census subdivisions in Niagara that had elevated rates, it was not possible to do so because of multiple changes within the census subdivisions in Essex during the study period. Therefore, census division is the smallest geostatistical unit in that area that can be considered reliable. The overall SIR for childhood leukemia from 1971-2000 was 0.92 (95% CI= 0.69, 1.22). The smoothed moving windows are shown in Figures 4.21.1-4. The smoothed SIRs remained near one for the first half of the study period and then began a downward trend for the rest of the study period.

Figure 4.21.1 – Census Division Essex, Age 0-14 (2 Year Increments)

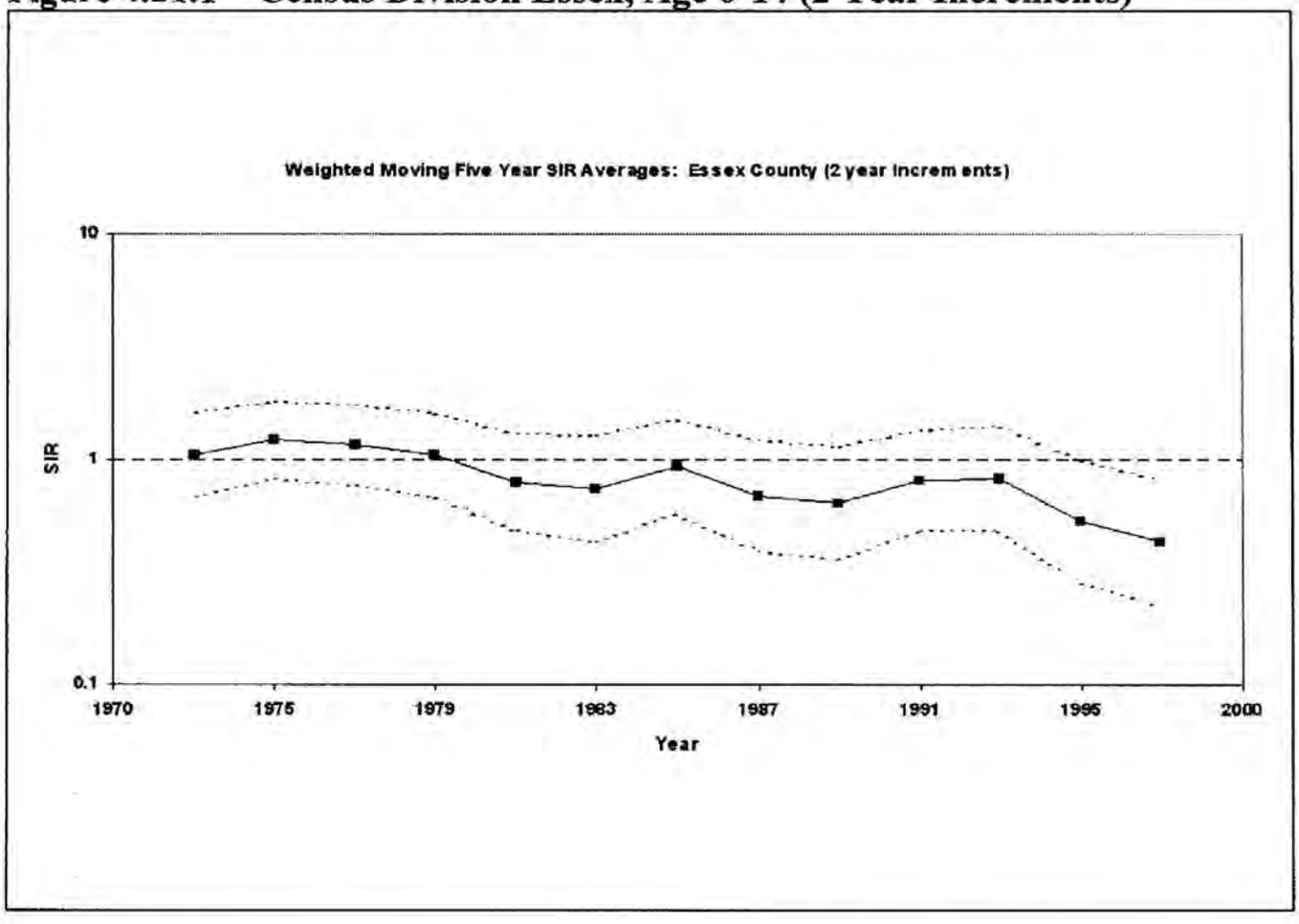


Figure 4.21.2 – Census Division Essex, Age 0-14 (3 Year Increments)

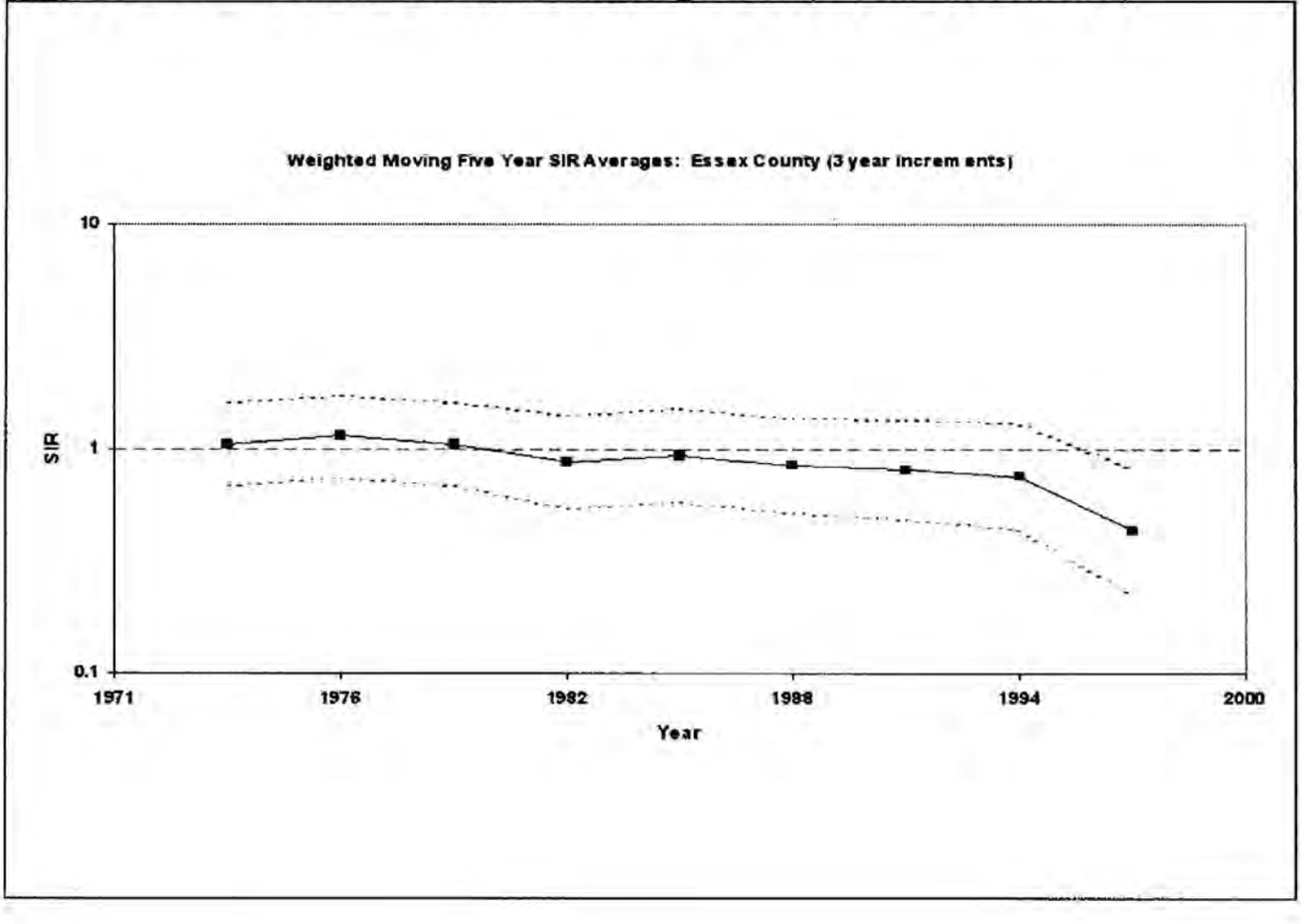


Figure 4.21.3 – Census Division Essex, Age 0-14 (4 Year Increments)

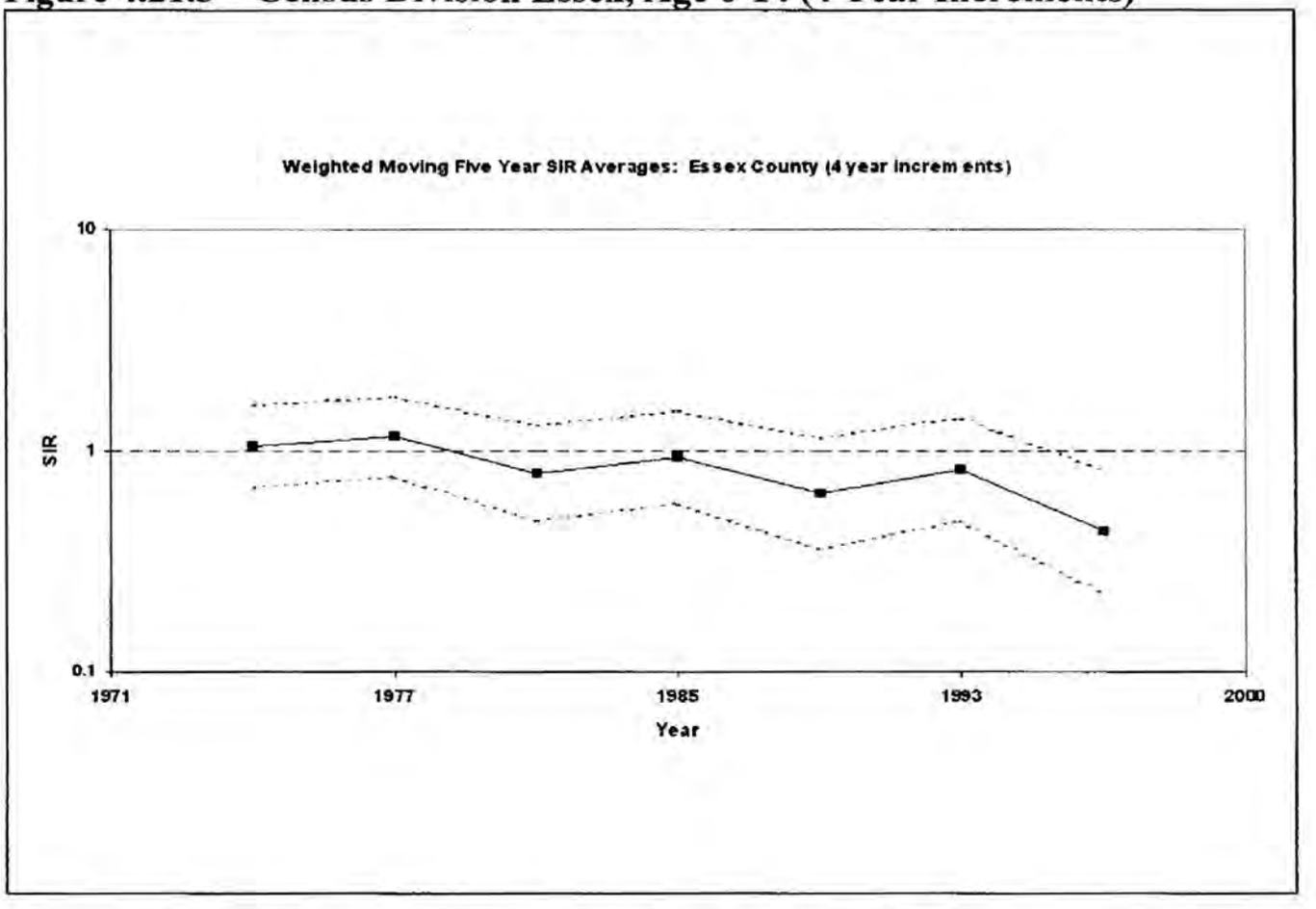
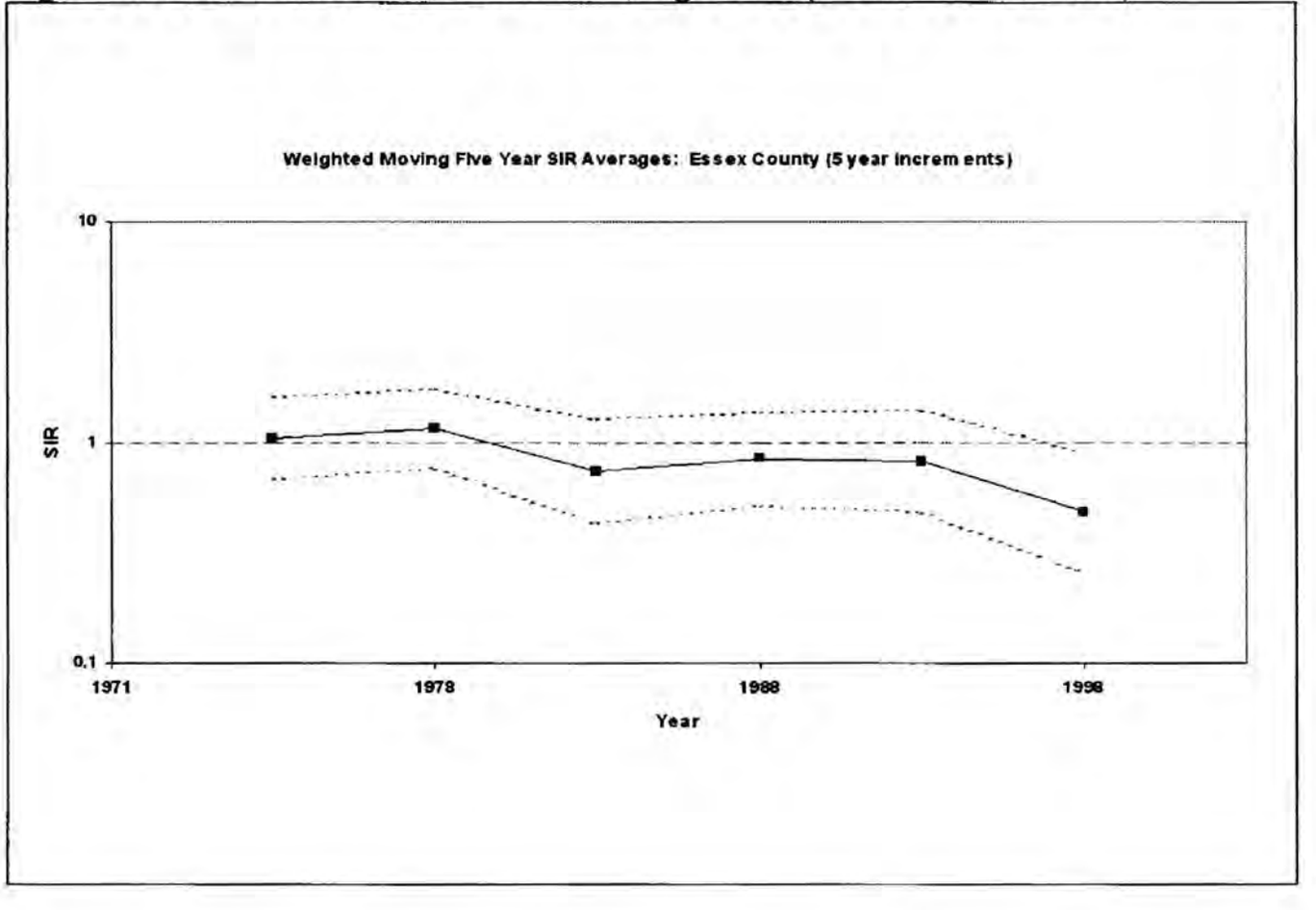


Figure 4.21.4 – Census Division Essex, Age 0-14 (5 Year Increments)



Smoothed Moving SIR for Census Division Essex: 0-4 Age Group

The overall SIR for childhood leukemia from 1971-2000 was 1.05 (95% CI= 0.80 1.36), higher than the 0-14 age group. The smoothed moving windows are shown in Figures 4.22.1-4. The smoothed SIRs followed the same general trend at the 0-14 age group, remaining near one for the first half of the study and below one for the rest of the time.

Figure 4.22.1 – Census Division Essex, Age 0-4 (2 Year Increments)

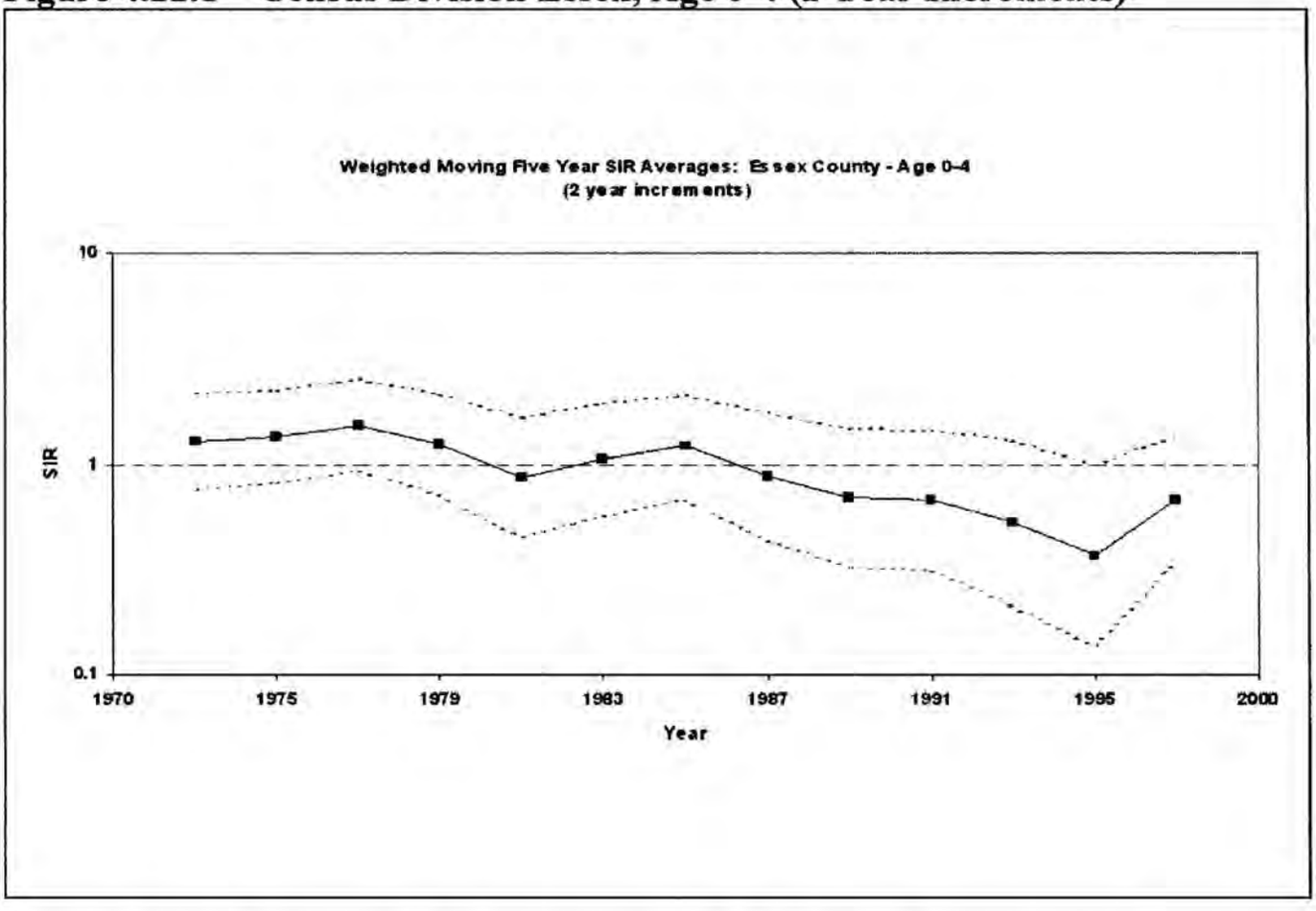


Figure 4.22.2 – Census Division Essex, Age 0-4 (3 Year Increments)

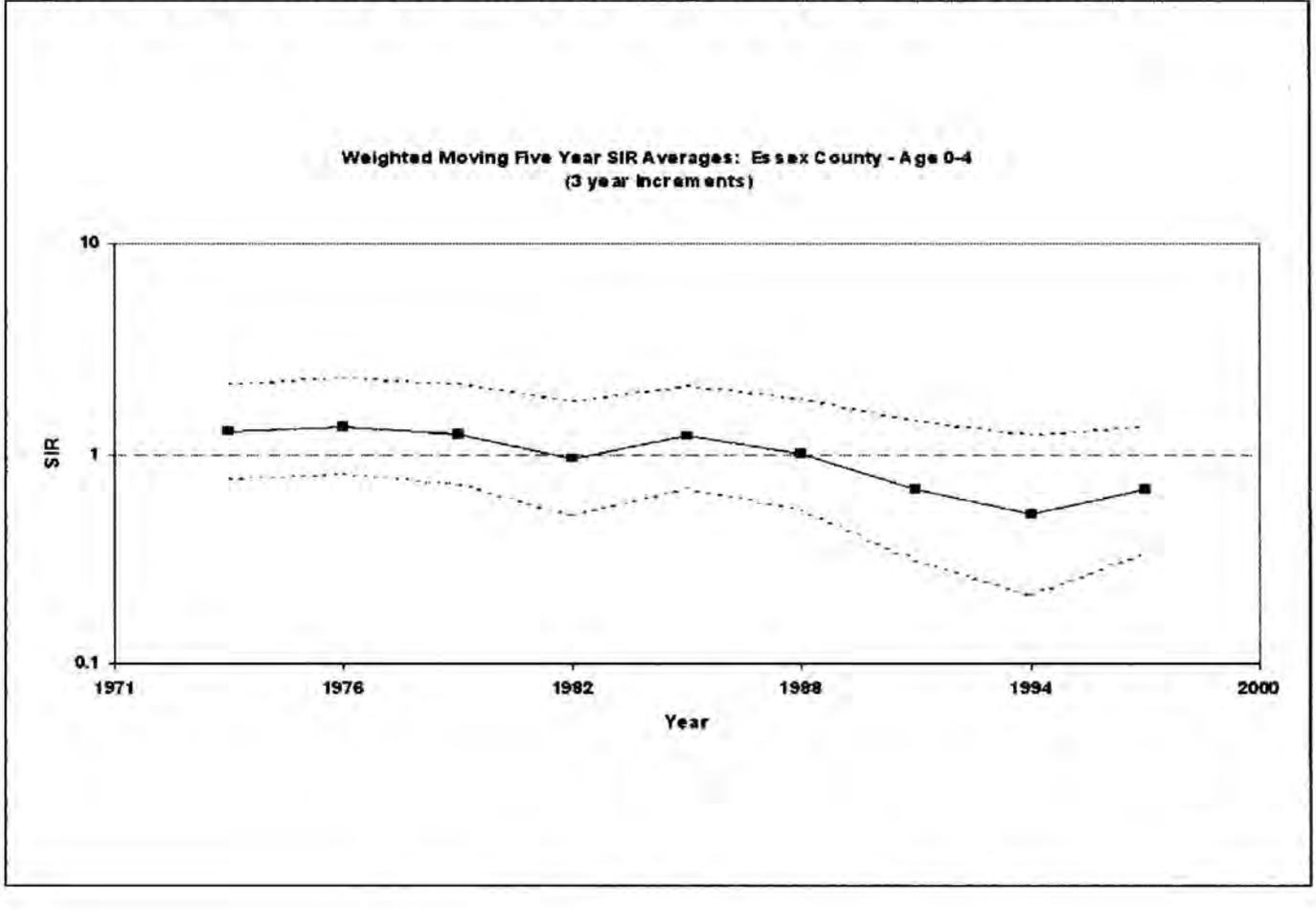


Figure 4.22.3 – Census Division Essex, Age 0-4 (4 Year Increments)

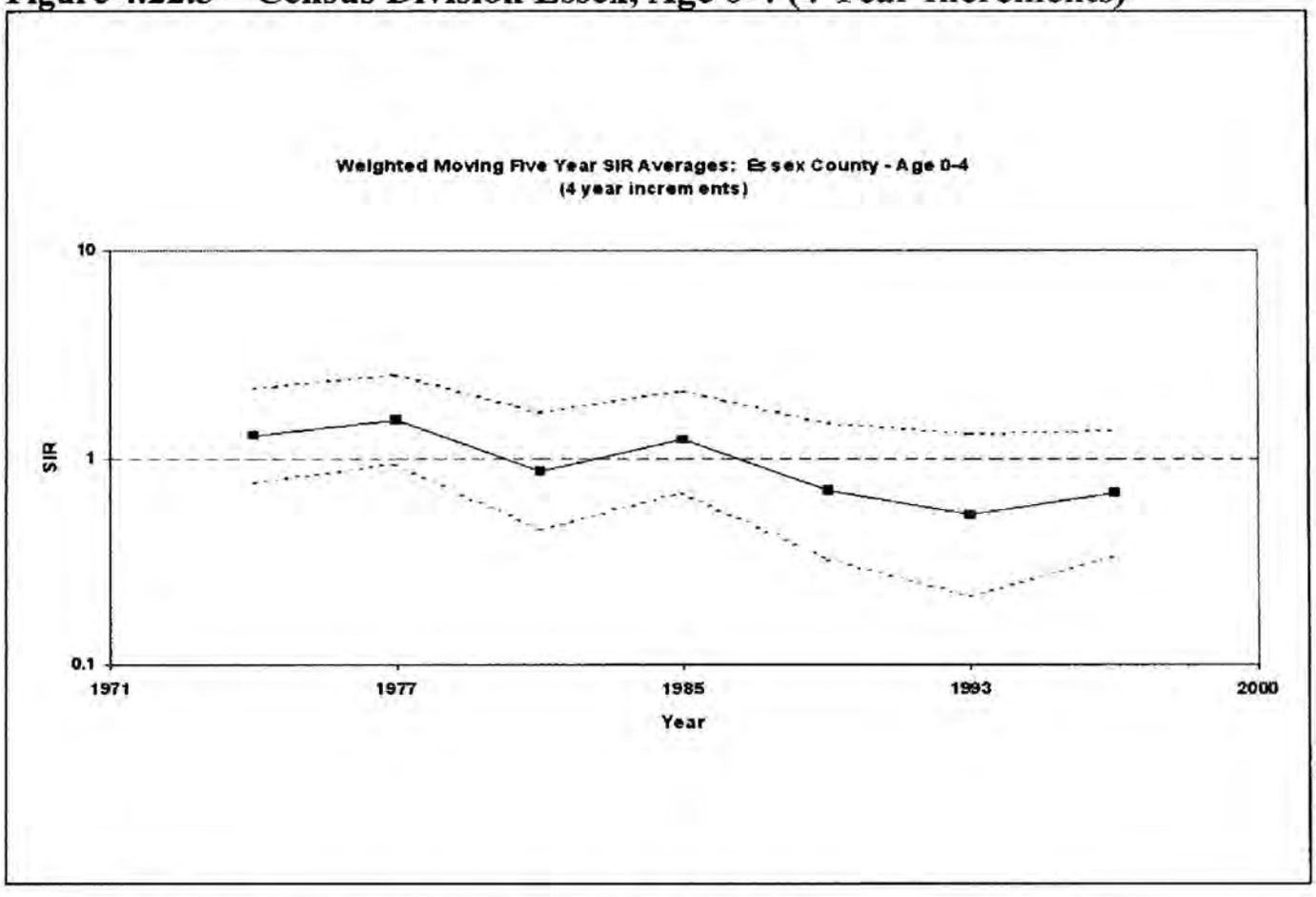
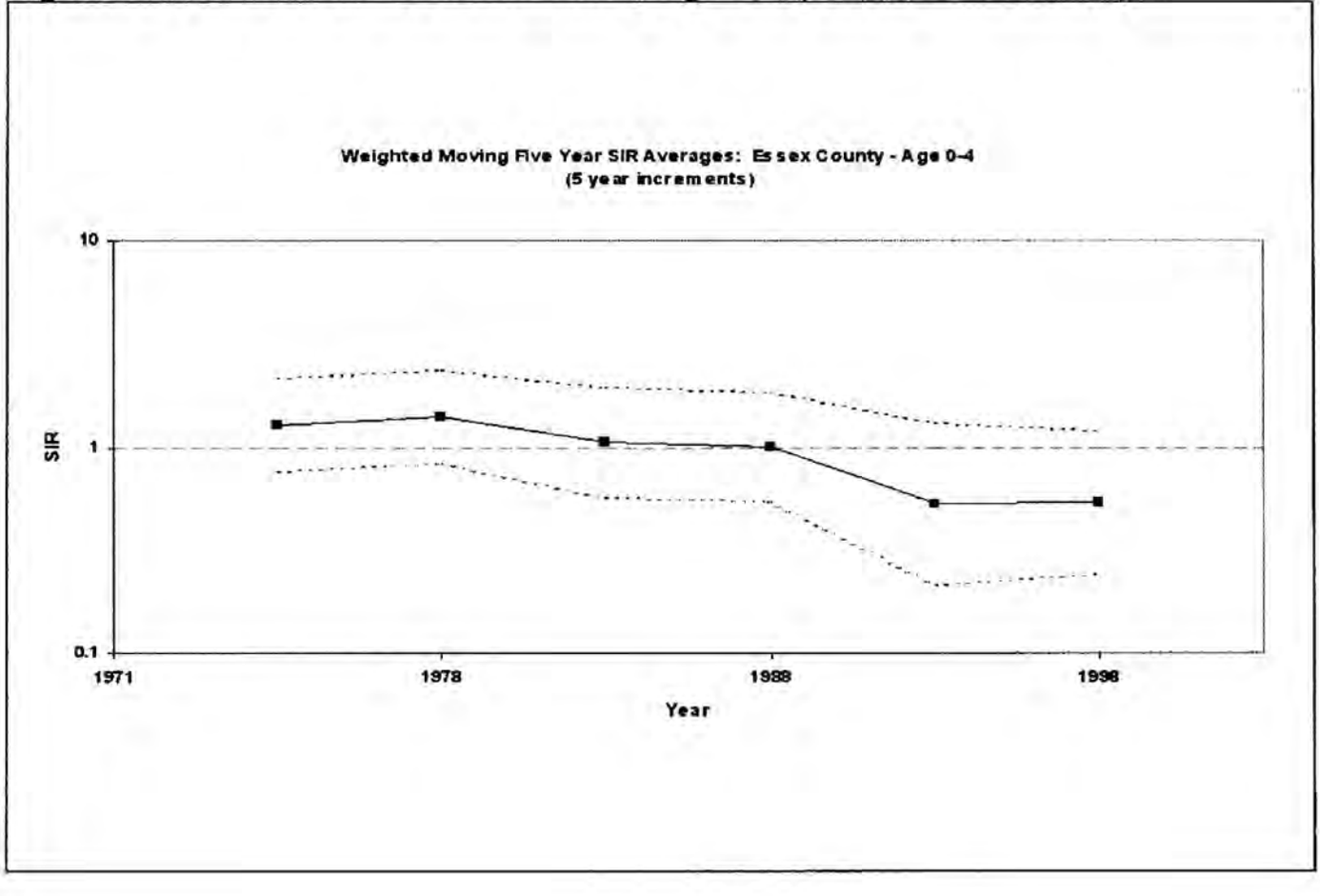


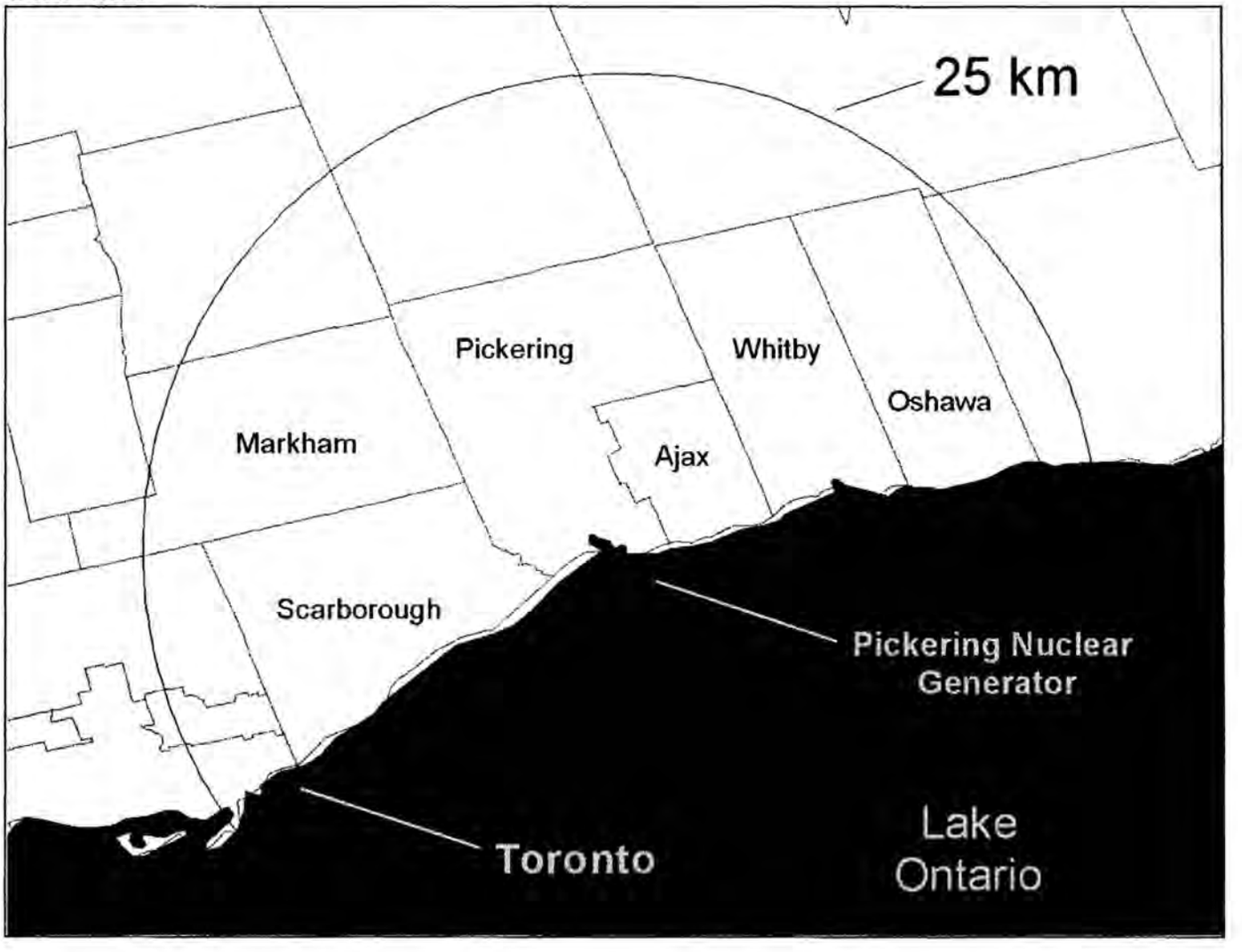
Figure 4.22.4 – Census Division Essex, Age 0-4 (5 Year Increments)



Additional Analysis: Overall SIR for Census Subdivisions Pickering, Ajax, Whitby, Oshawa, Scarborough, and Markham: 0-14 Age Group

The original studies by Clarke that analyzed childhood leukemia near PNG included the six census subdivisions of Pickering, Ajax, Whitby, Oshawa, Scarborough, and Markham (Figure 4.23) (11-12). Although it would have been preferable to reanalyze the original area, it was not possible because Scarborough dissolved in 1999 becoming part of Greater Toronto. It was possible to calculate an overall rate from 1971-1998. For the time period 1971-1998, the overall SIR was 0.94 (95% CI = 0.79, 1.13), slightly lower than the 1971-2000 overall SIR of 0.99 experienced by only Pickering and Ajax. Scarborough and Markham are the two census subdivisions that most likely receive the least amount of radiation yet contain the majority of the population. If Scarborough and Markham are excluded, the overall SIR from 1971-2000 for Pickering, Ajax, Oshawa, and Whitby is 1.13 (95% CI = 0.93, 1.36). The above analysis considered with the overall SIR=0.99 for Pickering and Ajax alone (see beginning of section), suggests that the excess cases for the study area were found in Oshawa and Whitby.

Figure 4.23 – Six Census Subdivisions within 25 Kilometers of Pickering Nuclear Generator



Spatial Analysis

The unadjusted zones for wind direction are shown in Figure 4.24. The semi-circles represent the five zones with each zone 2.5 km wide and extending 12.5 km from PNG. The remainder of the lines on the figure represents enumeration area boundaries. Because enumeration areas consist of between 125-440 dwellings, it is easy to determine on the map areas of high population density: geographically smaller enumeration areas are more densely populated than larger enumeration areas. For example, one can see that

the densely populated areas are near Lake Ontario. The outer three unadjusted zones include a large portion of Scarborough, a densely populated section of Toronto, west of PNG. The inner two zones include the densest sections of Pickering and Ajax, the areas most likely at risk. The zones adjusted for wind direction are shown in Figure 4.25. The adjusted zones retain a small section of Scarborough but only in the outer most band, thus adding little weight to the overall p-value while maintaining the densest sections of Pickering and Ajax in the two inner most zones, which receive the greatest weight.

Figure 4.24 – Pickering Nuclear Generator (unadjusted for wind). SIR for 0-14 age group.

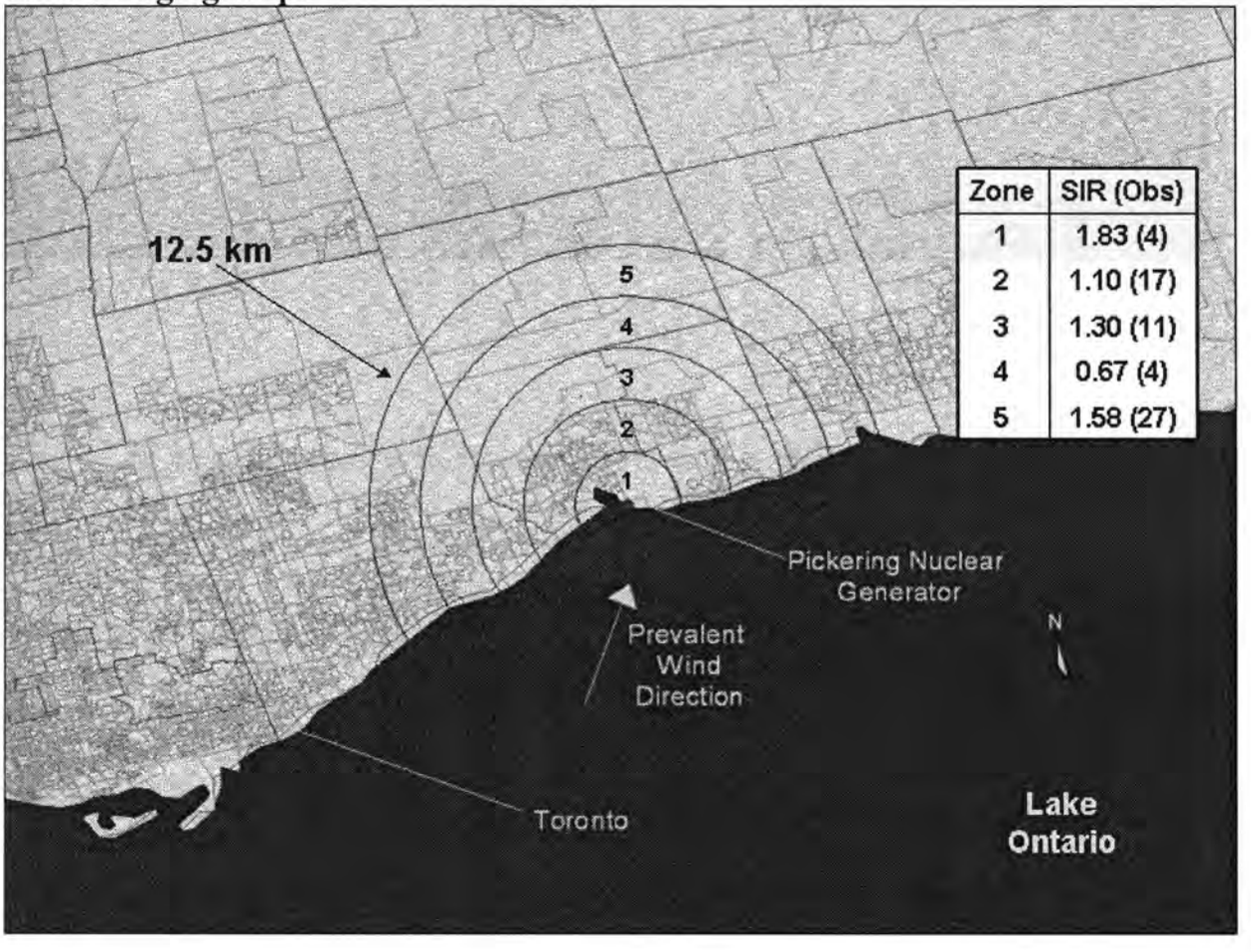


Figure 4.25 – Pickering Nuclear Generator (adjusted for wind). SIR for 0-14 age group.

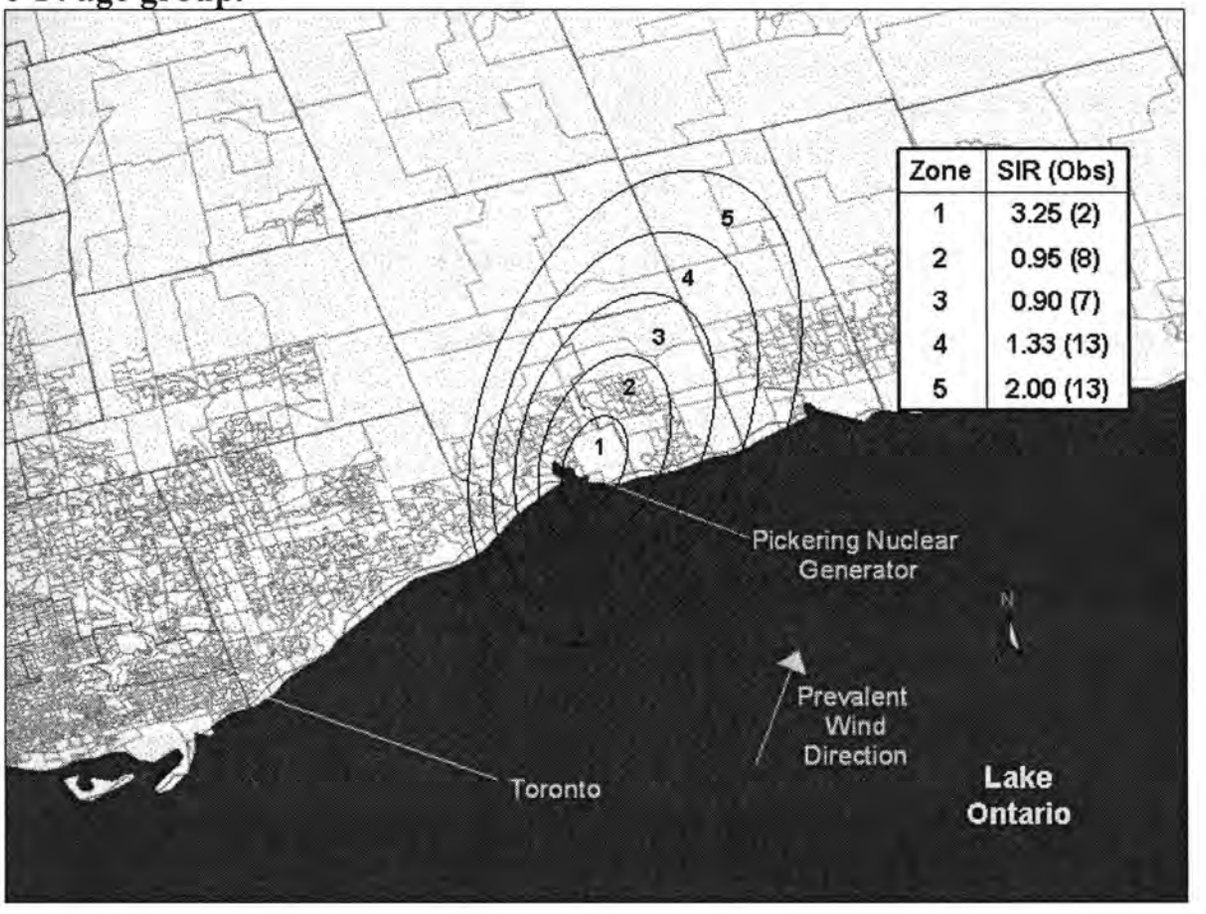


Table 4.16 shows the observed and expected cases of childhood leukemia by zones when there is no adjustment for wind. Zones one and five have the highest rates for both age groups. One can also see that the largest populations are found in zones two and five. Zone two contains the majority of the population of Pickering and Ajax; whereas zone five's population is primarily found near the water, Scarborough to the west and Whitby to the east, and sparsely populated to the north (Figure 4.24). There does not appear to be an obvious trend of decreasing rates with increasing distance.

Table 4.16 – Unadjusted Zones of SIR for Childhood Leukemia in Proximity to Pickering Nuclear Generator

	Age Group 0-4			Age Group 0-14		
Zone	Observed	Expected	SIR	Observed	Expected	SIR
1	3	1.27	2.36	4	2.18	1.83
2	9	8.89	1.01	17	15.47	1.10
3	4	4.77	0.84	11	8.47	1.30
4	0	3.27	-	4	5.99	0.67
5	16	9.81	1.63	27	17.13	1.58

Table 4.17 shows the observed and expected by zones when adjustment for wind. The highest rates are found in zones one, four, and five for both age groups. Compared to the unadjusted zones, the adjusted zones populations are more evenly distributed, with the exception of zone one. Although the highest rates are found in the first zone, there does not appear to be a trend with distance.

Table 4.17 –Wind adjusted Zones of SIR for Childhood Leukemia in Proximity to Pickering Nuclear Generator

	Age Group 0-4			Age Group 0-14		
Zone	Observed	Expected	SIR	Observed	Expected	SIR
1	2	0.36	5.54	2	0.62	3.25
2	1	5.01	0.20	8	8.42	0.95
3	4	4.64	0.86	7	7.76	0.90
4	8	5.36	1.49	13	9.77	1.33
5	5	3.44	1.45	13	6.50	2.00

Two weights were used to calculate the Score Test of Lawson and Waller. The first weight was the inverse of the distance, where distance is defined as the distance from the centroid of the zone to PNG. The second weight was the inverse of the square of the distance. Neither the 0-4 or 0-14 age groups had significant p-values for either zone type or either weight (Table 4.18). However, p-values were greater for adjusted zones compared to unadjusted zones when the weight was 1/distance. Adjusting for wind and using 1 /distance^2 decreased the p-value compared to the unadjusted model. Further, after adjusting for wind, p-values were smaller for 1/distance^2 when compared to 1/distance.

Table 4.18 – Score Test of Lawson and Waller P-values by Zone Type and Age Group

Weight and Exposure Zone	Age Group 0-4	Age Group 0-14
weight = 1 / distance		
Unadjusted for wind direction	0.260	0.088
Adjusted for wind direction	0.544	0.119
weight = 1 / distance^2		
Unadjusted for wind direction	0.146	0.160
Adjusted for wind direction	0.071	0.091

5. DISCUSSION

Meta-Analysis

We attempted to assemble the most complete list of professional journals and government publications, in English and other languages, from around the world that studied childhood leukemia in the vicinity of nuclear facilities. Observed and expected numbers were available for one hundred and forty-six nuclear sites in nine countries or former countries. The number of sites allowed for multiple analyses stratified by area and age. We were able to develop unadjusted models, fixed effects models and random effects models. Meta-SMRs and meta-SIRs were all at least one.

Tables 5.1 and 5.2 summarize the meta-rates by strata. Within geographic zones and for meta-SMRs and meta-SIRs, the 0-9 age group experienced higher standardized rates than the 0-25 age group, suggesting that the 0-9 age group accounted for the majority of the excess cases and deaths. No pattern was found when comparing geographic zones within age groups. When comparing geographic zones within age groups, meta-SMRs were consistently higher for the "< 16 km" zone compared to the "All" zone. For meta-SIRs, rates were essentially the same with a slight increase for the "All" zone compared to the "< 16 km" zone.

Table 5.1 – Meta-SMR for Childhood Leukemia by Strata

Age Group	Geographic Zone	Fixed Effects		Random Effects	
		Rate	95% CI	Rate	95% CI
0-9	All	1.06	(1.01, 1.11)	1.06	(1.01, 1.12)
0-9	< 16 km	1.23	(1.04, 1.46)	1.24	(1.03, 1.50)
0-25	All	1.02	(0.98, 1.06)	1.02	(0.98, 1.06)
0-25	< 16 km	1.09	(0.97, 1.23)	1.09	(0.97, 1.23)

Table 5.2 – Meta-SIR for Childhood Leukemia by Strata

Age Group	Geographic Zone	Fixed Effects		Random Effects	
		Rate	95% CI	Rate	95% CI
0-9	All	1.25	(1.13, 1.38)	1.24	(1.12, 1.38)
0-9	< 16 km	1.23	(1.07, 1.40)	1.22	(1.05, 1.41)
0-25	All	1.12	(1.06, 1.18)	1.12	(1.06, 1.18)
0-25	< 16 km	1.11	(1.03, 1.18)	1.10	(1.03, 1.19)

It is highly unlikely studies for different nuclear sites estimate the same underlying effect size. This is so because there are multiple types of nuclear facilities, including nuclear generators operating at differing capacities, nuclear reprocessing sites, nuclear weapons sites, and uranium mining sites. Therefore, even in the absence of evidence of heterogeneity between studies in a given strata, the use of a random effects model is more appropriate. In this meta-analysis, the meta-rates for the fixed effects and random effects models agree so closely, that the choice of model is not critical.

The most common childhood cancer is leukemia. The incidence rates for childhood leukemia are highest in the 0-4 age group and decrease with each increasing five-year age group until 25 years of age. Table 5.3 contains 1990 incidence rates per 100,000 for the United Kingdom, Canada, Osaka, Japan (Japan's largest cancer registry) (158) and, SEER region of the United States (comprising 14% of United States population) (159). Using these incidence rates and the meta-SIRs based on all zones to determine excess cases near nuclear facilities, we would expect between one and two cases associated with living near a nuclear facility in the 0-9 age group and under one case if the entire 0-24 age group is considered, again suggesting the excess cases are in the 0-9 age group.

Table 5.3 – 1990 Incidence Rates and Expected Excess Cases per 100,000 for Childhood Leukemia Based on Meta-SIR for All Zones

Region	Age Group			
	0-9 (meta-SIR=1.24)		0-24 (meta-SIR=1.12)	
	Rate	Excess Cases	Rate	Excess Cases
United Kingdom	5.13	1.23	3.29	0.39
Canada	5.73	1.38	3.59	0.43
USA (SEER)	5.52	1.32	3.60	0.43
Osaka, Japan.	4.35	1.04	3.15	0.38

Although many of the world's nuclear sites are represented in the meta-analysis, the inclusion rules did not allow certain sites to be used in calculating meta-rates. For example, four nuclear sites in Sweden were not included because a spatial analysis was conducted that presented only an overall p-value. The results in Sweden did not find a positive association between childhood leukemia and nuclear sites (47). An Israeli nuclear generator was not included because only incidence rates were reported. Similar to Sweden, no excess cases were found (48). The inclusion of the Swedish and Israeli

sites would have likely decreased the meta-rates, although it is difficult to determine whether that drop would have affected the statistical significance. It would also have been beneficial to include nuclear sites from the former Soviet Union, China, and other countries with nuclear facilities. However, that was not possible and the consistently significant results that were found in the meta-analysis cannot be ignored.

Model Limitations:

The unadjusted model makes no attempt at adjusting for study size and is simply the sum of the observed cases or deaths divided by the sum of the expected cases or deaths. Fixed effects models weight studies based on sample size. Thus, a larger study has more influence on the overall effect than smaller studies. This may be problematic when studying childhood leukemia, since a possible risk factor is population density. The EUROCLUS study suggests there might be an increase in cases in areas of intermediate population density (148). Therefore, weighting based on sample size has the unintended result of giving more influence to studies that may cover areas of higher population density, a possible risk factor. Another disadvantage is the underlying assumption that each study is estimating the same treatment effect and the treatment effect differs solely as a result of random sample variability (149-150). The assumption is highly unlikely for reasons explained throughout this document. Formal tests for heterogeneity were carried out to test the underlying assumptions of fixed effects models. The results were not significant but such tests suffer from low power (131). Due to the low power of the tests, we decided to go forward with random effects models. Random effects models have their own limitations. An important limitation is the assumption that

the studies included in the meta-analysis derive from a hypothetical random distribution that can be described by a common variance (149,151). Another potential problem is random effects models give greater weight to smaller studies than fixed effects models. Smaller studies may be more likely to reflect certain biases, including publication bias; and consequently, will affect the summary estimate (152,138,149). Last, distributions from random effects models often have no empirical, epidemiological, or biologic justification (138).

Meta-Analysis Limitations

Caution must be used when interpreting these results. The meta-analysis was able to show an increase in childhood leukemia near nuclear facilities, but could not support a hypothesis to explain the excess. Each type of model utilized has limitations. However, the fixed effects and random effects models often produced equivalent or nearly equivalent results making model selection less critical. Dose-response studies do not support the excess rates found near nuclear facilities, although it may be that we do not understand the risk from interactions of radiation and chemicals that may be emitted from a site. Several studies have also shown the rates of childhood leukemia pre and post start-up of operation remained consistent, even when rates were greater than one. Nor can we rule out the possibility of an infectious origin, which has been supported by many studies. Even in consideration of the limitations of this meta-analysis, it cannot be ignored that the majority of studies have found elevated rates, although not usually statistically significant.

Although a systematic approach was used to identify studies that met the criteria of interest, the determination of the inclusion rules is subjective and may not be the best set of rules; however, clearly defining the rules allows other researchers to criticize or suggest better methods. Similar to other common statistical methods, statistics in meta-analysis serve as a 'pattern recognition device' and cannot determine causation (138). Meta-analysis is a tool to aid researchers, but it is the researchers that must describe biologic plausibility. Nor does a meta-analysis directly evaluate the bias of the individual studies. A few *ad hoc* methods exist to adjust for quantifiable bias, but these are far from full proof. Many unquantifiable biases may exist that contribute to heterogeneity (138).

Spatial and Temporal Analysis Near Pickering Nuclear Generator

One of the goals of this dissertation was to gain a better understanding of the temporal and spatial relationship between childhood leukemia and Pickering Nuclear Generator (PNG). The census subdivisions of Pickering and Ajax, which includes PNG, had an SIR=0.99 for the 0-14 age group from 1971-2000. Clarke reported a statistically non-significant SIR of 1.15 in the <25 km area, 1971-1986. Several differences exist between the two studies:

1. Clarke used residence at birth for cases. We were unable to obtain birth records and therefore, relied on residence at diagnosis. If we look only at residence at diagnosis for the time-period 1971-1986, similar to the time-period used by Clarke, the SIR for Pickering/Ajax and the original 6 census subdivisions (including Pickering/Ajax) are 0.78 and 0.86, respectively. If one were testing

whether there is an association between paternal or *in utero* radiation exposure and childhood leukemia, then residence at birth would serve as a better indicator than residence at diagnosis. These hypotheses have been tested in past studies. Gardner found a strong association between paternal radiation exposure and leukemia in offspring near Sellafield (66). McLaughlin conducted a similar study in Ontario but was unable to find an association (82); nor have other studies supported Gardner's findings (153). The association between *in utero* exposure to ionizing radiation and childhood leukemia has been supported by various studies and is considered a known risk factor (98,107,154). However, the question remains as to whether the possible low levels of radiation received *in utero*, to residence near nuclear facilities would be significant enough to increase risk of developing childhood leukemia. Studies to date, suggest the dose to fetus would be too low to account for excess risk (8,109,25).

2. The focus of our study concentrated on residents primarily within 12.5 km, which we considered more likely to be at risk. Although it would have been preferable to compare the results of the 12.5 km area of Pickering/Ajax to the 25 km area containing 6 census subdivisions (including Pickering/Ajax), it was not possible due to Scarborough dissolving in 1998 and becoming part of Toronto. However, if only 1971-1997 were analyzed, the SIR for Pickering/Ajax and the original 6 census subdivisions are 0.96 and 0.94, respectively.
3. A spatial analysis within 25 km is not possible because Darlington Nuclear Generator began operation in 1991 approximately 35 km east of PNG. Although unlikely when considering prevailing wind directions, bands greater than 15 km

from PNG may be affected by radiation emitted from Darlington, compromising the use of distance as a surrogate for exposure from PNG. Further, the enumeration area census data used in the spatial analysis originated in 1986, not allowing for a meaningful spatial analysis to be conducted from 1986-1990, the period before Darlington began operation. We were able to calculate an overall SIR for 1971-1990: Pickering/Ajax and the original 6 census subdivisions (including Pickering/Ajax) are 0.96 and 0.99, respectively.

Smooth moving SIRs have the advantage of avoiding the bias of selecting arbitrary time intervals while allowing the researcher to determine whether excess cases, if present, were dispersed over time or clustered near a certain time point (138). In the case of Pickering/Ajax, moving SIRs consistently near one indicate that exposure to children near PNG from radiation has not led to excess cases above the provincial average. One control area, the census subdivisions of Niagara Falls/Welland/Thorold had unexpectedly high SIRs that persisted through the entire study period. However, Niagara County, the census division that contains Niagara Falls/Welland/Thorold, as a whole had moving SIRs remain near one. Further research is needed in the Niagara Falls area. Although control areas were only used for non-statistical comparisons, the selection of control areas based on population data at only one time point when a thirty-year period is studied is a limitation. It is essentially a snapshot in time that does not necessarily reflect temporal population growth patterns.

Ideally, in spatial analysis, exposure zones would be created based on dispersion models that take into account many parameters such as type and amount of substance,

median of exposure (i.e. air or water), stack heights, wind direction and speed, and terrain (117). Unfortunately, the aforementioned data is often not available in ecological studies, leaving distance as the best surrogate for exposure. The availability of wind data allowed us to construct exposure zones that are based on additional information other than rely solely on distance. The Score Test did not find an association between distance and PNG; nor was an association found when exposure zones were created based on prevalent wind direction. The inability to find an association may be because no association exists or the study lacks power to find an association.

Explaining Elevated Rates Near Nuclear Facilities

Although the meta-analysis found consistently elevated rates for all stratification levels, it is important to note that there are many questions still to be answered; and several hypotheses have been proposed to explain the excess of childhood leukemia in the vicinity of nuclear facilities, including environmental exposure, paternal exposure, and viral transmission.

Environmental exposure to radiation is a known risk factor for leukemia (2-3,5). However, there is a question as to whether the amount of exposure received by children living near nuclear sites is sufficient to increase risk. Authors that have used emissions data from nuclear facilities and conducted dose-response studies have consistently found that radiation discharge was too low to account for the excess cases of childhood leukemia (8,108-109,25). It also appears highly unlikely that preconception paternal exposure to radiation increases the risk of leukemia to the child, an original hypothesis from the Sellafield studies (79-82,103). Researchers have studied whether certain

lifestyles could lead to increased risk near nuclear facilities due to environmental contamination (66,81,103). Although significant results were found with use of beaches in the areas of Dounreay (81) and La Hague (103), it is difficult to determine the dose attributed to use of beaches and the relationship to childhood leukemia (7).

Several problems arise when conducting dose-response studies in an epidemiological setting. Determining an individual's dose relies not only on knowledge of facility emissions and geographic parameters but also the lifestyles of the individuals in the population. Another difficulty is that the expected dose-response relationship is established in an external population and exposure between the population of interest and the external population may differ. For example, many of the dose-response studies relied on the Life Span Study of Atomic Survivors (105) and the Oxford Survey of Childhood Cancers (107). The Life Span Study was a single acute high dose exposure and the Oxford Survey of Childhood Cancers was intermittent high doses; whereas, the potential exposure from a nearby nuclear facility is most likely a continuous low dose. It may also be that there are interactions between two or more environmental exposures that we are yet to understand. Gibson and Wheldon believe there may be a synergistic effect between radiation and chemicals that could increase the risk of developing childhood leukemia (119-120).

If the amount of exposure were too low to cause the excess risk, then one would expect that the rates remained consistent before and after the start-up of a nuclear facility. Several studies were able to calculate rates for regions before and after a nuclear facility began operation (11-12,45,143-144,17). Rates generally remained unchanged pre and post start-up, even in regions with elevated rates. For example, Jablon analyzed nuclear

sites in the USA and found that SMRs for childhood leukemia in the 0-9 age group were higher before start-up when compared to after start-up. For the four facilities that incidence data were available, three sites had higher SIRs after start-up than before start-up; however, rates were above one for both time periods (143). Other authors compared regions that were considered for the installation of a nuclear facility and regions that had an existing nuclear facility. Both types of areas had excess mortality from leukemia and Hodgkin's Disease. It was suggested that there might be an unidentified risk factor shared by these regions, other than environmental radiation (22).

A hypothesis that has been well received is the possibility of an infectious origin to childhood leukemia caused by population mixing (6). Among those hematologic cancers that are associated with infectious agents are Burkitt lymphoma and adult T-cell leukemia (7,155,84). Kinlen hypothesized that "childhood leukemia may be a rare response to an unidentified mild or subclinical infection, the transmission of which is facilitated when large numbers of people come together, particularly from a variety of origins." Further, this herd immunity may allow individuals in a population to be infected with the virus, but not develop the disease. When this population is mixed with another population that has not previously been exposed to the virus, individuals in the susceptible population may develop the disease (86). Although the possibility of a viral agent is suggested by several studies (86,89-91,95-96), an infectious agent has yet to be identified.

Potential Bias

Potential Bias and Concerns with Studies of Radiation from Nuclear Facilities and Childhood Leukemia.

1. Case Ascertainment—A few of the smaller studies did not address the completeness of case ascertainment. The issue was generally seen in small follow-up studies, but should always be addressed.
2. Types of leukemia—It is always preferable when studies include information on which types of leukemia are included in the analysis. Only rarely do studies break down rates by different types (see attached study table). The most dominant leukemia below the age of 25 is ALL, followed by AML, and last is CML (expecting less than 1 case per 100,000). CLL is not found in children. Although all three types may be caused by radiation, it remains to be seen whether, radiation increases the risk of one type of these leukemias more than the others in the childhood age groups.
3. Age—At all age groups through 25, ALL is the dominant leukemia, followed by AML, and last is CML (see Table 1).
4. Multiple testing—Multiplicity becomes an issue when a study calculates multiple rates. It is quite common for these studies to calculate rates for multiple age groups, areas, and sites with no adjustment for multiple comparisons. Although it is common for epidemiological studies to not adjust for multiple testing, at the very least, the studies should mention that no adjustments were made. In only a few studies included in the background, was there mention of the issue of multiplicity.
5. Over Exposure—Often, multiple studies examine the same site where a significant cluster was found. The follow-up studies may:
    - use a different statistic (i.e. SIR or comparison to control area),

- a slightly modified age group that often includes much of the same population that was in the original studies,
- or slightly modified area that also may include much of the same area as the original study,
- or simply additional years of data (presenting overall results that include the original years).

When reviewing the literature, it is important to keep in mind that although there may be many significant results in multiple publications, in reality, they are on the same population or just a slightly modified population.

6. *A posteriori* studies—A few studies were conducted after knowledge of a cluster of leukemias had already been suggested. This was true in the original Sellafield study and also when a second study was done on the same population, or subset of that population where a cluster had been identified. *A posteriori* studies are not able to test a hypothesis but rather confirm the existence of a cluster. This limitation should be mentioned by the authors of these studies, but was not always done.
7. Foreign language publications—In a few studies included in the literature review section, it was not possible to read the entire publication because only the abstract was in English. Without reading the publication, it is difficult to determine whether the study was conducted at a high level or may contain bias. This was the case for the Hungarian study (51).

Ecological Fallacy

One pitfall that all studies designed to examine geographic patterns of disease must avoid is ecological fallacy, that is, the bias that may occur when concluding that elevated risks based on aggregate data represent the possible elevated risks that exists at the individual level. Simply said, it is the individuals not the geographic area that contracts the disease. For example, one could say, correctly, in a study that found a SIR of 1.5 that 50% excess cases are expected in that area. However, it would be incorrect to state that all individuals living in the study area are equally at an increased risk of developing the disease. It may be that within the area of study, only those residing very close to the nuclear facility are at elevated risk or even an individual's particular lifestyle that increases risk. The majority of publications on the association of childhood leukemia and nuclear facilities are designed to calculate an overall incidence rate for an area and do not collect data on the individuals, it is these studies that must be careful in presenting their results.

6. CONCLUSION

Meta-Analysis

The meta-analysis was conducted to combine and statistically analyze the many studies of childhood leukemia in the vicinity of nuclear facilities. Our focus was on studies that calculated SMRs or SIRs for individual nuclear sites. Due to variability between studies in defining age and geographic zones, eight separate analyses were performed based on age and zone stratification levels. One hundred and forty-six sites were used in at least one analysis. Unadjusted models, fixed effects models, and random effects models were used for each of the eight analyses. Meta-rates greater than one were found in all models at all stratification levels. Further, statistical significance at 95% confidence intervals was often achieved. Within geographic zones (as established by the meta-analysis), the 0-9 age group experienced higher rates than the 0-25 age group. There does not appear to be publication bias in the meta-analysis.

Caution must be used when interpreting these results. The meta-analysis was able to show an increase in childhood leukemia near nuclear facilities, but could not support a hypothesis to explain the excess. Each type of model utilized has limitations. However, the fixed effects and random effects models often produced equivalent or nearly equivalent results making model selection less critical. Dose-response studies do not support the excess rates found near nuclear facilities, although it may be that we do not understand the risk from interactions of radiation and chemicals that may be emitted from a site. Several studies have also shown the rates of childhood leukemia pre and post start-up of operation remained consistent, even when rates were greater than one. Nor can we rule out the possibility of an infectious origin, which has been supported by many

studies. Even in consideration of the limitations of this meta-analysis, it cannot be ignored that the majority of studies have found elevated rates, although not usually statistically significant.

Spatial and Temporal Analysis Near Pickering Nuclear Generator

The analysis was designed to better understand the temporal and spatial relationship between radiation from PNG and childhood leukemia. The analysis used much of the same data as Clarke (11-12), and therefore, could only be considered exploratory. We attempted to use data as similar to Clarke as possible, but there were limitations. For example, Clarke used residence at birth while we used residence as diagnosis. Scarborough, the most populated census subdivision included in the Clarke analysis has since dissolved and become part of Toronto. The above mentioned data limitations were not of great concern because we were focusing on post conception exposure, and due to prevailing wind directions, Scarborough was believed to receive insignificant exposure.

Most studies of nuclear radiation and childhood leukemia simply calculate an SIR or SMR for a given time frame, usually limited by data availability and without consideration of geographic distribution. However, we believe by using smoothed moving rates through time and a spatial analysis allows for a more comprehensive description of disease patterns. No apparent relationship between childhood leukemia and PNG was detected with the methods used. In the temporal analysis, moving SIRs remained near one for the entire time-period for the census subdivisions of Pickering and Ajax. Nonsignificant p-values were produced in the spatial analysis. The highest rates

were found in the innermost and outermost bands, with the highest population in the outer bands.

Future Work

The focus of future work should include spatial and temporal analyses perhaps focusing on the 0-9 age group. In a temporal analysis, the use of moving windows for rates would allow researchers to understand whether rates remain consistent over time or experience temporal peaks (7). To understand the spatial relationship between childhood leukemia and nuclear facilities, multiple zones should be established and analyzed with basic trend tests or specific spatial statistics, such as the Score Test of Lawson and Waller (156) or Stone's Test (157). It is understood that the limitations of data availability by geostatistical units often does not allow or makes it difficult to establish exposure zones close to a nuclear site. However, every effort should be made to establish multiple zones. Unfortunately, the low populations normally found near nuclear facilities may not allow for adequate power for spatial analysis. Including multiple sites will increase sample size and power (139).

7. APPENDICES

Appendix A - Sites used in Meta-analysis

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
1					X		X		Aldermaston	COMARE III	Britain	I	0 - 24	0 - 16	20	82	70.09	1.17	0.93, 1.45
2						X		X	Aldermaston	COMARE III	Britain	M	0 - 24	0 - 16	22	55	67.9	0.81	0.61, 1.05
3	X		X						Aldermaston	COMARE III	Britain	I	0 - 9	0 - 16	20	51	42.15	1.21	0.9, 1.6
4		X		X					Aldermaston	COMARE III	Britain	M	0 - 9	0 - 16	22	29	28.16	1.03	0.69, 1.49
5		X		X		X		X	Amersham	Goldsmith	Britain	M	0 - 9	0 - 16	10	35	28.34	1.24	0.86, 1.72
6	X		X		X		X		Amersham	Goldsmith	Britain	I	0 - 9	0 - 16	10	60	40.63	1.48	1.13, 1.9
7						X		X	Berkeley	Baron	Britain	M	0 - 14	0 - 8	17	14	8.74	1.6	0.88, 2.69
8		X		X					Berkeley	Goldsmith	Britain	M	0 - 9	0 - 16	10	4	6.46	0.62	0.17, 1.59
9	X		X		X		X		Berkeley	Goldsmith	Britain	I	0 - 9	0 - 16	10	9	11.72	0.77	0.35, 1.46
10						X		X	Bradwell	Baron	Britain	M	0 - 14	0 - 8	17	8	3.98	2.01	0.87, 3.96
11		X		X					Bradwell	Goldsmith	Britain	M	0 - 9	0 - 16	10	4	2.35	1.7	0.46, 4.36
12	X		X		X		X		Bradwell	Goldsmith	Britain	I	0 - 9	0 - 16	10	4	6.53	0.61	0.17, 1.57
13									Burghfield	Roman	Britain	I	0 - 14	0 - 10	14	38	23.86	1.59	1.13, 2.19
14									Burghfield	Roman	Britain	I	0 - 4	0 - 10	14	27	12.19	2.21	1.46, 3.22
15		X		X		X		X	Capenhurst	Goldsmith	Britain	M	0 - 9	0 - 16	10	21	20.04	1.05	0.65, 1.6
16	X		X		X		X		Capenhurst	Goldsmith	Britain	I	0 - 9	0 - 16	10	29	28.5	1.02	0.68, 1.46
17		X		X		X		X	Dungeness	Goldsmith	Britain	M	0 - 9	0 - 16	10	2	0.7	2.84	0.34, 10.23
18	X		X		X		X		Dungeness	Goldsmith	Britain	I	0 - 9	0 - 16	10	2	1.01	1.98	0.24, 7.15
19					X		X		Harwell	COMARE III	Britain	I	0 - 14	0 - 10	12	4	5.87	0.68	0.19, 1.74
20		X		X		X		X	Harwell	Goldsmith	Britain	M	0 - 9	0 - 16	10	3	5.4	0.56	0.11, 1.62

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
21	X		X						Harwell	Goldsmith	Britain	I	0 - 9	0 - 16	10	4	7.8	0.51	0.14, 1.31
22						X		X	Hinkley	Baron	Britain	M	0 - 14	0 - 8	17	9	7.17	1.26	0.57, 2.38
23							X		Hinkley	Ewing	Britain	I	0 - 24	0 - 12.5	23	13	7.91	1.64	0.88, 2.81
24					X				Hinkley	Ewing	Britain	I	0 - 24	District	23	100	83.47	1.2	0.97, 1.46
25		X		X					Hinkley	Goldsmith	Britain	M	0 - 9	0 - 16	10	5	1.89	2.65	0.85, 6.14
26	X		X						Hinkley	Goldsmith	Britain	I	0 - 9	0 - 16	10	9	6.11	1.47	0.67, 2.8
27		X		X		X		X	Sellafield	Goldsmith	Britain	M	0 - 9	0 - 16	10	3	2	1.5	0.31, 4.38
28	X		X		X		X		Sellafield	Goldsmith	Britain	I	0 - 9	0 - 16	10	8	4.18	1.91	0.83, 3.77
29						X		X	Sizewell	Baron	Britain	M	0 - 14	0 - 8	17	1	0.76	1.32	0.03, 7.33
30		X		X					Sizewell	Goldsmith	Britain	M	0 - 9	0 - 16	10	2	1.11	1.8	0.22, 6.51
31	X		X		X		X		Sizewell	Goldsmith	Britain	I	0 - 9	0 - 16	10	3	2.06	1.46	0.3, 4.26
32		X		X		X		X	Spingfields	Goldsmith	Britain	M	0 - 9	0 - 16	10	20	14.56	1.37	0.84, 2.12
33	X		X		X		X		Spingfields	Goldsmith	Britain	I	0 - 9	0 - 16	10	28	25.2	1.11	0.74, 1.61
34						X		X	Trawsfynydd	Baron	Britain	M	0 - 14	0 - 8	17	1	0.64	1.56	0.04, 8.71
35		X		X					Trawsfynydd	Goldsmith	Britain	M	0 - 9	0 - 16	10	1	0.16	6.1	0.15, 33.97
36		X		X		X		X	Winfrith	Goldsmith	Britain	M	0 - 9	0 - 16	10	4	3.89	1.03	0.28, 2.63
37	X		X		X		X		Winfrith	Goldsmith	Britain	I	0 - 9	0 - 16	10	9	7.05	1.28	0.58, 2.42
38		X		X		X		X	Wylfa	Goldsmith	Britain	M	0 - 9	0 - 16	10	2	0.56	3.56	0.43, 12.88
39					X				Chalk River	McLaughlin	Canada	I	0 - 14	County	23	16	23	0.7	0.4, 1.13
40						X			Chalk River	McLaughlin	Canada	M	0 - 14	County	38	17	23.9	0.71	0.41, 1.14
41	X								Chalk River	McLaughlin	Canada	I	0 - 4	County	22	8	11.4	0.7	0.3, 1.38
42		X							Chalk River	McLaughlin	Canada	M	0 - 4	County	37	8	10.4	0.77	0.33, 1.52
43					X				Douglas Point	McLaughlin	Canada	I	0 - 14	County	20	9	7.2	1.25	0.57, 2.37
44						X			Douglas Point	McLaughlin	Canada	M	0 - 14	County	21	5	3.2	1.56	0.51, 3.65

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
45	X								Douglas Point	McLaughlin	Canada	I	0 - 4	County	19	6	4.6	1.3	0.48, 2.84
46		X							Douglas Point	McLaughlin	Canada	M	0 - 4	County	20	3	1.6	1.88	0.39, 5.48
47					X				Elliot Lake	McLaughlin	Canada	I	0 - 14	County	23	43	33.7	1.28	0.92, 1.72
48						X			Elliot Lake	McLaughlin	Canada	M	0 - 14	County	34	38	27.6	1.38	0.97, 1.89
49	X								Elliot Lake	McLaughlin	Canada	I	0 - 4	County	22	18	17.5	1.03	0.61, 1.63
50		X							Elliot Lake	McLaughlin	Canada	M	0 - 4	County	33	14	11.6	1.21	0.66, 2.02
51					X				Pickering	McLaughlin	Canada	I	0 - 14	County	16	75	65.7	1.14	0.9, 1.43
52						X			Pickering	McLaughlin	Canada	M	0 - 14	County	17	33	25.7	1.28	0.88, 1.8
53	X								Pickering	McLaughlin	Canada	I	0 - 4	County	15	52	43.1	1.21	0.9, 1.58
54		X							Pickering	McLaughlin	Canada	M	0 - 4	County	16	17	13	1.31	0.76, 2.09
55					X				Port Hope	McLaughlin	Canada	I	0 - 14	County	23	21	18.8	1.12	0.69, 1.71
56						X			Port Hope	McLaughlin	Canada	M	0 - 14	County	38	20	17.5	1.14	0.7, 1.77
57	X								Port Hope	McLaughlin	Canada	I	0 - 4	County	22	14	9.8	1.43	0.78, 2.4
58		X							Port Hope	McLaughlin	Canada	M	0 - 4	County	37	12	8.1	1.48	0.77, 2.59
59					X		X		Greifswald	Michaelis	East Germany	I	0 - 14	0 - 15	10	3	2.69	1.12	0.23, 3.26
60					X		X		Rheinsberg	Michaelis	East Germany	I	0 - 14	0 - 15	10	2	1.62	1.23	0.15, 4.46
61					X		X		Rossendorf	Michaelis	East Germany	I	0 - 14	0 - 15	10	14	10.73	1.3	0.71, 2.19
62						X		X	Bugey	Hattchouel	France	M	0 - 25	0 - 16	19	8	11.16	0.72	0.31, 1.41
63						X		X	Chinon	Hattchouel	France	M	0 - 25	0 - 16	22	8	8.88	0.9	0.39, 1.78
64						X		X	Chooz	Hattchouel	France	M	0 - 25	0 - 16	22	9	5.65	1.59	0.73, 3.02
65						X		X	Cruas	Hattchouel	France	M	0 - 25	0 - 16	7	3	3.3	0.91	0.19, 2.66
66						X		X	Dampierre	Hattchouel	France	M	0 - 25	0 - 16	10	2	2.44	0.82	0.1, 2.96
67						X		X	Fessenheim	Hattchouel	France	M	0 - 25	0 - 16	13	2	2.92	0.68	0.08, 2.47
68						X		X	Gravelines	Hattchouel	France	M	0 - 25	0 - 16	10	11	10.2	1.08	0.54, 1.93

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
69							X		La Hague	Veil	France	I	0 - 24	0 - 10	15	4	1.4	2.86	0.78, 7.32
70					X				La Hague	Veil	France	I	0 - 24	0 - 35	15	25	22.8	1.1	0.71, 1.62
71						X			La Hague	Veil	France	M	0 - 24	0 - 35	19	21	23.6	0.89	0.55, 1.36
72								X	La Hague	Hattchouel	France	M	0 - 25	0 - 16	22	2	5.36	0.37	0.05, 1.35
73			X						La Hague	Veil	France	I	0 - 4	0 - 10	15	1	0.3	3.33	0.08, 18.57
74	X								La Hague	Veil	France	I	0 - 4	0 - 35	15	9	5	1.8	0.82, 3.42
75		X							La Hague	Veil	France	M	0 - 4	0 - 35	19	5	4.77	1.05	0.34, 2.45
76						X		X	Marcoule	Hattchouel	France	M	0 - 25	0 - 16	22	19	23.3	0.81	0.49, 1.27
77						X		X	St. Laurent	Hattchouel	France	M	0 - 25	0 - 16	21	5	6.57	0.76	0.25, 1.78
78						X			Genkai	Iwasaki	Japan	M	0 - 14	36	10	1	0.38	2.63	0.07, 14.66
79						X			Mihama	Iwasaki	Japan	M	0 - 14	152.24	15	2	0.97	2.06	0.25, 7.45
80						X			Naraha	Iwasaki	Japan	M	0 - 14	103.45	5	2	0.16	12.27	1.51, 45.15
81						X			Takahama	Iwasaki	Japan	M	0 - 14	72.07	10	1	0.54	1.85	0.05, 10.32
82						X			Tokai	Iwasaki	Japan	M	0 - 14	37.48	15	3	2.75	1.09	0.22, 3.19
83						X			Tsuruga	Iwasaki	Japan	M	0 - 14	250.74	15	4	5.25	0.76	0.21, 1.95
84					X		X		Chapel Cross	Heasman	Scotland	I	0 - 24	0 - 12.5	17	5	3.65	1.37	0.44, 3.2
85							X		Dounreay	COMARE II	Scotland	I	0 - 24	0 - 12.5	17	5	1.53	3.26	1.06, 7.63
86					X				Dounreay	COMARE II	Scotland	I	0 - 24	0 - 25	17	6	2.95	2.03	0.75, 4.43
87					X				Faslane	Hole	Scotland	I	0 - 14	Postcodes	22	5	4.2	1.19	0.39, 2.78
88					X		X		Holy Loch	Heasman	Scotland	I	0 - 24	0 - 12.5	17	18	15.01	1.2	0.71, 1.9
89					X		X		Hunterston	Heasman	Scotland	I	0 - 24	0 - 12.5	17	14	10.21	1.37	0.75, 2.3
90					X		X		Rosyth	Heasman	Scotland	I	0 - 24	0 - 12.5	17	30	30.62	0.98	0.66, 1.4
91								X	Andujar	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	13	10.57	1.23	0.65, 2.1
92						X			Andujar	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	30	22.38	1.34	0.9, 1.91

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
93								X	Asco	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	1	1.14	0.88	0.02, 4.89
94						X			Asco	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	2	2.6	0.77	0.09, 2.78
95						X			Cofrentes	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	2	2.04	0.98	0.12, 3.54
96								X	Cuidad Rodrigo	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	3	1.72	1.74	0.36, 5.1
97						X			Cuidad Rodrigo	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	3	3.03	0.99	0.2, 2.89
98						X			El Cabril	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	7	6.08	1.15	0.46, 2.37
99								X	Garona	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	1	0.45	2.22	0.06, 12.38
100						X			Garona	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	10	9.8	1.02	0.49, 1.88
101								X	Juzbado	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	1	0.77	1.3	0.03, 7.23
102						X			Juzbado	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	5	8.06	0.62	0.2, 1.45
103								X	La Haba	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	2	2.13	0.94	0.11, 3.39
104						X			La Haba	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	16	14.68	1.09	0.62, 1.77
105								X	Vandellos	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	3	1.33	2.26	0.47, 6.6
106						X			Vandellos	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	9	12.16	0.74	0.34, 1.41
107								X	Zorita	Lopez-Abente	Spain	M	0 - 24	0 - 15	19	2	0.98	2.05	0.25, 7.37
108						X			Zorita	Lopez-Abente	Spain	M	0 - 24	0 - 30	19	4	3.64	1.1	0.3, 2.81
109						X			Arkansas	Jablon	USA	M	0 - 19	County	11	3	2.33	1.29	0.27, 3.76
110		X							Arkansas	Jablon	USA	M	0 - 9	County	11	2	1.13	1.77	0.21, 6.39
111						X			Big Rock Point	Jablon	USA	M	0 - 19	County	23	6	7.34	0.82	0.3, 1.78
112		X							Big Rock Point	Jablon	USA	M	0 - 9	County	23	4	4.17	0.96	0.26, 2.46
113						X			Brown's Ferry	Jablon	USA	M	0 - 19	County	12	2	2.74	0.73	0.09, 2.64
114						X			Brunswick	Jablon	USA	M	0 - 19	County	10	2	0.94	2.13	0.26, 7.69
115		X							Brunswick	Jablon	USA	M	0 - 9	County	10	2	0.94	2.13	0.26, 7.69
116						X			Calvert Cliffs	Jablon	USA	M	0 - 19	County	11	2	2.05	0.98	0.12, 3.52

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
117		X							Calvert Cliffs	Jablon	USA	M	0 - 9	County	11	1	0.99	1.01	0.03, 5.63
118						X			Cook	Jablon	USA	M	0 - 19	County	10	5	9.06	0.55	0.18, 1.29
119		X							Cook	Jablon	USA	M	0 - 9	County	10	2	4.44	0.45	0.05, 1.63
120						X			Cooper Station	Jablon	USA	M	0 - 19	County	11	1	0.76	1.32	0.03, 7.33
121						X			Crystal River	Jablon	USA	M	0 - 19	County	8	1	0.79	1.27	0.03, 7.05
122						X			Davis Besse	Jablon	USA	M	0 - 19	County	8	1	0.75	1.33	0.03, 7.43
123		X							Davis Besse	Jablon	USA	M	0 - 9	County	8	1	0.75	1.33	0.03, 7.43
124						X			Dresden	Jablon	USA	M	0 - 19	County	25	49	65.66	0.75	0.55, 0.99
125		X							Dresden	Jablon	USA	M	0 - 9	County	25	32	39.51	0.81	0.55, 1.14
126						X			Duane Arnold	Jablon	USA	M	0 - 19	County	11	13	11.6	1.12	0.6, 1.92
127					X				Duane Arnold	Jablon	USA	I	0 - 19	County	11	31	22.52	1.38	0.94, 1.95
128		X							Duane Arnold	Jablon	USA	M	0 - 9	County	11	4	5.71	0.7	0.19, 1.79
129	X								Duane Arnold	Jablon	USA	I	0 - 9	County	11	17	13.49	1.26	0.73, 2.02
130						X			Farley	Jablon	USA	M	0 - 19	County	8	3	3.51	0.85	0.18, 2.5
131		X							Farley	Jablon	USA	M	0 - 9	County	8	1	1.75	0.57	0.01, 3.18
132						X			Fermi	Jablon	USA	M	0 - 19	County	22	26	24.9	1.04	0.68, 1.53
133		X							Fermi	Jablon	USA	M	0 - 9	County	22	15	14.42	1.04	0.58, 1.72
134						X			Fernald	Jablon	USA	M	0 - 19	County	34	337	345.47	0.98	0.87, 1.09
135		X							Fernald	Jablon	USA	M	0 - 9	County	34	218	220.2	0.99	0.86, 1.13
136									Fort Calhoun	Jablon	USA	M	0 - 19	County	12	2	1.09	1.83	0.22, 6.63
137									Fort Calhoun	Jablon	USA	I	0 - 19	County	12	4	1.28	3.13	0.85, 8
138		X							Fort Calhoun	Jablon	USA	M	0 - 9	County	12	2	1.09	1.83	0.22, 6.63
139	X								Fort Calhoun	Jablon	USA	I	0 - 9	County	12	4	1.28	3.13	0.85, 8
140						X			Fort St Vrain	Jablon	USA	M	0 - 19	County	9	20	20.33	0.98	0.6, 1.52

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
141		X							Fort St Vrain	Jablon	USA	M	0 - 9	County	9	7	9.59	0.73	0.29, 1.5
142						X			Ginna	Jablon	USA	M	0 - 19	County	16	8	9.48	0.84	0.36, 1.66
143		X							Ginna	Jablon	USA	M	0 - 9	County	16	2	5.13	0.39	0.05, 1.41
144						X			Haddam Neck	Jablon	USA	M	0 - 19	County	18	19	14.89	1.28	0.77, 1.99
145					X				Haddam Neck	Jablon	USA	I	0 - 19	County	18	24	25.38	0.95	0.61, 1.41
146		X							Haddam Neck	Jablon	USA	M	0 - 9	County	18	9	7.89	1.14	0.52, 2.17
147	X								Haddam Neck	Jablon	USA	I	0 - 9	County	18	16	16.49	0.97	0.55, 1.58
148						X			Hallam	Jablon	USA	M	0 - 19	County	23	45	35.83	1.26	0.92, 1.68
149		X							Hallam	Jablon	USA	M	0 - 9	County	23	29	20.14	1.44	0.96, 2.07
150						X			Hanford	Jablon	USA	M	0 - 19	County	35	63	54.58	1.15	0.89, 1.48
151		X							Hanford	Jablon	USA	M	0 - 9	County	35	45	35.43	1.27	0.93, 1.7
152						X			Hatch	Jablon	USA	M	0 - 19	County	11	1	1.2	0.83	0.02, 4.64
153		X							Hatch	Jablon	USA	M	0 - 9	County	11	1	1.2	0.83	0.02, 4.64
154						X			Humboldt Bay	Jablon	USA	M	0 - 19	County	22	21	17.74	1.18	0.73, 1.81
155		X							Humboldt Bay	Jablon	USA	M	0 - 9	County	22	8	10	0.8	0.35, 1.58
156						X			Idaho Natnl Engineer Lab	Jablon	USA	M	0 - 19	County	35	20	20.33	0.98	0.6, 1.52
157		X							Idaho Natnl Engineer Lab	Jablon	USA	M	0 - 9	County	35	13	13.4	0.97	0.52, 1.66
158						X			Indian Point	Jablon	USA	M	0 - 19	County	23	201	189.24	1.06	0.92, 1.22
159		X							Indian Point	Jablon	USA	M	0 - 9	County	23	122	106.09	1.15	0.95, 1.37
160						X			La Cross (Genoa)	Jablon	USA	M	0 - 19	County	18	6	3.19	1.88	0.69, 4.09
161		X							La Cross (Genoa)	Jablon	USA	M	0 - 9	County	18	1	1.69	0.59	0.01, 3.3
162						X			Maine Yankee	Jablon	USA	M	0 - 19	County	13	5	4	1.25	0.41, 2.92
163		X							Maine Yankee	Jablon	USA	M	0 - 9	County	13	4	2.12	1.89	0.51, 4.83

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
164						X			McGuire	Jablon	USA	M	0 - 19	County	4	3	8.82	0.34	0.07, 0.99
165		X							McGuire	Jablon	USA	M	0 - 9	County	4	1	4.17	0.24	0.01, 1.34
166						X			Millstone	Jablon	USA	M	0 - 19	County	15	29	22.84	1.27	0.85, 1.82
167					X				Millstone	Jablon	USA	I	0 - 19	County	15	58	42.82	1.35	1.03, 1.75
168		X							Millstone	Jablon	USA	M	0 - 9	County	15	17	11.72	1.45	0.84, 2.32
169	X								Millstone	Jablon	USA	I	0 - 9	County	15	44	28.39	1.55	1.13, 2.08
170						X			Monticello	Jablon	USA	M	0 - 19	County	14	4	8.12	0.49	0.13, 1.26
171		X							Monticello	Jablon	USA	M	0 - 9	County	14	2	4.35	0.46	0.06, 1.66
172						X			Mound	Jablon	USA	M	0 - 19	County	35	292	294.1	0.99	0.88, 1.11
173		X							Mound	Jablon	USA	M	0 - 9	County	35	189	189	1	0.86, 1.15
174						X			Nine Mile Point	Jablon	USA	M	0 - 19	County	16	11	13.07	0.84	0.42, 1.51
175		X							Nine Mile Point	Jablon	USA	M	0 - 9	County	16	6	6.82	0.88	0.32, 1.91
176						X			North Anna	Jablon	USA	M	0 - 19	County	7	2	1.53	1.31	0.16, 4.72
177						X			Nuclear Fuel Services	Jablon	USA	M	0 - 19	County	19	16	12.41	1.29	0.74, 2.09
178		X							Nuclear Fuel Services	Jablon	USA	M	0 - 9	County	19	8	6.78	1.18	0.51, 2.32
179						X			Oak Ridge	Jablon	USA	M	0 - 19	County	35	48	38.68	1.24	0.91, 1.65
180		X							Oak Ridge	Jablon	USA	M	0 - 9	County	35	33	24.63	1.34	0.92, 1.88
181						X			Oconee	Jablon	USA	M	0 - 19	County	12	6	8.44	0.71	0.26, 1.55
182		X							Oconee	Jablon	USA	M	0 - 9	County	12	2	4	0.5	0.06, 1.81
183						X			Oyster Creek	Jablon	USA	M	0 - 19	County	16	23	28.5	0.81	0.51, 1.21
184		X							Oyster Creek	Jablon	USA	M	0 - 9	County	16	10	15.63	0.64	0.31, 1.18
185						X			Paducah	Jablon	USA	M	0 - 19	County	35	18	20.55	0.88	0.52, 1.38
186		X							Paducah	Jablon	USA	M	0 - 9	County	35	9	12.86	0.7	0.32, 1.33

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
187						X			Palisades	Jablon	USA	M	0 - 19	County	14	5	2.82	1.77	0.58, 4.14
188						X			Pathfinder	Jablon	USA	M	0 - 19	County	21	13	19.24	0.68	0.36, 1.16
189		X							Pathfinder	Jablon	USA	M	0 - 9	County	21	6	10.91	0.55	0.2, 1.2
190						X			Peach Bottom	Jablon	USA	M	0 - 19	County	11	37	38.67	0.96	0.67, 1.32
191		X							Peach Bottom	Jablon	USA	M	0 - 9	County	11	21	18.92	1.11	0.69, 1.7
192						X			Pilgrim	Jablon	USA	M	0 - 19	County	13	29	32.52	0.89	0.6, 1.28
193		X							Pilgrim	Jablon	USA	M	0 - 9	County	13	16	16.67	0.96	0.55, 1.56
194						X			Point Beach/ Kewaunee	Jablon	USA	M	0 - 19	County	15	10	10.43	0.96	0.46, 1.76
195		X							Point Beach/ Kewaunee	Jablon	USA	M	0 - 9	County	15	5	5.38	0.93	0.3, 2.17
196						X			Portsmouth	Jablon	USA	M	0 - 19	County	33	4	7.11	0.56	0.15, 1.44
197		X							Portsmouth	Jablon	USA	M	0 - 9	County	33	2	4.44	0.45	0.05, 1.63
198						X			Prarie Island	Jablon	USA	M	0 - 19	County	12	6	5.02	1.2	0.44, 2.6
199		X							Prarie Island	Jablon	USA	M	0 - 9	County	12	2	2.41	0.83	0.1, 3
200						X			Quad Cities	Jablon	USA	M	0 - 19	County	13	15	18.13	0.83	0.46, 1.36
201		X							Quad Cities	Jablon	USA	M	0 - 9	County	13	12	9.3	1.29	0.67, 2.25
202						X			Rancho Seco	Jablon	USA	M	0 - 19	County	11	85	63.4	1.34	1.07, 1.66
203		X							Rancho Seco	Jablon	USA	M	0 - 9	County	11	47	30.92	1.52	1.12, 2.02
204						X			Robinson	Jablon	USA	M	0 - 19	County	15	12	9.27	1.29	0.67, 2.26
205		X							Robinson	Jablon	USA	M	0 - 9	County	15	6	4.76	1.26	0.46, 2.74
206						X			Rocky Flats	Jablon	USA	M	0 - 19	County	32	108	104.02	1.04	0.85, 1.25
207		X							Rocky Flats	Jablon	USA	M	0 - 9	County	32	63	61.17	1.03	0.79, 1.32
208						X			Salem	Jablon	USA	M	0 - 19	County	9	14	20.1	0.7	0.38, 1.17
209		X							Salem	Jablon	USA	M	0 - 9	County	9	5	9.26	0.54	0.18, 1.26

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
210						X			San Onofre	Jablon	USA	M	0 - 19	County	18	400	406.36	0.98	0.89, 1.09
211		X							San Onofre	Jablon	USA	M	0 - 9	County	18	229	212.04	1.08	0.94, 1.23
212						X			Savannah River	Jablon	USA	M	0 - 19	County	35	31	42.32	0.73	0.5, 1.04
213		X							Savannah River	Jablon	USA	M	0 - 9	County	35	21	25.93	0.81	0.5, 1.24
214						X			Sequoyah	Jablon	USA	M	0 - 19	County	5	9	5.25	1.71	0.78, 3.25
215		X							Sequoyah	Jablon	USA	M	0 - 9	County	5	4	2.45	1.63	0.44, 4.18
216						X			Shipping Port/ Beaver Valley	Jablon	USA	M	0 - 19	County	28	65	61.86	1.05	0.81, 1.34
217		X							Shipping Port/ Beaver Valley	Jablon	USA	M	0 - 9	County	28	41	37.61	1.09	0.78, 1.48
218						X			St Lucie	Jablon	USA	M	0 - 19	County	9	3	3.42	0.88	0.18, 2.56
219		X							St Lucie	Jablon	USA	M	0 - 9	County	9	2	1.72	1.16	0.14, 4.2
220						X			Surry	Jablon	USA	M	0 - 19	County	13	2	1.91	1.05	0.13, 3.78
221		X							Surry	Jablon	USA	M	0 - 9	County	13	1	0.9	1.11	0.03, 6.19
222						X			Three Mile Island	Jablon	USA	M	0 - 19	County	11	50	50.44	0.99	0.74, 1.31
223		X							Three Mile Island	Jablon	USA	M	0 - 9	County	11	28	24.56	1.14	0.76, 1.65
224						X			Trojan	Jablon	USA	M	0 - 19	County	10	5	6.14	0.81	0.26, 1.9
225		X							Trojan	Jablon	USA	M	0 - 9	County	10	3	3.16	0.95	0.2, 2.77
226						X			Turkey Point	Jablon	USA	M	0 - 19	County	13	94	96.25	0.98	0.79, 1.2
227		X							Turkey Point	Jablon	USA	M	0 - 9	County	13	37	46.25	0.8	0.56, 1.1
228						X			Vermont Yankee	Jablon	USA	M	0 - 19	County	13	6	11.76	0.51	0.19, 1.11
229		X							Vermont Yankee	Jablon	USA	M	0 - 9	County	13	5	5.88	0.85	0.28, 1.98
230						X			Yankee Rowe	Jablon	USA	M	0 - 19	County	25	38	42.65	0.89	0.63, 1.22
231		X							Yankee Rowe	Jablon	USA	M	0 - 9	County	25	20	25	0.8	0.49, 1.24
232						X			Zion	Jablon	USA	M	0 - 19	County	13	31	45.97	0.67	0.46, 0.96

Appendix A – continued

ID	A1	A2	A3	A4	A5	A6	A7	A8	Site	Author	Country	End-point	Age	Zone (km)	Duration	Obs	Exp	Rate	95% CI
233		X							Zion	Jablon	USA	M	0 - 9	County	13	12	22.22	0.54	0.28, 0.94
234					X		X		Biblis	Kaletsch	West Germany	I	0 - 14	0 - 15	16	32	30.19	1.06	0.73, 1.5
235					X		X		Brokdorf	Kaletsch	West Germany	I	0 - 14	0 - 15	16	4	5.71	0.7	0.19, 1.79
236					X		X		Brunsbuettel	Kaletsch	West Germany	I	0 - 14	0 - 15	16	3	6.52	0.46	0.09, 1.34
237					X		X		Grafenrheinf	Kaletsch	West Germany	I	0 - 14	0 - 15	16	16	16	1	0.57, 1.62
238					X		X		Grohnde	Kaletsch	West Germany	I	0 - 14	0 - 15	16	7	8.14	0.86	0.35, 1.77
239					X		X		Gundremmingen	Kaletsch	West Germany	I	0 - 14	0 - 15	16	14	14.29	0.98	0.54, 1.64
240					X		X		Hamm	Kaletsch	West Germany	I	0 - 14	0 - 15	16	27	29.03	0.93	0.61, 1.35
241					X		X		Juelich	Kaletsch	West Germany	I	0 - 14	0 - 15	16	34	34.34	0.99	0.69, 1.38
242					X		X		Kahl	Kaletsch	West Germany	I	0 - 14	0 - 15	16	74	71.15	1.04	0.82, 1.31
243					X		X		Karlsruhe	Kaletsch	West Germany	I	0 - 14	0 - 15	16	39	45.88	0.85	0.6, 1.16
244					X		X		Kruemmel	Kaletsch	West Germany	I	0 - 14	0 - 15	16	16	10.96	1.46	0.83, 2.37
245					X		X		Lingen	Kaletsch	West Germany	I	0 - 14	0 - 15	16	21	18.75	1.12	0.69, 1.71
246					X		X		Muelheim-K.	Kaletsch	West Germany	I	0 - 14	0 - 15	16	30	19.11	1.57	1.06, 2.24
247					X		X		Neckarwestheim	Kaletsch	West Germany	I	0 - 14	0 - 15	16	49	46.67	1.05	0.78, 1.39
248					X		X		Niederaichbach	Kaletsch	West Germany	I	0 - 14	0 - 15	16	15	15	1	0.56, 1.65
249					X		X		Obrigheim	Kaletsch	West Germany	I	0 - 14	0 - 15	16	21	16.15	1.3	0.8, 1.99
250					X		X		Phillippsburg	Kaletsch	West Germany	I	0 - 14	0 - 15	16	31	34.83	0.89	0.6, 1.26
251					X		X		Stade	Kaletsch	West Germany	I	0 - 14	0 - 15	16	15	18.52	0.81	0.45, 1.34
252					X		X		Unterweser	Kaletsch	West Germany	I	0 - 14	0 - 15	16	19	22.35	0.85	0.51, 1.33
253					X		X		Wuergassen	Kaletsch	West Germany	I	0 - 14	0 - 15	16	4	7.02	0.57	0.16, 1.46

Appendix B – Summary of Papers Considered for Meta-Analysis

Paper (Author, Year)	Country	Site	Age Group(s)	Area	Disease Types	Rate	Significance?
COMARE II, 1988	UK	Dounreay	0-14 0-24	<12.5 km <25 km	Leukemia (only), Leukemia and Non-Hodgkin's Lymphoma	Incidence	Yes
COMARE III, 1989	UK	Harwell, Burghfield, Aldermaston	0-4 0-14	<10 km >10 km	Leukemia	Incidence	Yes
COMARE IV, 1996	UK	Sellafield	0-24	Village	Leukemia and Non-Hodgkin's Lymphoma	Incidence	Yes
Roman, 1987	UK	Harwell, Burghfield, Aldermaston	0-4 0-14	<10 km >15 km	Leukemia	Incidence	Yes
Baron, 1984	UK	14 sites	0-14	5 miles	Leukemia	Mortality	Yes, for some
Ewings, 1989	UK	Hinkley	0-25	< 12.5 km	Leukemia and Non-Hodgkin's Lymphoma	Incidence	Yes
Bithell, 1994	UK	Hinkley	0-14	< 25 km	Leukemia and Non-Hodgkin's Lymphoma	Incidence	No
Goldsmith, 1992	UK	21 sites	0-9		Leukemia	Incidence and Mortality	Yes, for some
Heasman, 1986	UK	Dounreay	0-24	< 12.5 km < 25 km	Leukemia	Incidence	Yes

Appendix B - continued

Paper (Author, Year)	Country	Site	Age Group(s)	Area	Disease Types	Rate	Significance?
Cook-Mozaffari, 1989	UK	Amersham	0-24	< 16 km	Leukemia	Mortality	No
Bithell, 1994	UK	14 sites	0-14	< 25 km	Leukemia and Non-Hodgkin's Lymphoma	Incidence	Yes, for some
Cook-Mozaffari, 1988	UK	14 sites	0-24	10 km	Leukemia ALL	Mortality	Yes, for some
Sofer, 1991	Israel	Dimona (the Negev)	0-9 0-24	< 45 km (east) < 30 km (west)	Leukemia ALL	Incidence	No
McLaughlin, 1993	Canada	5 regions	0-4 5-9 10-14	< 25 km	Leukemia	Incidence and Mortality	No
McLaughlin, 1993 (BMJ)	Canada	5 regions	0-4 5-9 10-14	Based on postal codes and labor force data or < 25 km	Leukemia, ALL and AML	Incidence and Mortality	No
Iwasaki, 1995	Japan	18 sites	0-14	Municipality	Leukemia	Mortality	No
Lopez-Abente, 1999	Spain	12 sites	0-24	< 30 km	Leukemia	Mortality	Yes, for some
Hattchouel, 1994	France	13 sites	0-24	< 5 km 5-10 km 10-13 km 13-16 km	Leukemia	Mortality	No

Appendix B - continued

Paper (Author, Year)	Country	Site	Age Group(s)	Area	Disease Types	Rate	Significance?
Viel, 1990	France	La Hague	0-4 5-14 15-24	< 10 km < 20 km < 30 km	Leukemia	Mortality	No
Viel, 1993	France	La Hague	0-4 5-14 15-24	< 10 km 10-20 km 20-35 km	Leukemia	Incidence	Yes (0-4 years, 20-35 km)
Dousset, 1989	France	Beaumont-Hague	0-4 5-14 15-24	"Canton"	Leukemia	Mortality	No
Viel, 1995	France	La Hague	0-4 5-14 15-24	< 10 km 10-20 km 20-35 km	Leukemia	Incidence	No
Hill, 1990	France	La Hague	0-24	< 5 km 5-10 km 10-13 km 13-16 km	Leukemia	Mortality	No
Grosche, 1992	Germany	Kruemmel	0-14	Village	Leukemia	Incidence	Yes
Mohner, 1993	Germany	Rossendorf Rheinsberg Greifswald	0-14	< 5 km 5-10 km 10-15 km	Leukemia	Incidence	No
Michaelis, 1992	Germany	20 sites	0-14	< 15 km	Leukemia Acute Leukemia	Incidence	Yes (Acute leukemias < 5)
Kaatsch, 1998	Germany	20 sites	0-14	< 15 km	Leukemia Acute Leukemia	Incidence	No

Appendix B - continued

Paper (Author, Year)	Country	Site	Age Group(s)	Area	Disease Types	Rate	Significance?
Hoffman, 1997	Germany	Kruemmel	0-14	< 5 km	Leukemia	Incidence	Yes
Grosche, 1999	USA	Savannah River Region	0-14	Counties: 10 in SC 12 in GA	Leukemia	Incidence	No
Mangano, 2003	USA	38 sites	0-9	< 30 miles	Leukemia	Incidence and Mortality	Yes
Jablon, 1990	USA	100+ sites	0-9 0-19	County	Leukemia	Incidence and Mortality	Yes for some SIR
Waller, 1995	Sweden	4 sites	0-14	< 25 km	Leukemia	Incidence	No
Zaridze, 1994	Kazakhstan	Multiple test sites	0-14	< 200 km	Acute Leukemia	N/A	Yes, for some
Torok, 2002	Hungary	Response from Chernobyl	0-14	Country	Leukemia	Incidence	No
Gapanovich, 2001	Belarus	Response from Chernobyl	N/A	Country	Leukemia	Incidence	No

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