Challenges in assessing disease latency for cancer in environmental epidemiology

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CANCER PREVENTION INSTITUTE OF CALIFORNIA

Preventing Cancer. Promoting Life.

Outline

- Latency
  - The concept
  - The problems
  - Windows of susceptibility
- Residential mobility
  - Studies of childhood cancers
  - Studies of breast cancer

Latency

- Typically defined as the period of time from initial exposure to a carcinogen and the date a cancer is diagnosed.
  - Sometimes defined by doubling time

- A few classic examples:
  - Asbestos exposure and mesothelioma (long latency)
  - Hiroshima/Nagasaki and leukemia (short latency)

- But this generally:
  - Assumes a one-hit theory of cancer causation
  - Fails to account for dose effects
  - Fails to account for timing effects
  - Fails to account for multifactorial influences
  - Fails to account for heterogeniety in cancers
  - Fails to account for genetic susceptibility

Windows of susceptibility

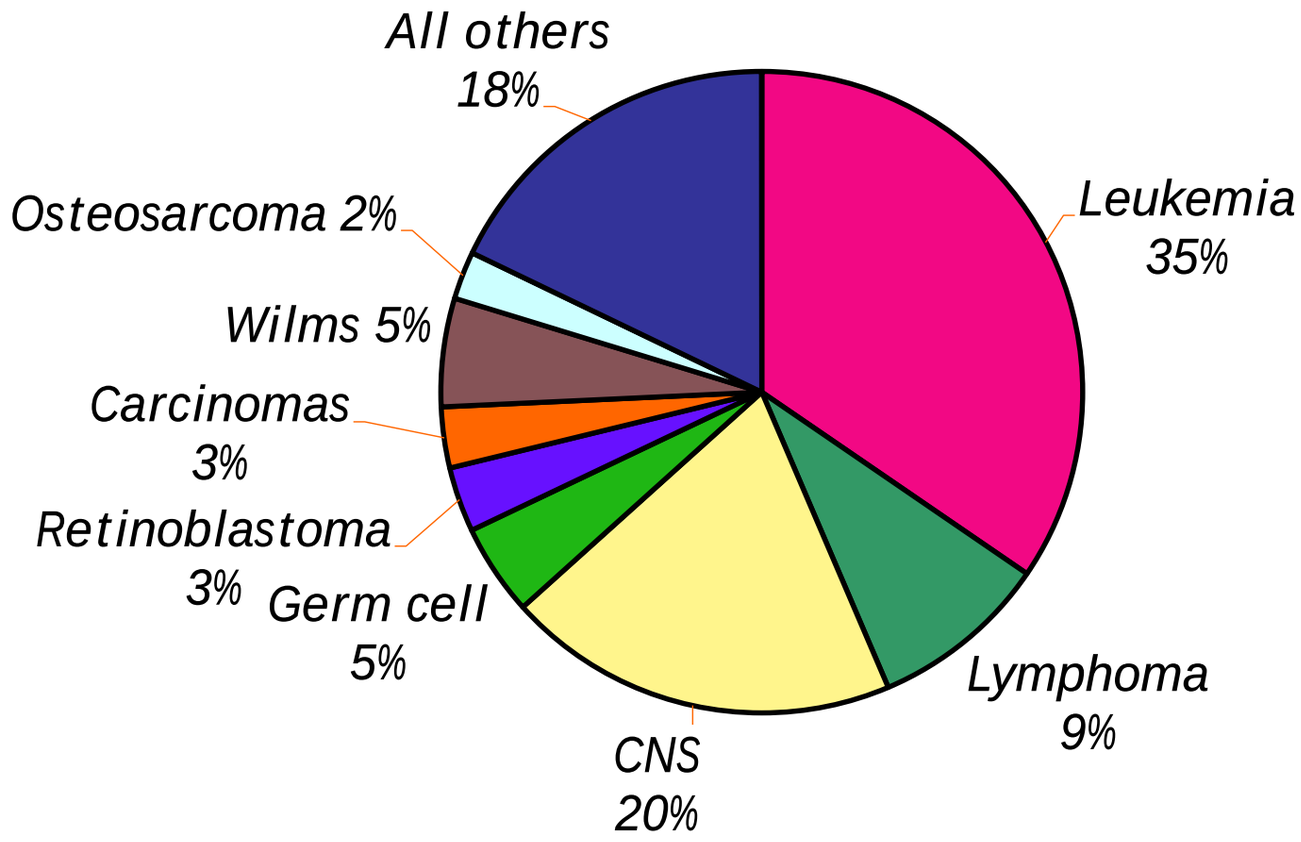
- Periods of life during which exposures may have the greatest effect
- Vary by cancer site and hypothesized mechanisms
- Have been most studied for the childhood cancers and breast cancer

Childhood Leukemia

Latency/windows of susceptibility

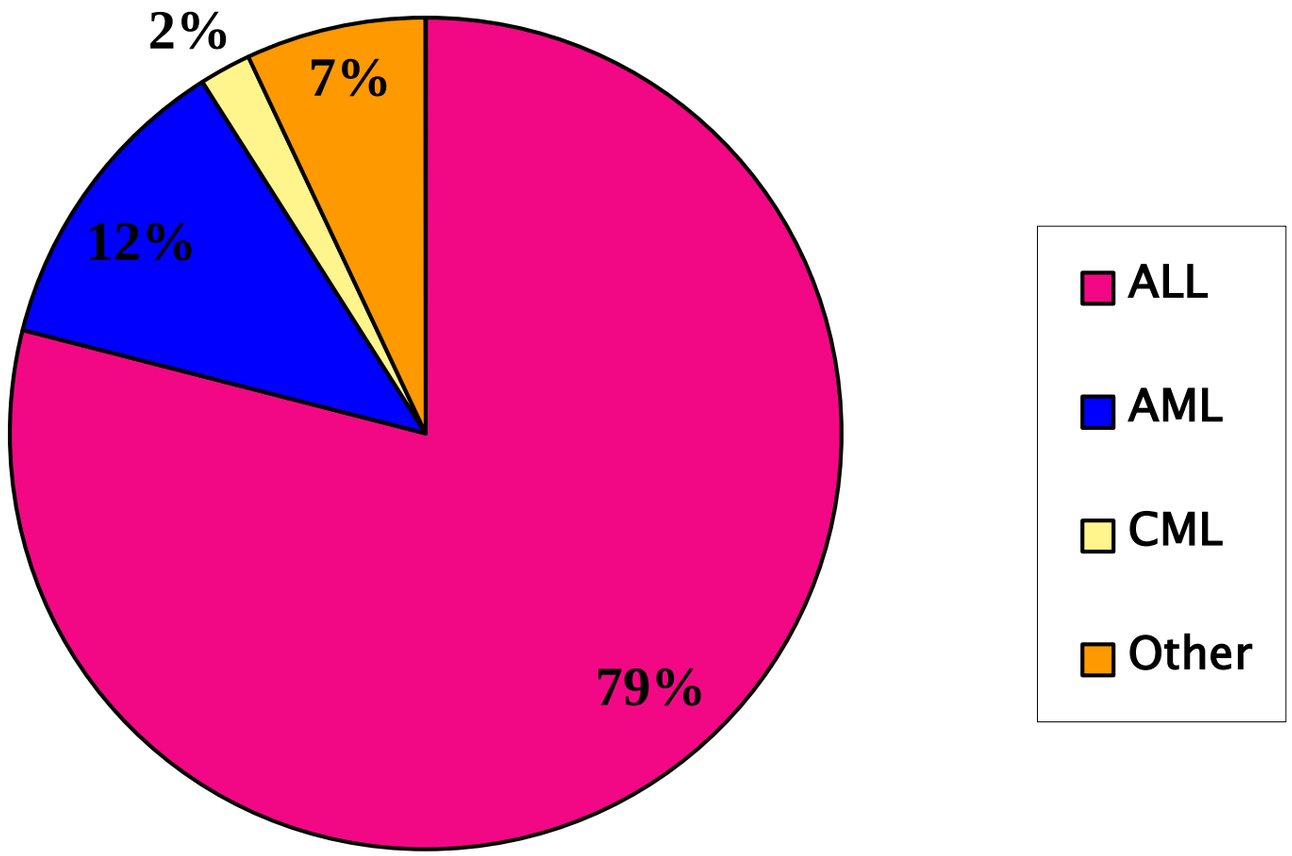
- Limited time frame for latency in children
- Some potentially key windows of susceptibility to environmental exposures:
  - Pre-conception exposures to mother/father
  - *In utero* exposures
  - First few years of life
  - Recent exposures
  - Lifetime cumulative exposures

Types of Childhood Cancer in California, 1988-94



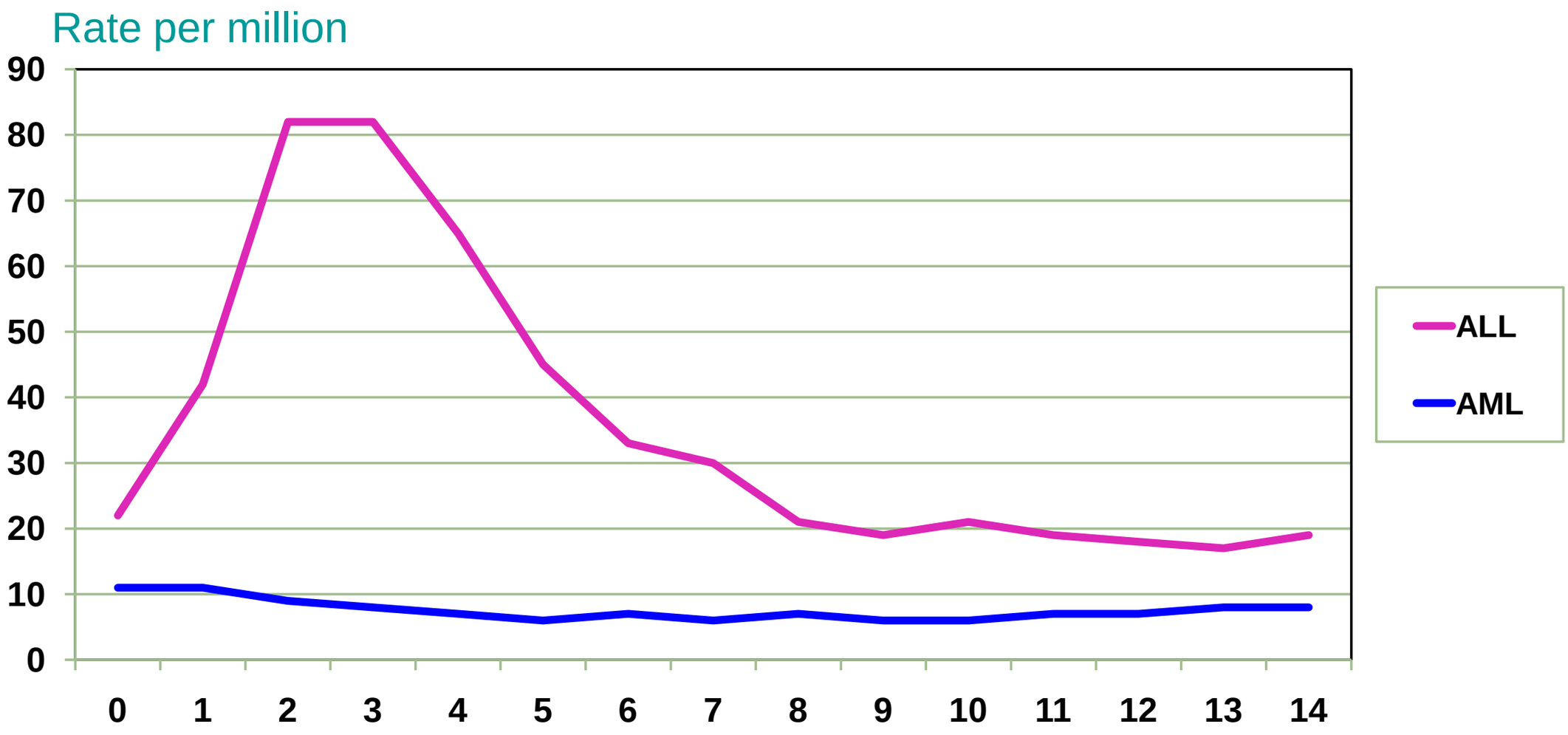
Childhood Leukemias (ages 0-14)

Percent Distribution by Type



Source: Cancer in California, 1988-1991

Age-Specific Incidence Rates of Child Leukemia – by Subtype



SEER 1976-1994

Causes of childhood leukemia

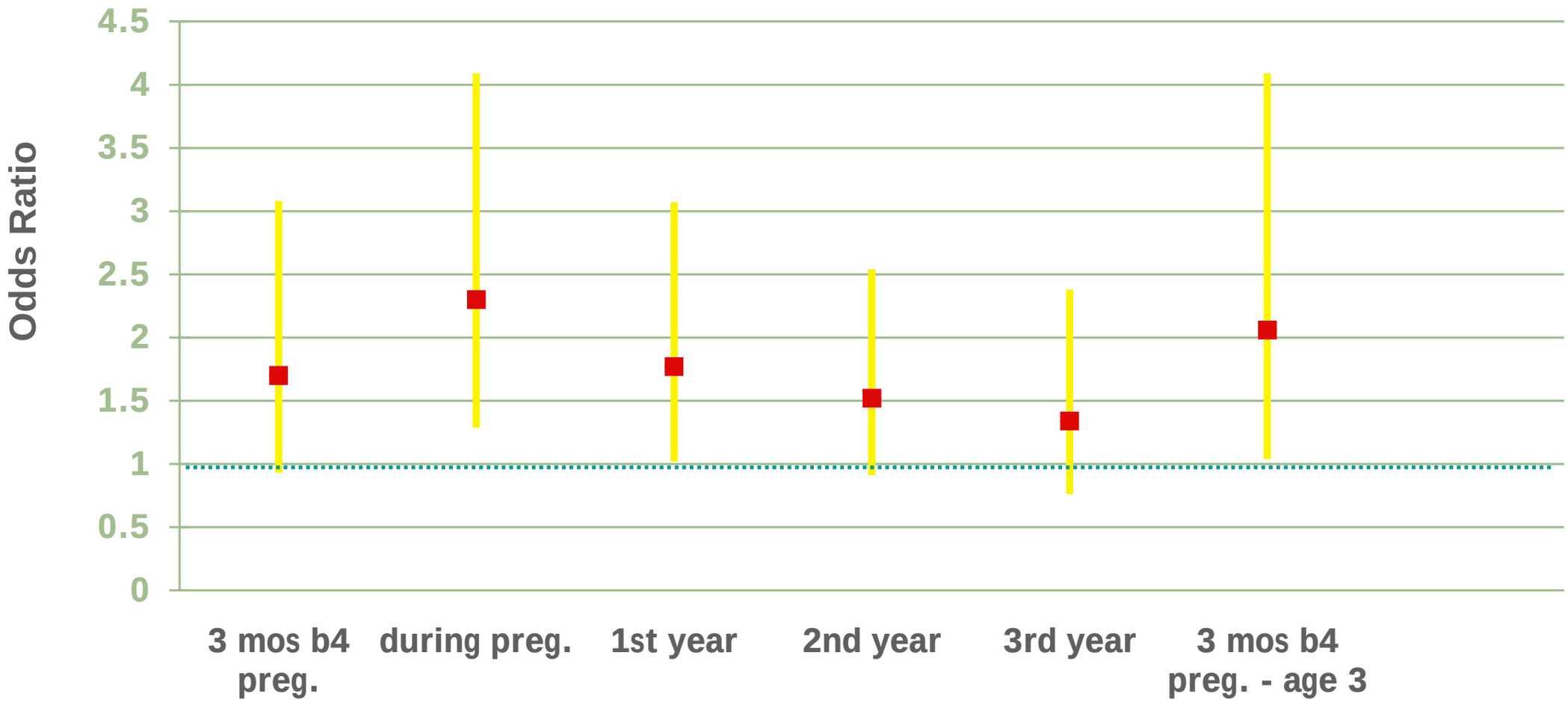
- The causes of 90% of childhood leukemias are unknown

- Known risk factors include:
  - genetic factors (eg. association with Down syndrome)
  - ionizing radiation (especially *in utero* exposures)

Viral Hypotheses for Childhood Leukemia

- Two-step mutations in progenitor B cells (Melvyn Greaves)
  - In utero (while immature B cells are rapidly dividing)
  - Later in childhood, especially among children without early exposures/immunity to common infectious agents
- New Towns (Leo Kinlen)
  - Direct exposure to specific viruses associated with population mixing

Childhood Leukemia and Indoor Pesticide Exposures

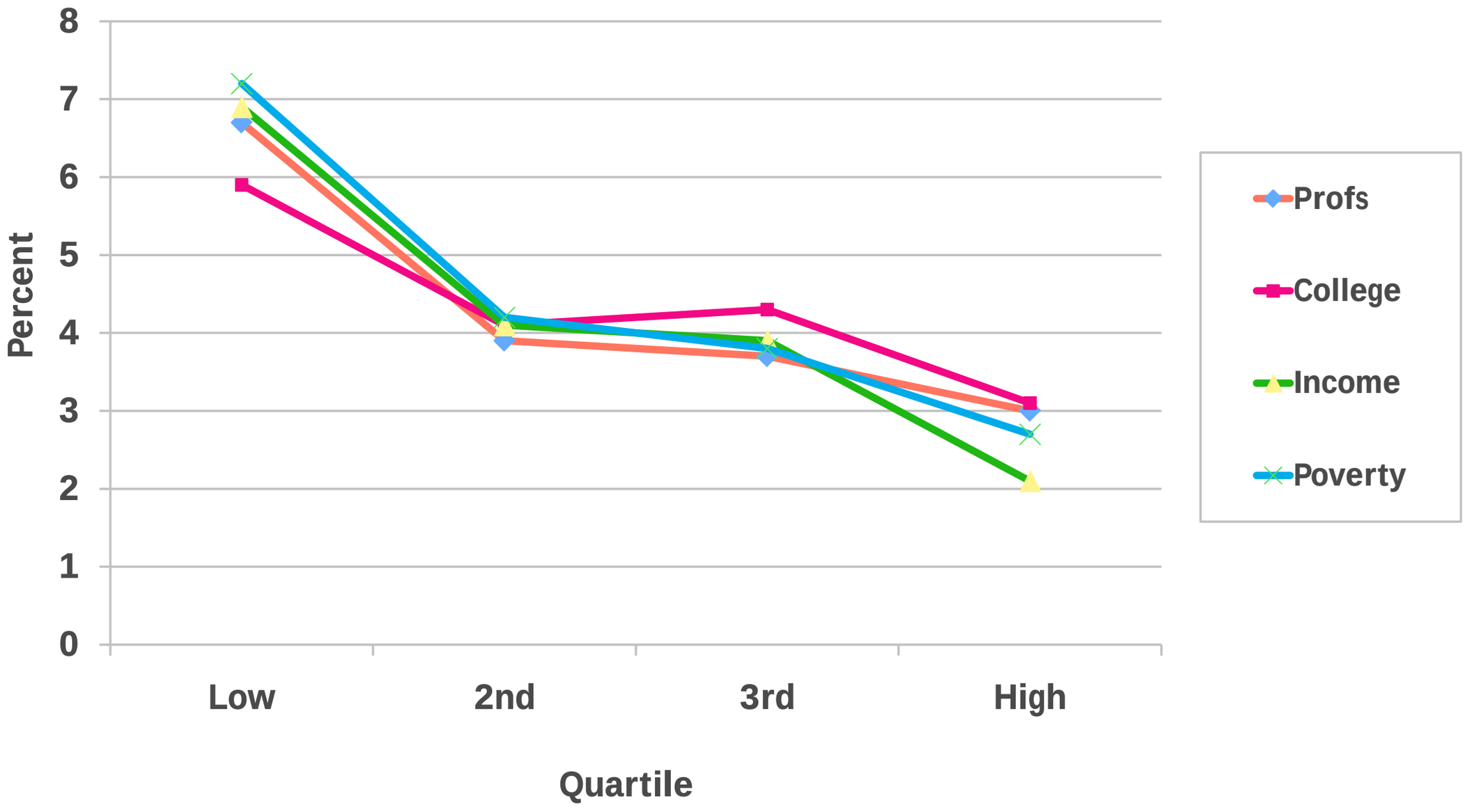


Ma et.al., EHP, 2002

For GIS Studies What Address is Best?

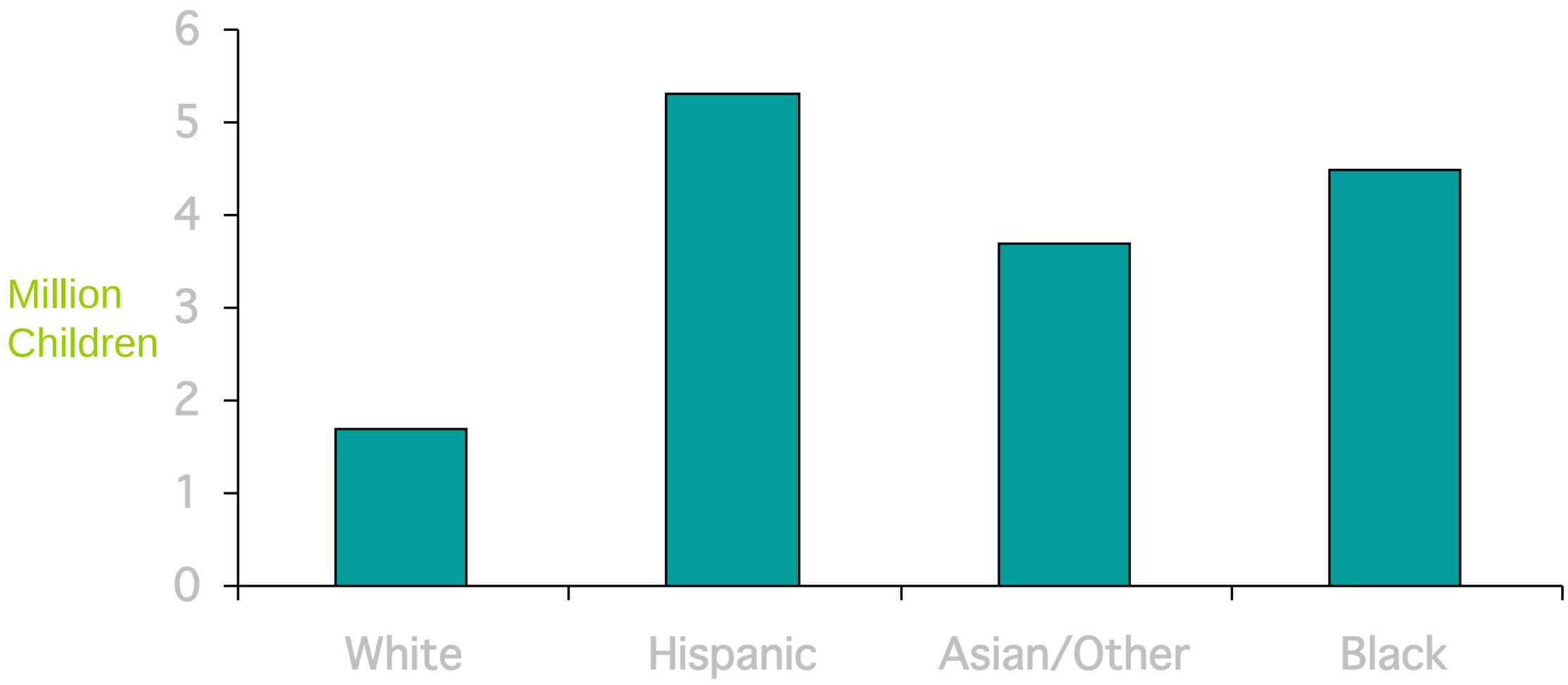
- When is the biologically important time window of risk?
- Where do mothers/children spend the most time?
- Is residential mobility different by:
  - Demographic characteristics?
    - e.g. SES status?
  - Environmental exposures?
    - e.g. Proximity to traffic?

Percent of Block Groups in Each Quartile with Traffic Density Greater than 500,00 vmt/mi^2



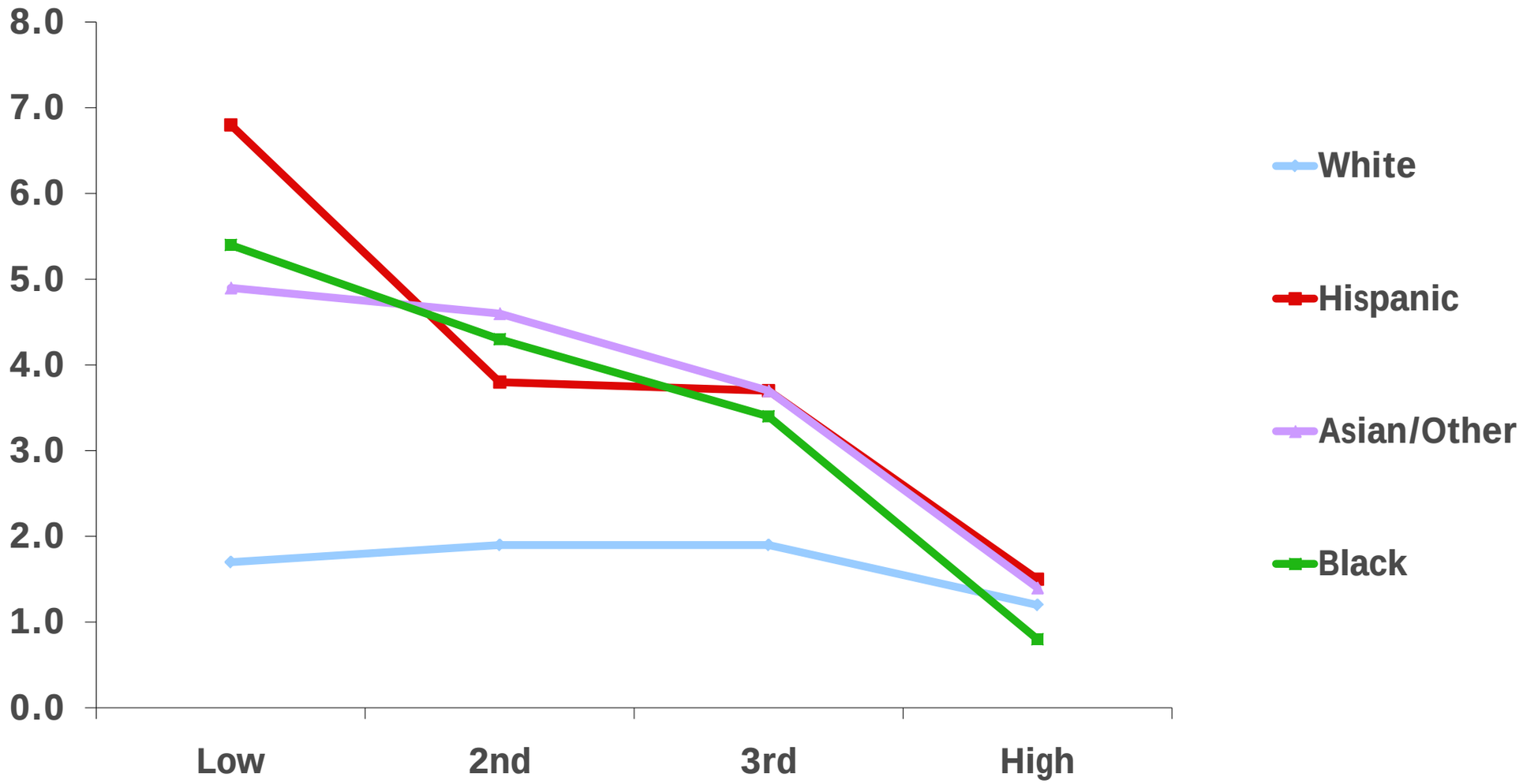
Gunier et. al, J Exp Anal Env Epidemiol 2003

Population Under Five Years of Age Living in Block Groups with Traffic Density Greater than 500,000 vmt/mi²



Gunier et. al, J Exp Anal Env Epidemiol 2003

Percent of Income Quartile by Race Living in Block Groups with Traffic Density Greater than 500,000 vmt/mi^2



Gunier et. al, J Exp Anal Env Epidemiol 2003

San Diego Pilot Study Designed to Pretest Statewide Protocol

- Records-based study
- Use of GIS technology to assess exposures
- Control selection from birth files
- Effect of residential mobility

Case-Control Design

- *Cases (n=92)*:
  1988-94 leukemia diagnoses under the age of 5 among children born to San Diego County mothers

- *Controls (n=368)*:
  Children of the same gender, born the same day to San Diego mothers, and not known to have had cancer

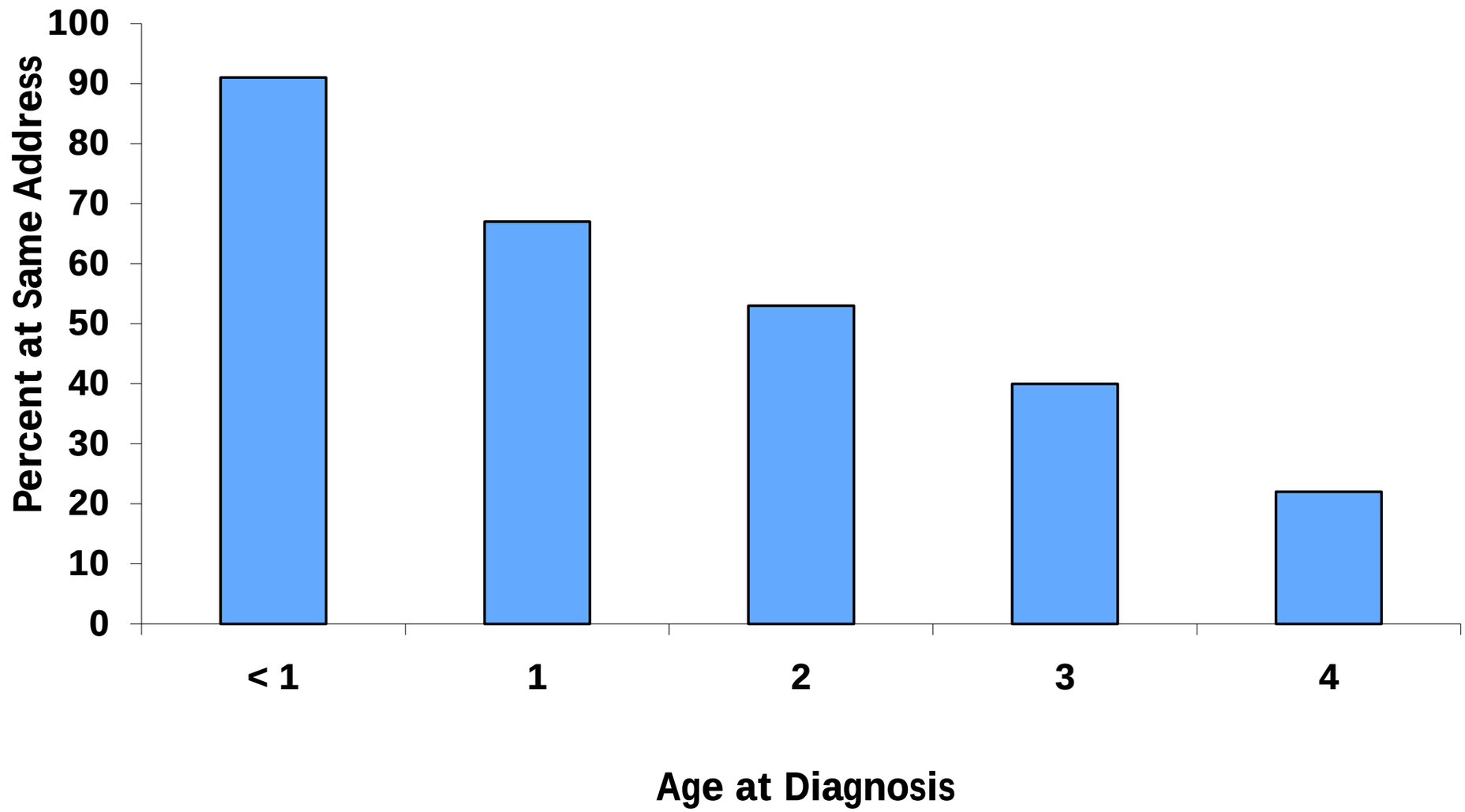
Two Risk Factors of Interest

- Socioeconomic Status
- Traffic density

Exposure Assessment Using GIS

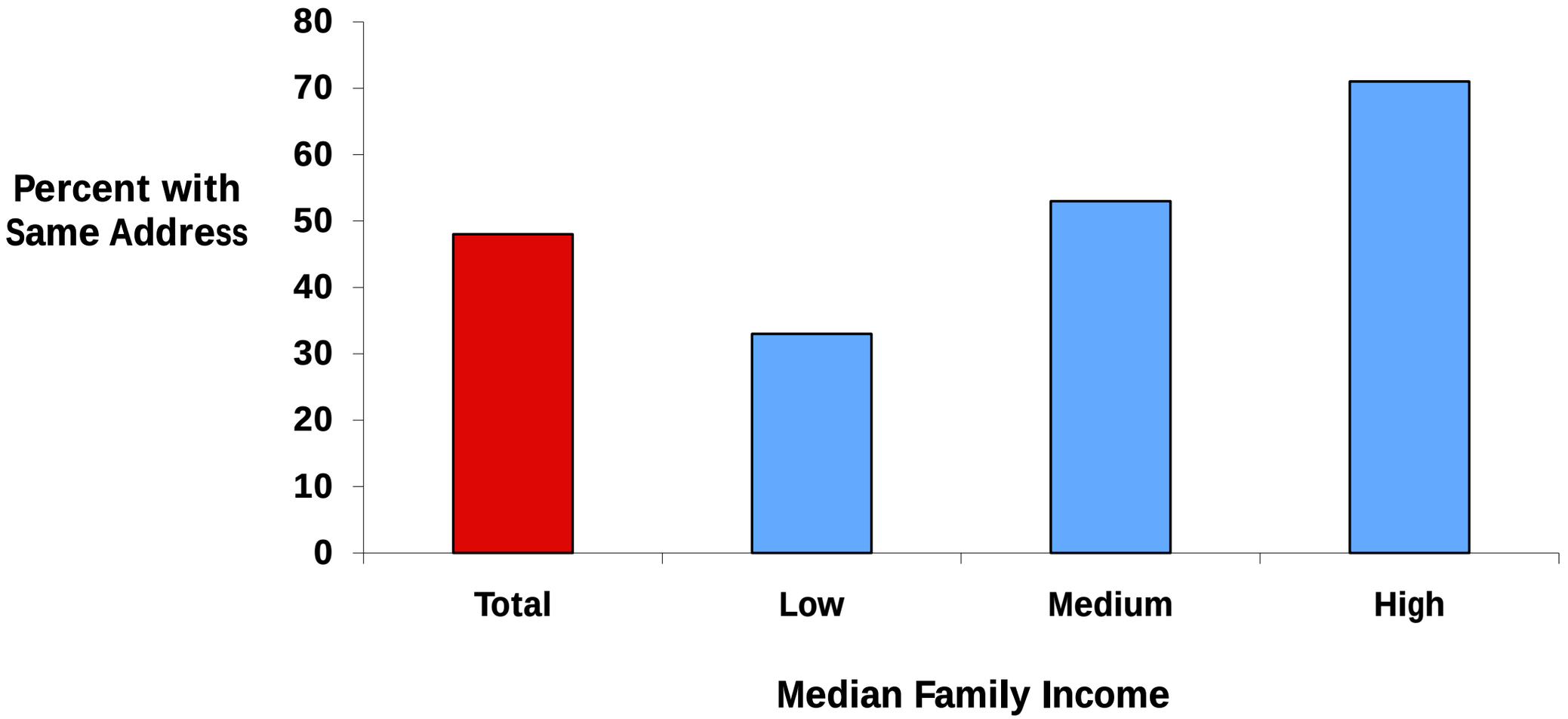
- Mother's residential address at birth geocoded to lat/long for 91 cases (99%) and 360 controls (98%)
- Socioeconomic characteristics from the 1990 census for block groups
- Average Daily Traffic (ADT) for 1993 (1:24,000 scale street network layer)

Percent of Case Children with the Same Address: Birth to Diagnosis



Reynolds et. al., Bioelectricmagnetics 2001

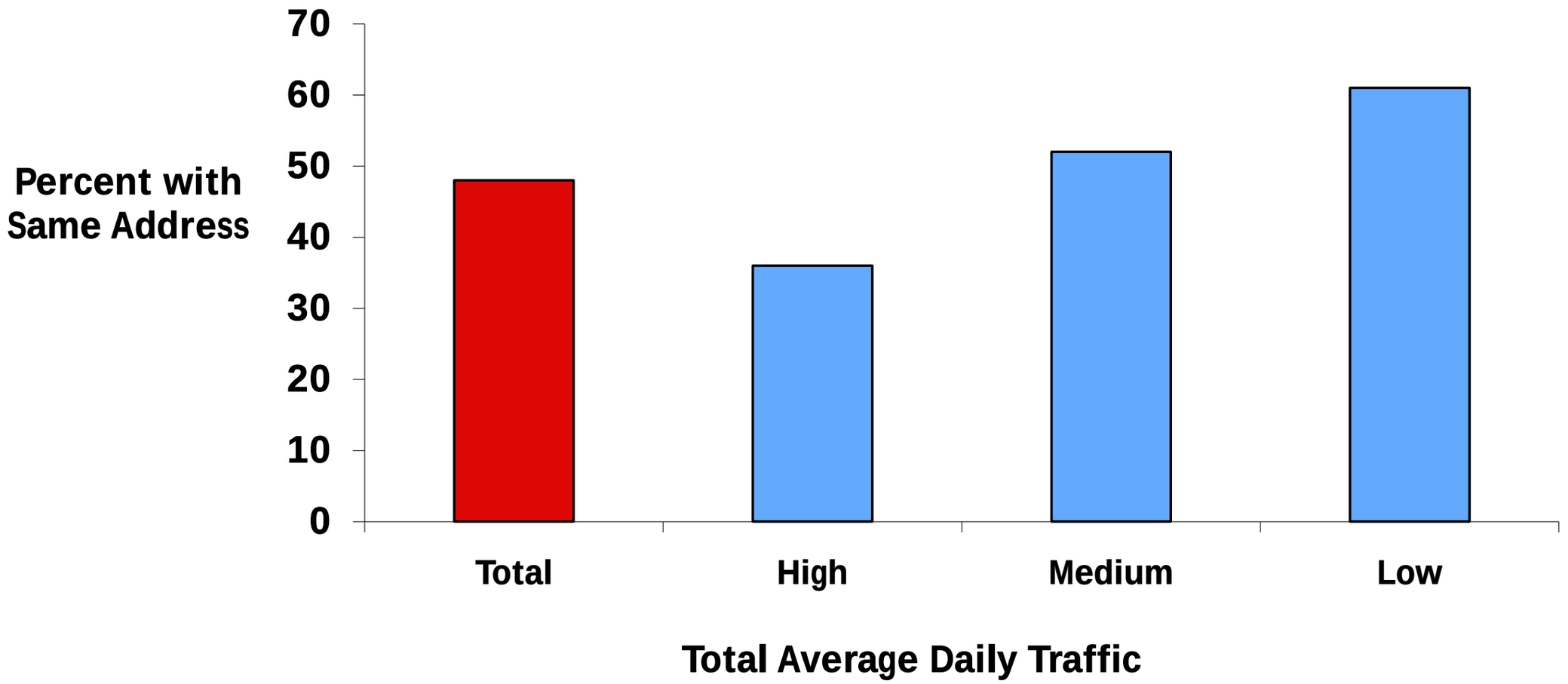
Residential Stability by SES:
San Diego Pilot Study



p=0.03

Reynolds et. al., Bioelectricmagnetics 2001

Residential Stability by Traffic Density: Total ADT



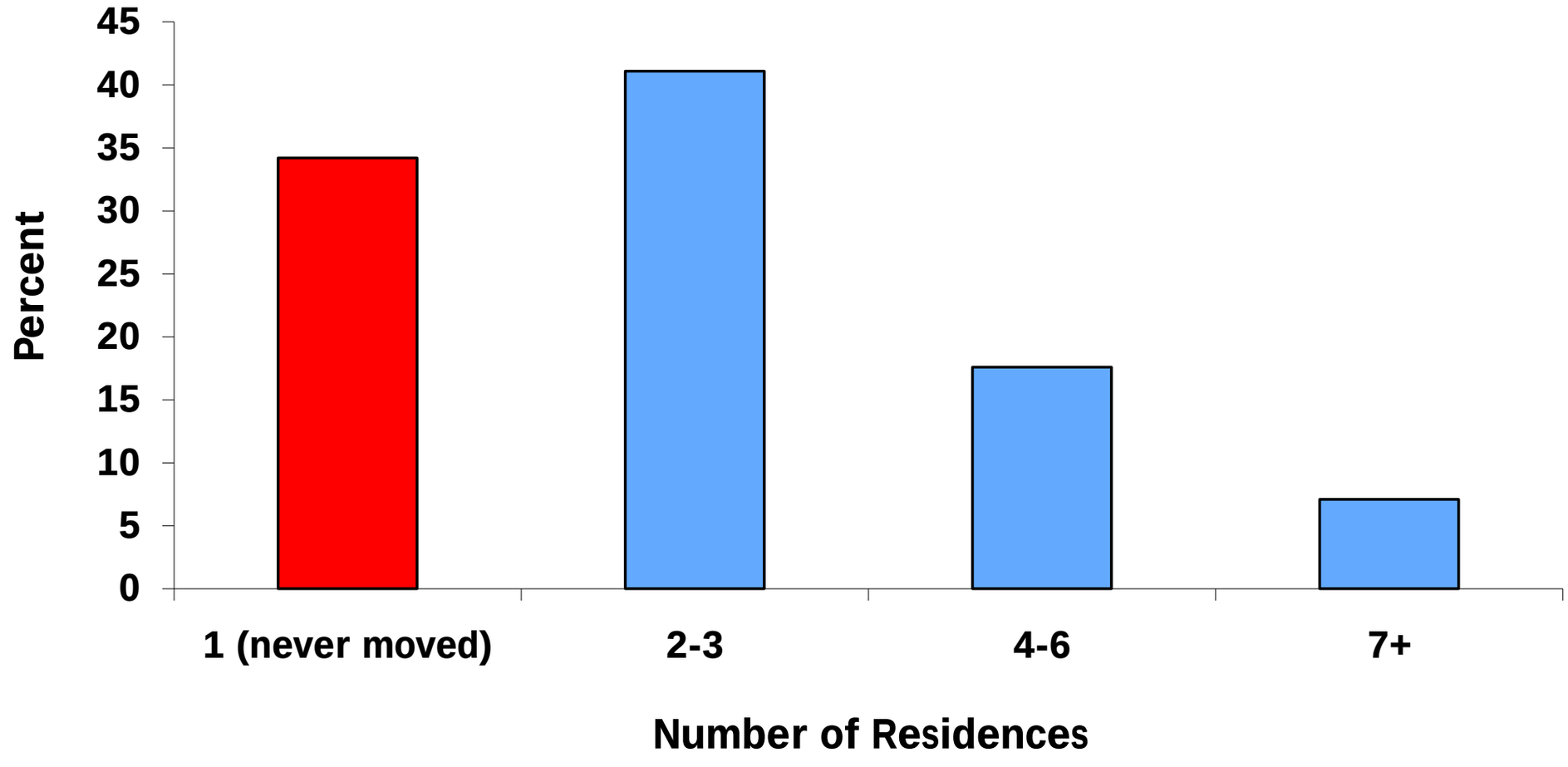
p=0.29

Reynolds et. al., Bioelectricmagnetics 2001

Residential Mobility in the Northern California Childhood Leukemia Study (NCCLS)

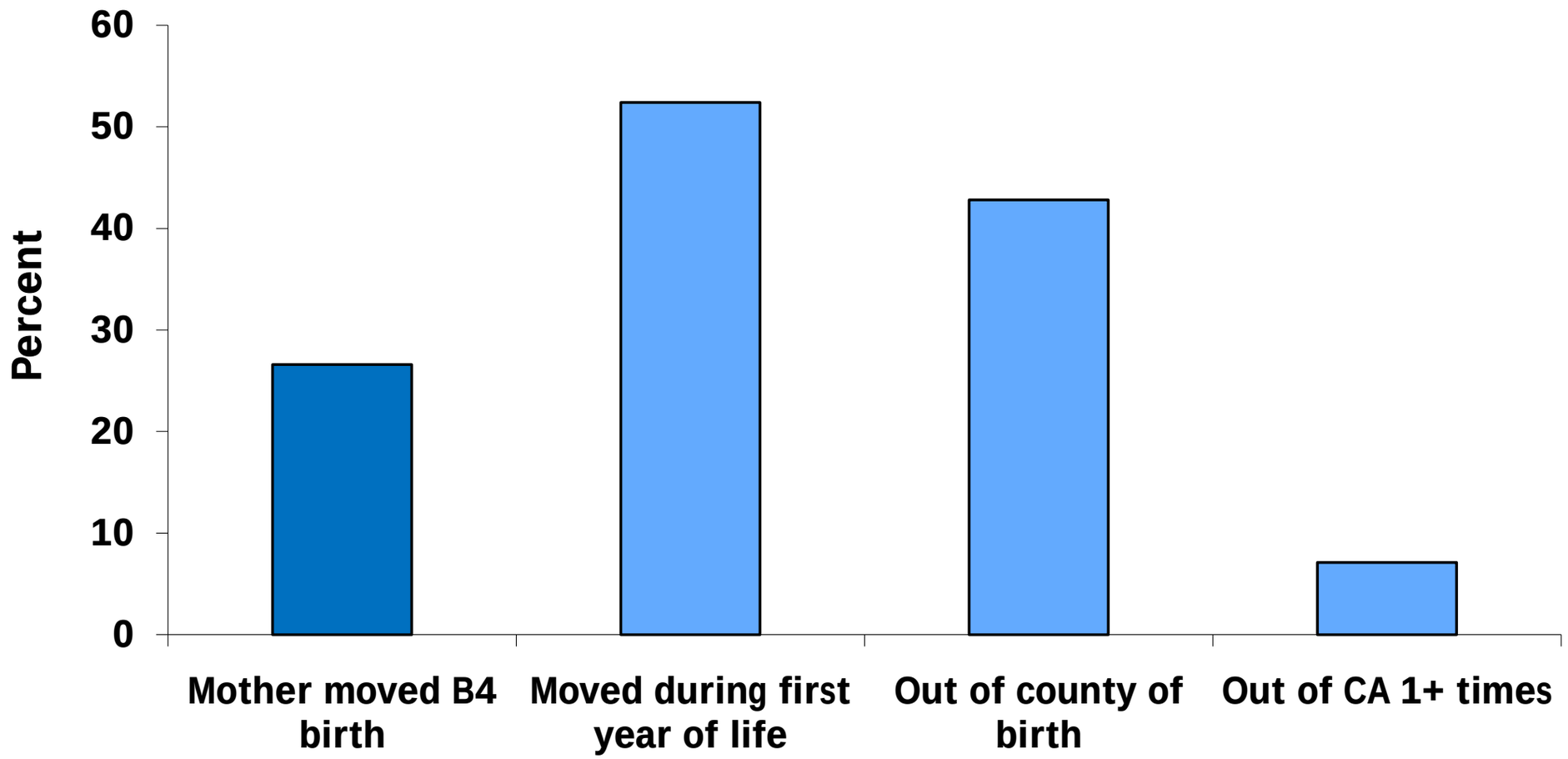
- Cases (n=380):
  - 1997-1999 leukemia diagnoses under the age of 15 in 35 northern California counties
- Detailed residential history collected via interview
- Addresses geocoded to a lat/long
- Urbanization and SES metrics from 1990 and 2000 census data

Number of Residences for Case Children: NCCLS Study



Urayama et. al., Ann. Epidemiol 2009

Residential Mobility among Case Children: NCCLS Study



Urayama et. al., Ann. Epidemiol 2009

Concordance of Birth vs. Diagnosis Block Group SES: NCCLS Study

Diagnosis Residence	Birth Residence		
	Low SES	Medium SES	High SES
Low SES	62%	16.7%	2.3%
Medium SES	32%	62%	25.6%
High SES	6%	21.3%	72.1%

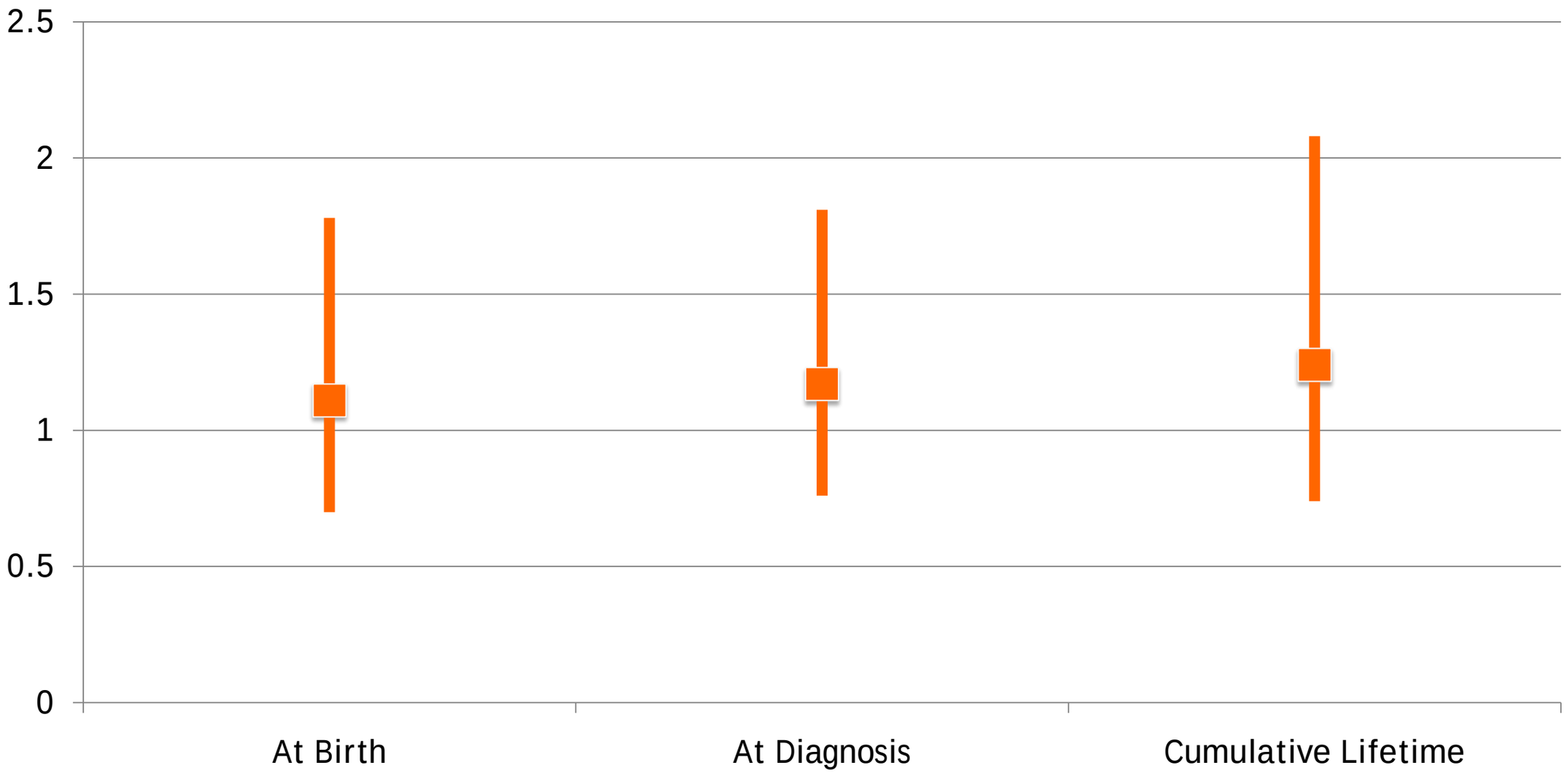
Urayama et. al., Ann. Epidemiol 2009

Concordance of Birth vs. Diagnosis Block Group Urbanization: NCCLS Study

Diagnosis Residence	Birth Residence		
	Rural	City	Large Metro
Rural	86.7%	16%	11.6%
City	13.3%	74%	6.6%
Large Metro	0%	10%	60.2%

Urayama et. al., Ann. Epidemiol 2009

Odds Ratios and 95% CI for childhood leukemia at the 75th percentile of residential ADT in the NCCLS study



Von Behren, et.al., CEBP, 2008

Findings for Childhood Leukemia

- High residential mobility even among very young children
  - Usually only address information for one or two points in time
  - Difficulties in assigning exposures from environmental agents
  - Birth address may not be a good indicator of *in utero* exposures

- Residential mobility non-random
  - Differences by SES
  - Differences by residential ADT

- Some suggestion of windows of susceptibility, particularly:
  - *In utero*
  - For cumulative exposures in early life
  - Recent exposures
  - Not necessarily time to event

Breast Cancer

Latency/windows of susceptibility

- Breast cancer is a very heterogeneous disease

- Risk relationships differ by
  - Age at onset (premenopausal vs. postmenopausal)
  - Cell type (ductal vs. lobular)
  - Hormone receptor status (ER/PR)

- Some potentially key windows of susceptibility to environmental exposures:
  - *In utero* exposures
  - Early life
  - Adolescence
  - Prior to a first full term pregnancy
  - Recent exposures
  - Lifetime cumulative exposures

Clues for windows of susceptibility for breast cancer

- *In utero*
  - Birth characteristics (eg. high birth weight, older maternal age)

- Puberty
  - Ionizing radiation
  - DDT/DDE
  - NIEHS Centers for Breast Cancer and the Environment

- Prior to a first pregnancy
  - Active smoking

- Recent
  - Breast cancer rates post-WHI

For GIS Studies What Address is Best?

- When is the biologically important time window of risk?
- Where do women spend the most time?
- Is residential mobility different by:
  - Demographic characteristics?
    - e.g. SES status?

California Teachers Study - Overview

- Funded with breast cancer tobacco tax $
- Mailing to female STRS members in 1995
- Statewide cohort (133,479)
- Annual re-contact/biennial questionnaire
- Outcome follow-up via linkage to CCR/vital records
- Largest prospective study specifically designed to study breast cancer

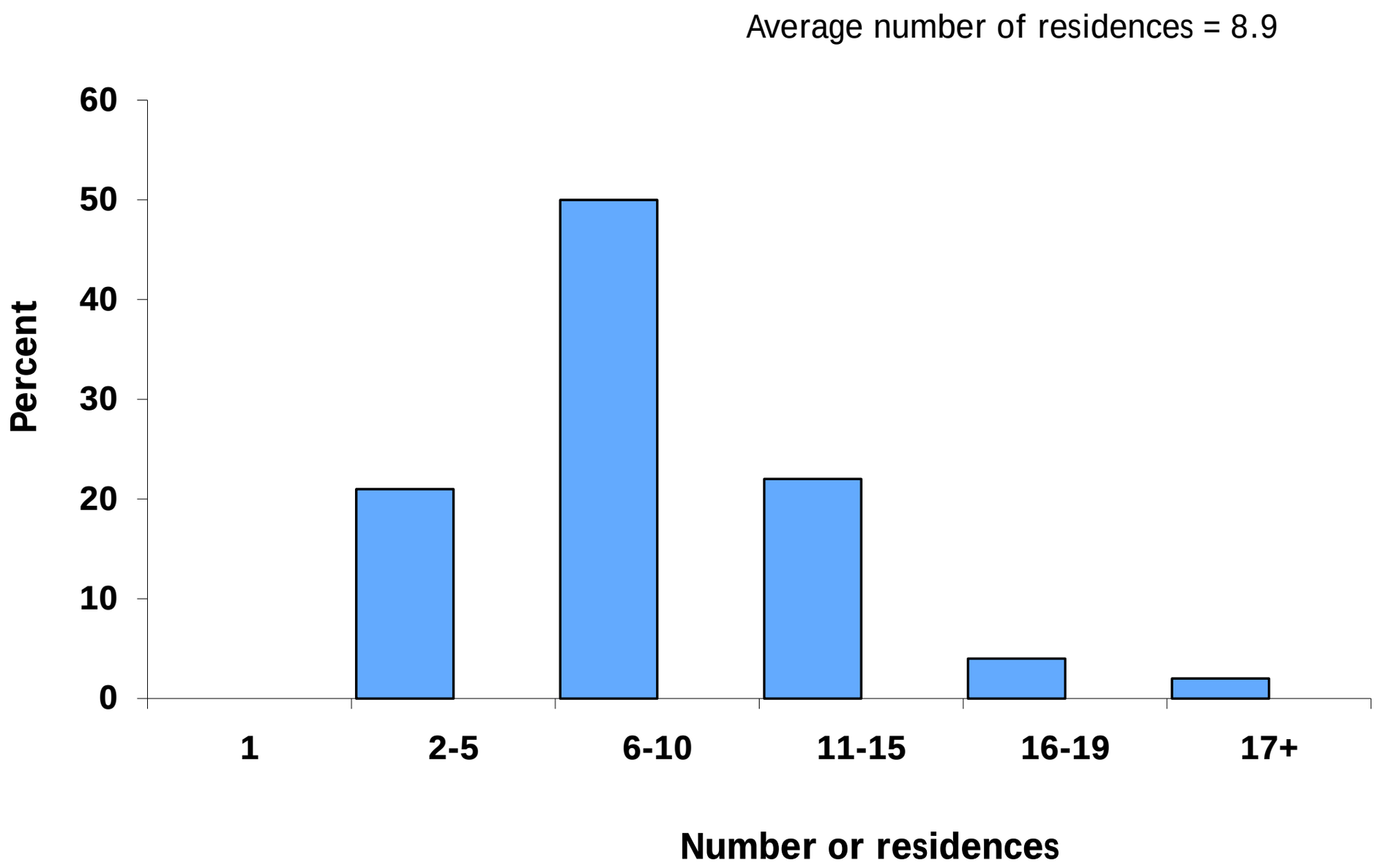
Residential Mobility in the California Teachers Study

- Sample of 328 participants
  - Balanced on urban/rural residences

- Detailed residential history information via interview
  - All addresses for residences of 6 months or longer
  - Move dates -- in and out

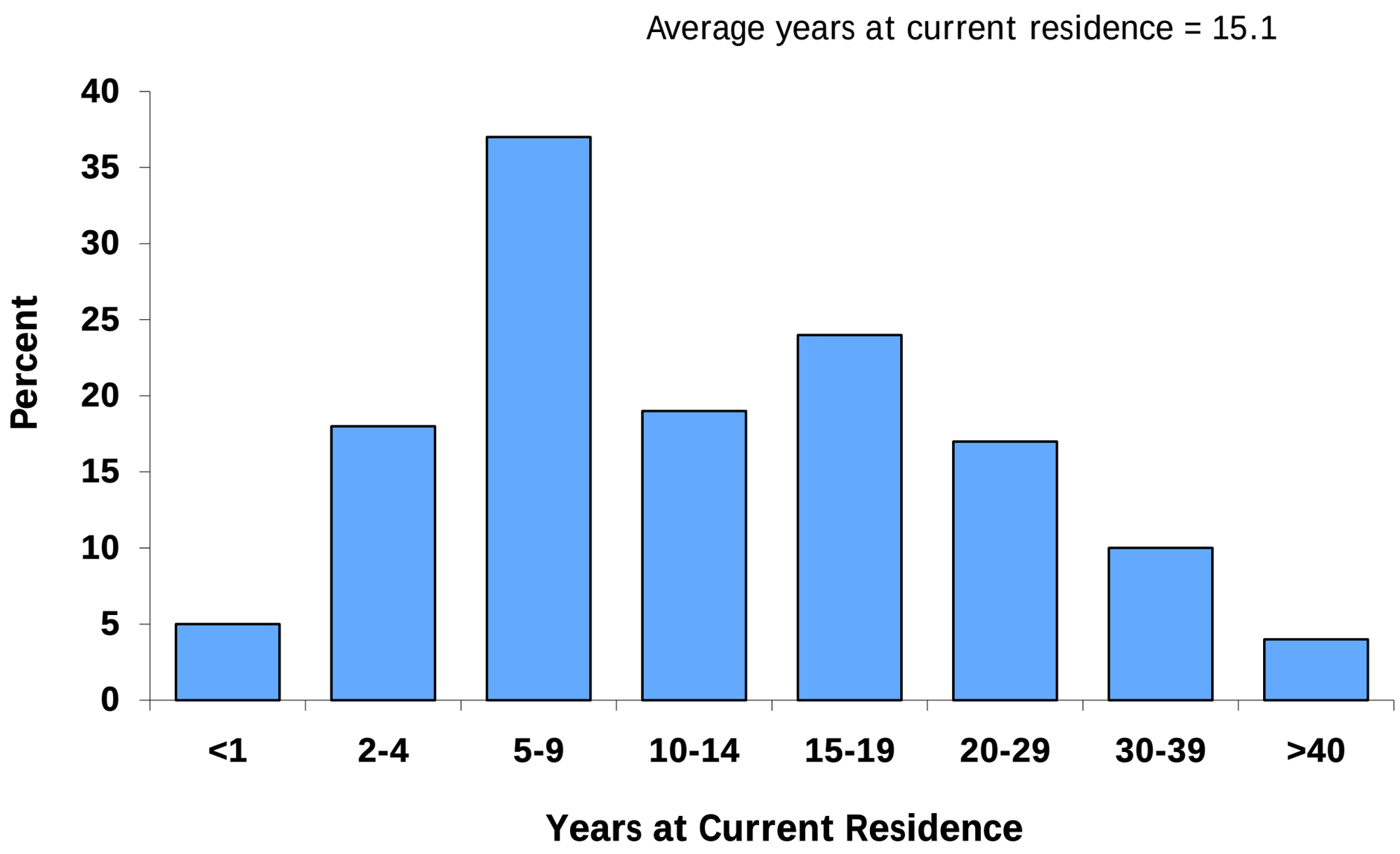
- Geocoded addresses for previous 10 years to lat/long

Number of Lifetime Residences among CTS Participants



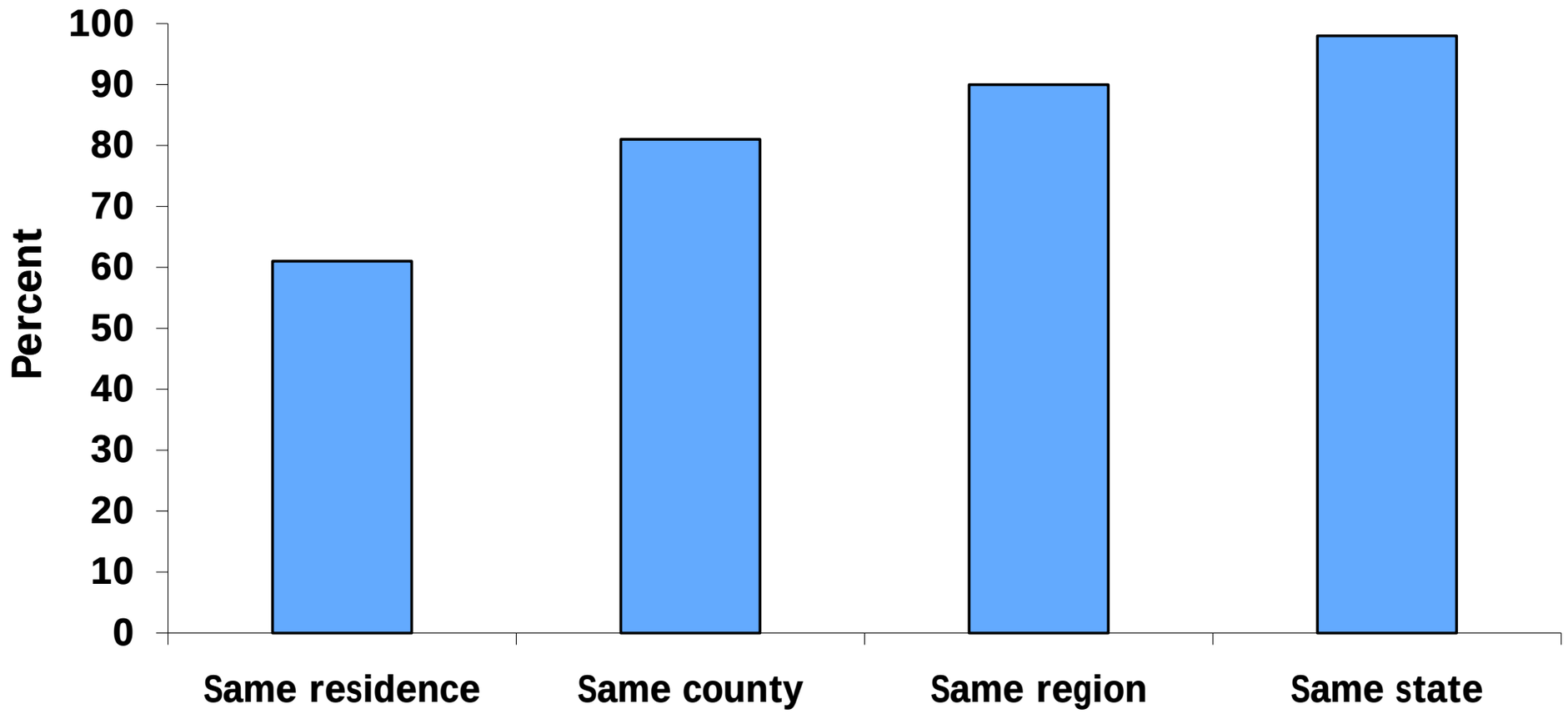
Hurley et al., Soc Sci Med 2005

Years at Current Residence among CTS Participants



Hurley et al., Soc Sci Med 2005

Residential Mobility among CTS Participants in Previous 10 years



Hurley et al., Soc Sci Med 2005

Predictors of Residential Stability

(number of years at current residence)

- Age:
  - OR for age 65+ (vs. <44)=3.7 (95% CI 2.7-5.0)
- Birthplace:
  - OR for California-born (vs. other US)=1.2 (95% CI 1.02-1.4)
- SES:
  - Highest quartile (vs. lowest)=1.3 (95% CI 1.04-1.5)

(none of these predicted number of residences)

Hurley et al., Soc Sci Med 2005

Findings for Breast Cancer Studies

- Older adults less residentially mobile
- Residential mobility non-random
  - Differences by age
  - Differences by birthplace
  - Differences by SES
- Current residence may be relevant for short latency exposures (HT model)
- Recent residential history may not be useful for early life exposures (DDT/DDE model)

Summary

- Residential location important for studies of the physical environment
  - Difficult to obtain detailed lifetime residential histories
- Residential mobility non-random
  - Importance of age, SES, other factors
- Windows of susceptibility differ by agent(s) of interest and type of cancer
  - Increasing work in this area
- More research is needed. . .

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