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Host, family and community proxies for infections associated with leukaemia

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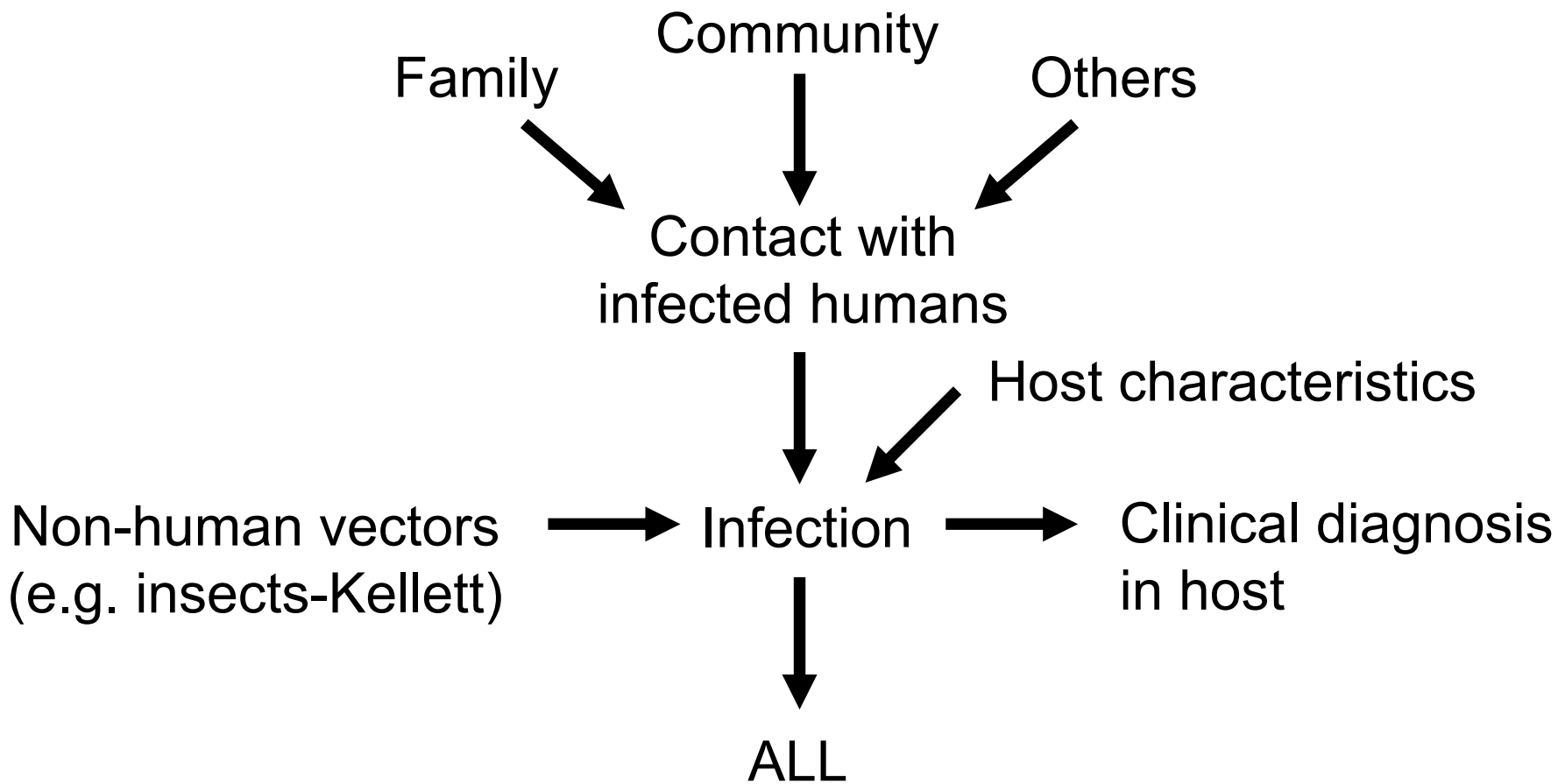
Infections and leukaemia

- Long history linking childhood leukaemia with infection, for example Kellett (1937)
- No specific infection discovered
- Proxies usually used - why?
  - Infectious disease difficult to measure
  - Biomarker for candidate infection, identification of specific pathogen, time window of exposure, sample availability
  - General pattern has no biomarker

Causal pathway for infections



Proxy measures for infection

- Age distribution of incidence
- Birth order and older siblings
- Breastfeeding
- Day care during infancy
- Genetic variation in immune response (e.g. TLR)
- Increase in incidence
- Parents' occupation
- Population mixing
- Seasonal variation
- Spatial and space-time clustering of cases

Heath's cluster investigation in USA

- Heath (2005) published a report of childhood leukaemia clusters in USA
  - 1961-1977
  - 50 clusters identified
  - 8 clusters "linked" with infections
- 7/8 cases/siblings attended same church/school
- 5/8 rapid population growth
- 3/8 unusual community infection patterns
- 1/8 three Burkitt lymphomas in neighbourhood

Clusters of leukaemia

- A cluster is “suggestive” of an infectious aetiology (McNally and Eden, 2004)
- For a cluster of leukaemia to be used to identify the cause (Rothman, 1990)
  - The cause must also cluster
  - The induction period must be short and constant
  - The cause must be rare
- Not necessarily an infection (McNally, 2008)
  - Endemic/common infection leads to homogeneity

Family: birth order

- A characteristics of the family circumstances
- Represents older siblings in the household

> "High birth order may be taken as a surrogate for early exposure to infection from siblings."
>
> McNally & Eden, 2004

Birth order and childhood leukaemia

Risk with increasing birth order	Leukaemia	ALL
Increased	2	4
No change	7	3
Decreased	1	2

- Studies 1997-2008
- 19 studies
- 1997-2004 from McNally & Eden 2004 and PubMed

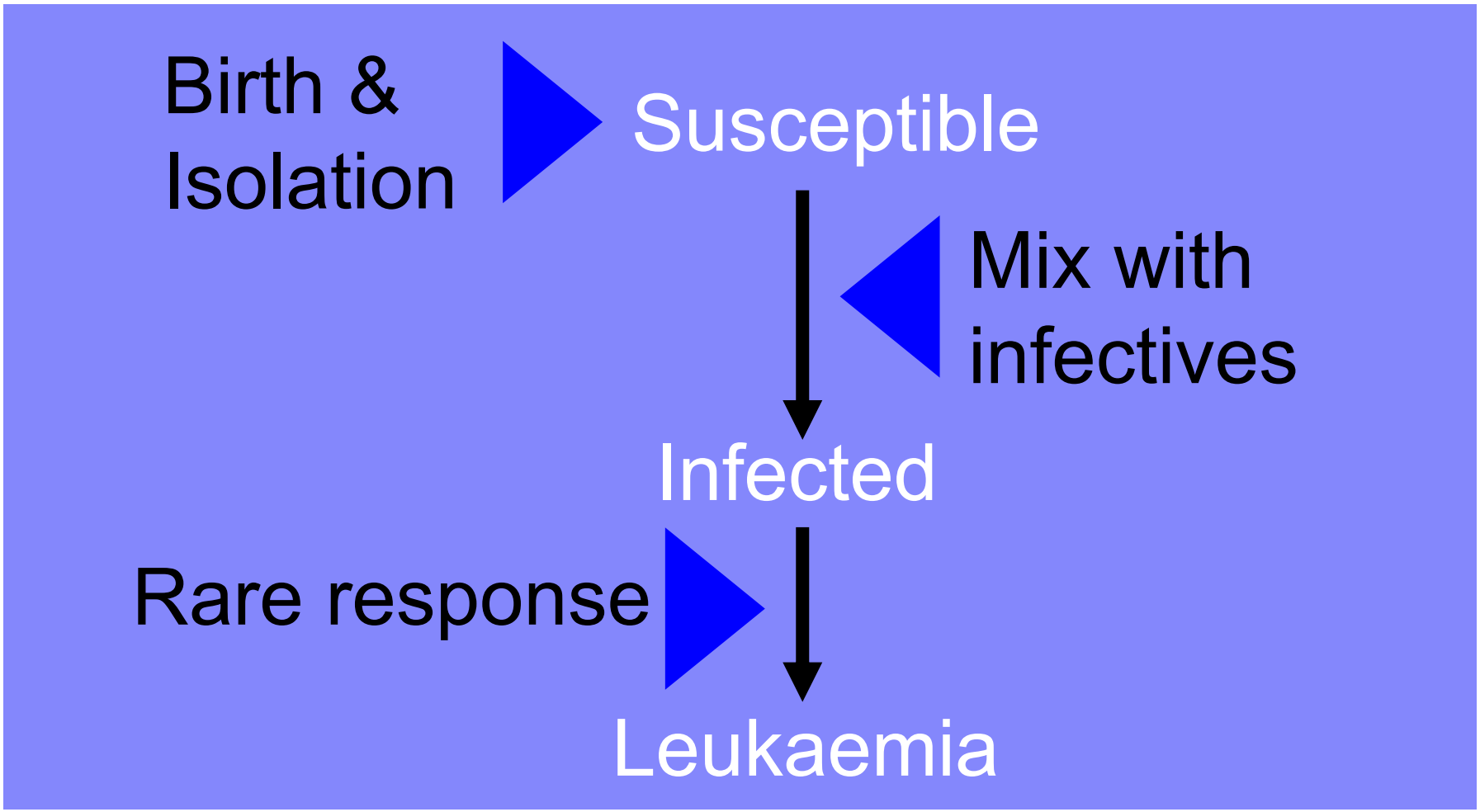
Birth order/parity and infection

	Infection	Raises risk
Virus	HSV1	↑ younger siblings
	EBV	→ younger siblings
	RSV	↑ birth order x 2
Bacteria	H.pylori	↑ birth order x 2, ↑ siblings
Protozoa		↑ birth order
'General'	GP records	↓ birth order, → birth order

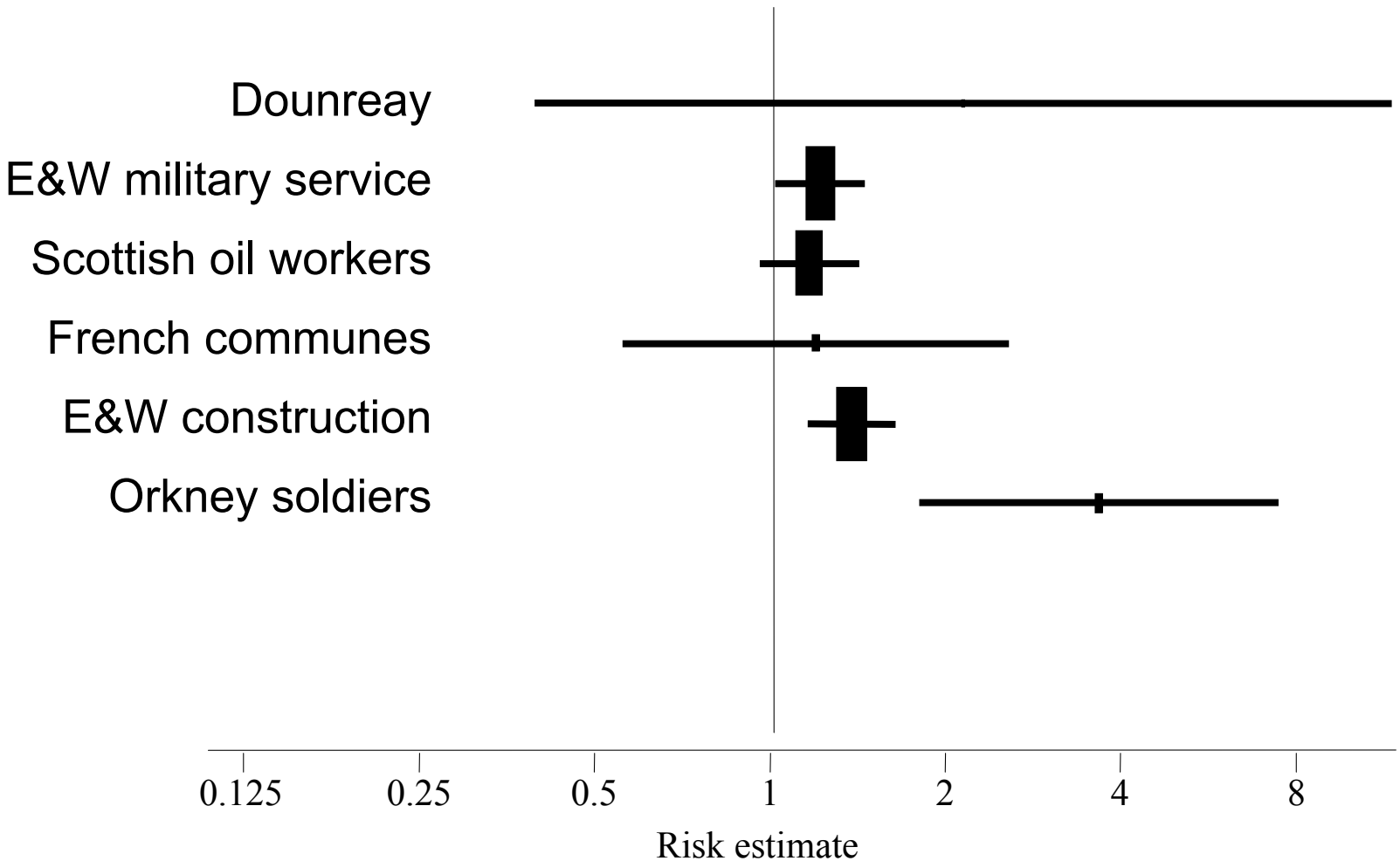
Community: population mixing

- Migration
  - Residential, permanent one-way
  - Commuting, daily two-way
- Proxy for
  - Movement of infections

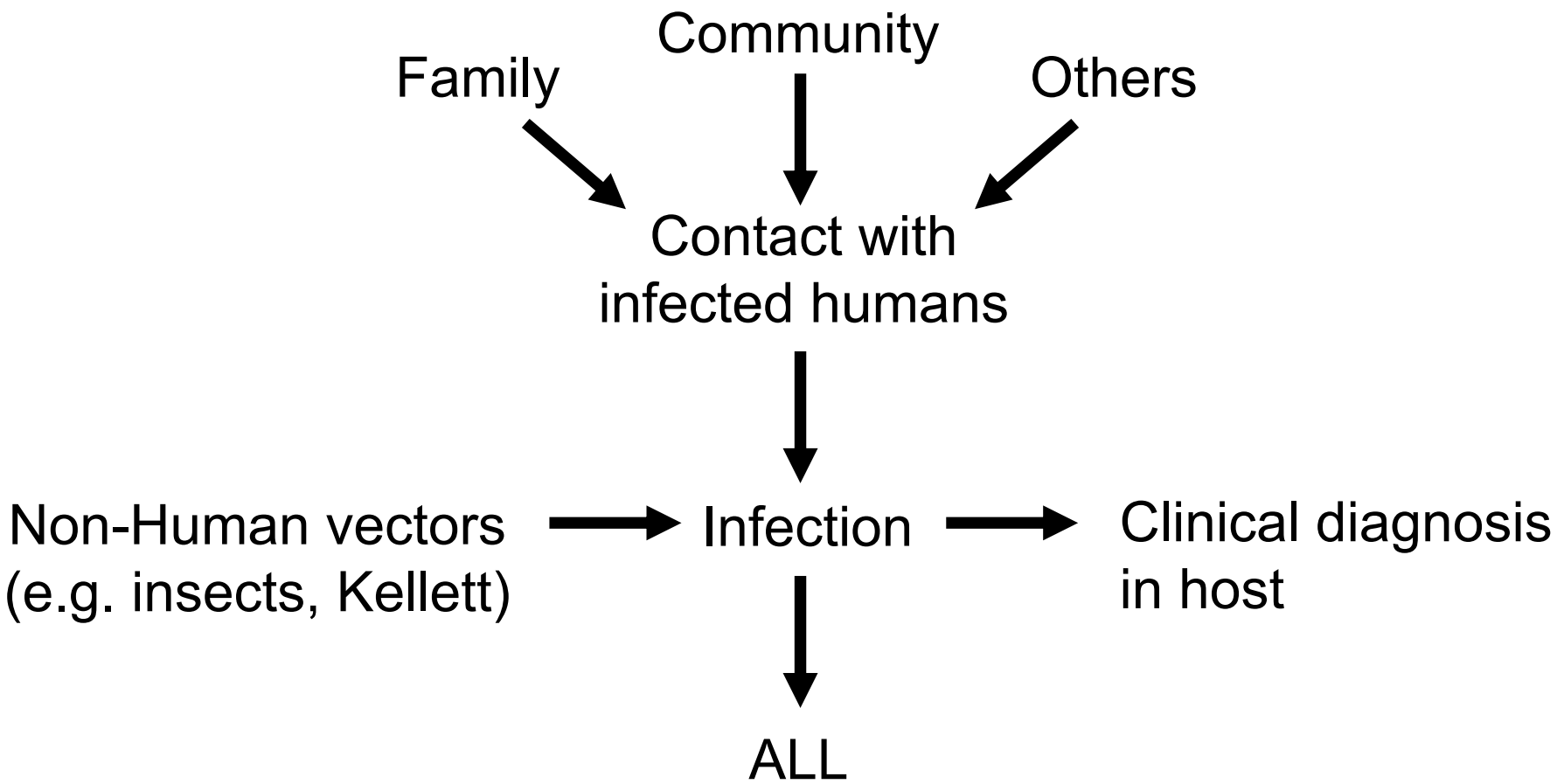
Population mixing hypothesis



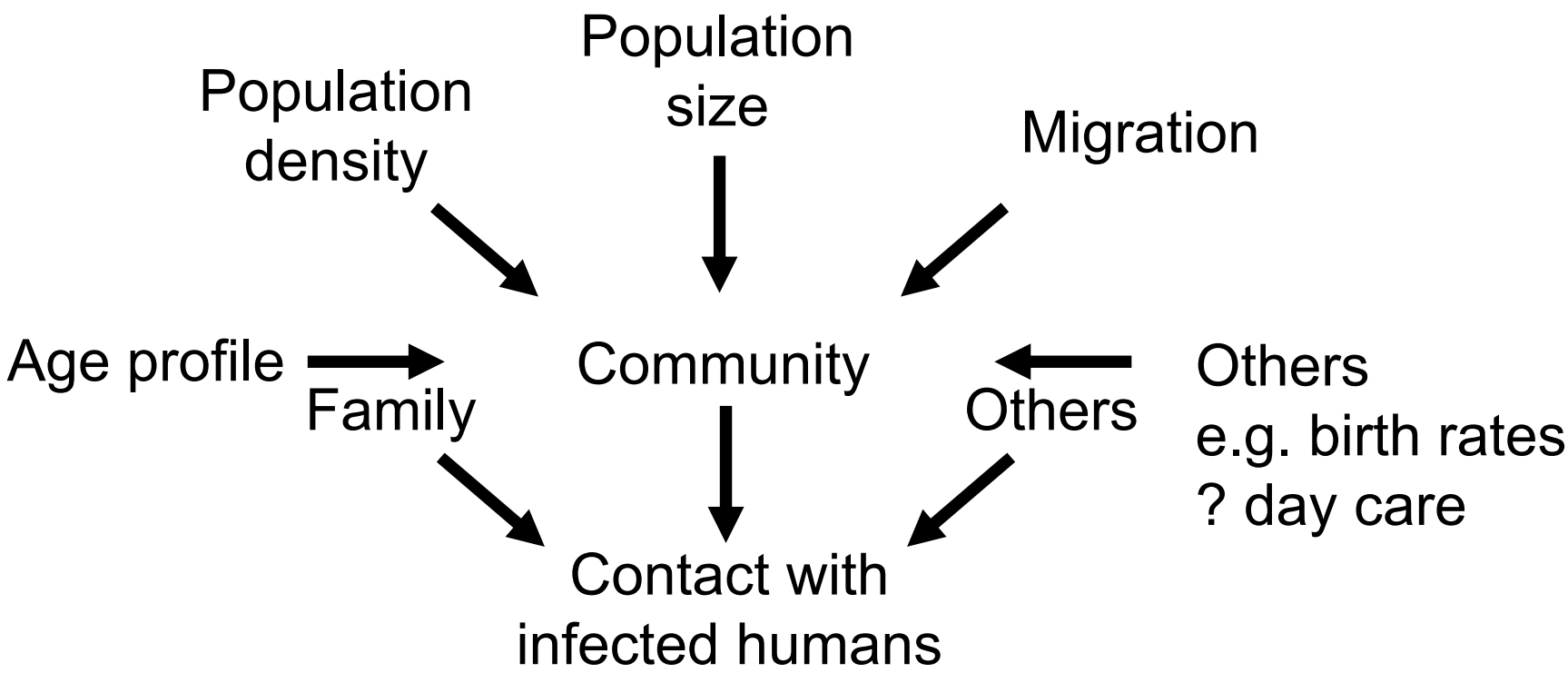
“Natural experiments”



Community: causal pathway for infections



Community: causal pathway for infections

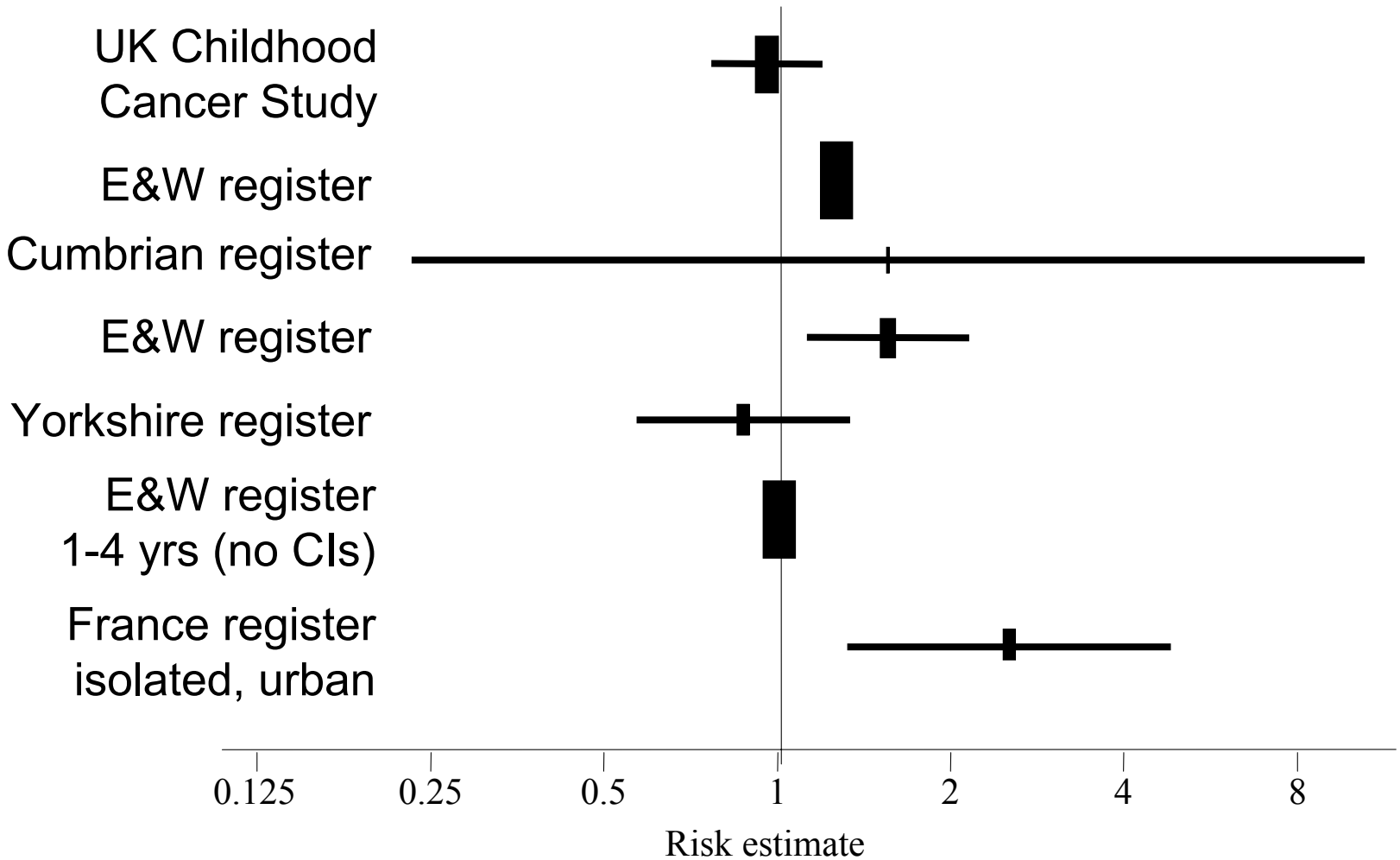


Objective measures of migration

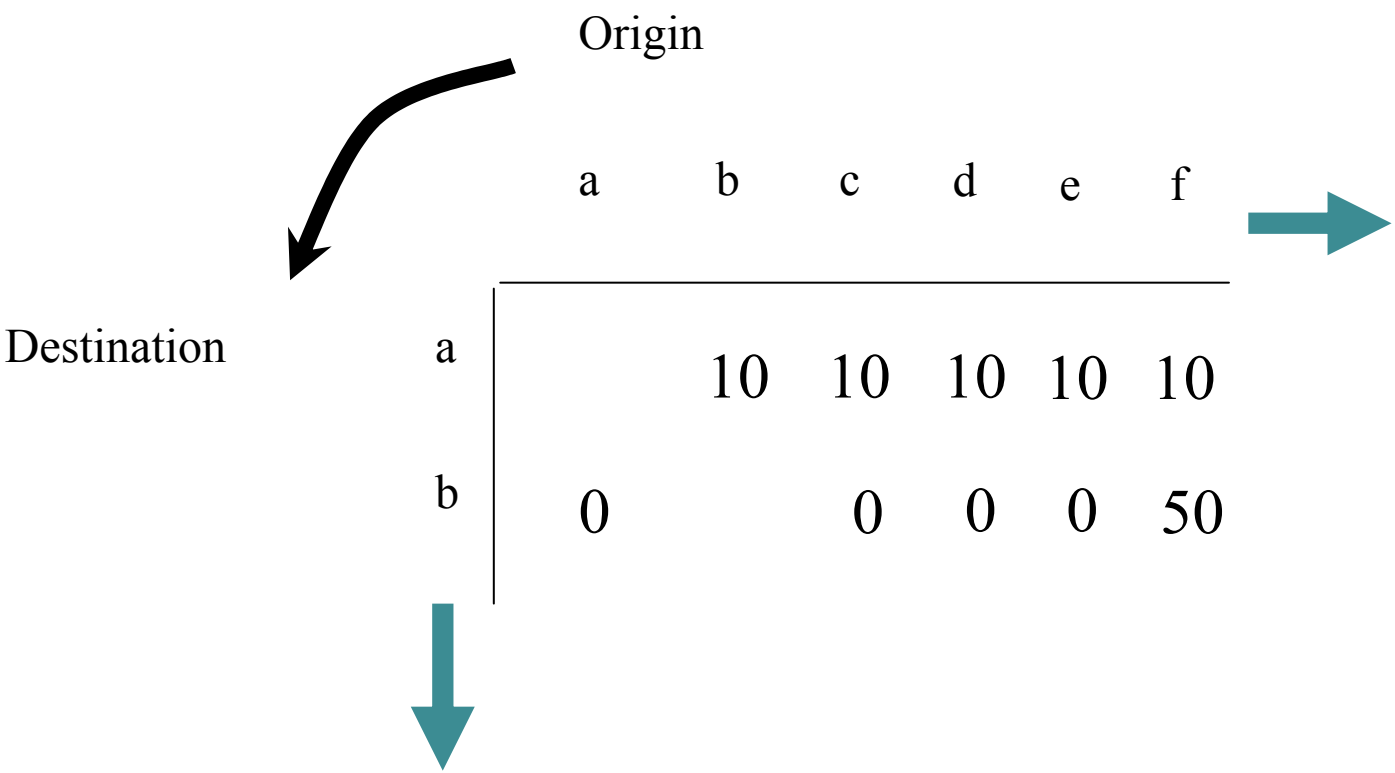
"Where did you live one year ago?"

- For all in-migrants for each area data on
  - Number and proportion of in-migrants
  - The origin of all in-migrants (down to Ward)
  - Age and sex of in-migrants by origin
- For each area we estimate
  - Proportion of in-migrants
  - Diversity in the origin of in-migrants
  - 'Childhood' (0-14) and 'All ages' (0+) separately

Proportion of total immigrants



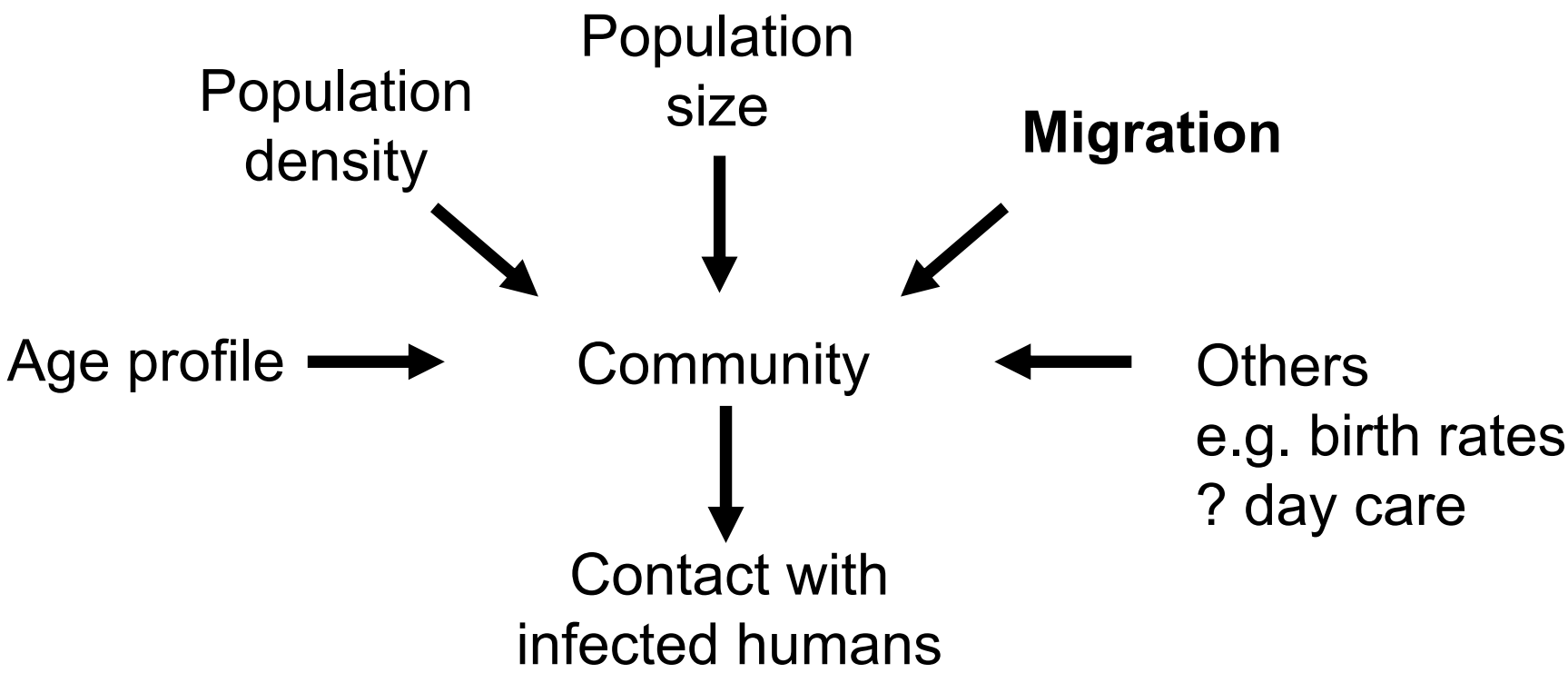
Diversity of in-migrant origins



Diversity of migration at diagnosis - UKCCS

		ALL		Other tumours	
Diversity of in-migrant origins					
All ages	Low	**1.37**	**(1.00-1.86)**	1.04	(0.80-1.35)
	Med	1	(-)	1	(-)
	High	0.88	(0.70-1.10)	1.07	(0.90-1.29)
0-14	Low	1.37	(0.93-2.01)	0.97	(0.69-1.35)
	Med	1	(-)	1	(-)
	High	1.04	(0.87-1.24)	1.09	(0.94-1.26)

Community characteristics and infection



Population density

- Represents the likelihood of a susceptible encountering an infected person
- Assessment may be subjective…
  - "Farm/Not farm"
  - Identifying "built-up areas" from maps

…or may be objective

  - Population density
  - Persons per hectare
  - Rural < 1.5 pph
  - Urban >25.0 pph

Population density at diagnosis

		ALL		Other tumours
All ages				
Rural	1.12	(0.93-1.35)	1.05	(0.91-1.21)
Suburban	1.09	(0.97-1.23)	1.02	(0.93-1.13)
Urban	1	(-)	1	(-)
0-14				
Rural	1.07	(0.88-1.29)	1.03	(0.90-1.19)
Suburban	1.07	(0.94-1.20)	1.03	(0.94-1.14)
Urban	1	(-)	1	(-)

Population density at birth

		ALL		Other tumours
All ages				
Rural	1.16	(0.95-1.41)	1.00	(0.86-1.16)
Suburban	1.07	(0.94-1.21)	0.98	(0.89-1.08)
Urban	1	(-)	1	(-)
0-14				
Rural	**1.99**	**(1.24-3.20)**	0.78	(0.61-1.00)
Suburban	1.36	(0.82-2.25)	0.92	(0.71-1.19)
Urban	1	(-)	1	(-)

Moving between birth and diagnosis

	Diagnosis		
Birth	Rural	Suburban	Urban
Rural	**2.12**	**2.14**	**2.08**
Suburban	1.52	1.62	1.48
Urban	-	1.41	1

Proxy assessment: general infectious load

- Hospital Episode Data
  - April 2001-March 2002
  - Aged <15 years
- Admissions for
  - Infection: intestinal, unspecified viral, acute respiratory, influenza and pneumonia
  - Non-infectious: superficial injury
- Admission counts for census wards from
  - West Midlands, England
  - Eastern England

Childhood residential migration

	Eastern region		West Midlands		Non-infectious	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Volume	1.02	0.92 – 1.13	0.88	0.78 – 0.98	1.31	1.11 – 1.55
Diversity	1.10	1.04 – 1.19	1.04	0.96 – 1.12	0.90	0.81 – 1.00
Distance	1.00	0.96 – 1.03	0.92	0.88 – 0.96	1.05	0.99 – 1.11

Commuting

	Eastern region		West Midlands		Non-infectious	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Volume	1.32	1.00 – 1.75	1.69	1.31 – 2.18	0.42	0.30 – 0.60
Diversity	0.86	0.80 – 0.92	0.99	0.90 – 1.10	0.82	0.71 – 0.94
Distance	0.82	0.77 – 0.87	0.84	0.78 – 0.90	1.01	0.92 – 1.12

Summary

- Commuting volume - fairly consistent association
  - ↑ risk in areas with ↑ volume of commuters
  - – adjusting for pop density removes significance
- Commuting distance demonstrated the most consistent association
  - ↓ risk in areas with ↑ median distance commuted
- Deprivation and population density are reliable proxies for the level of infectious disease

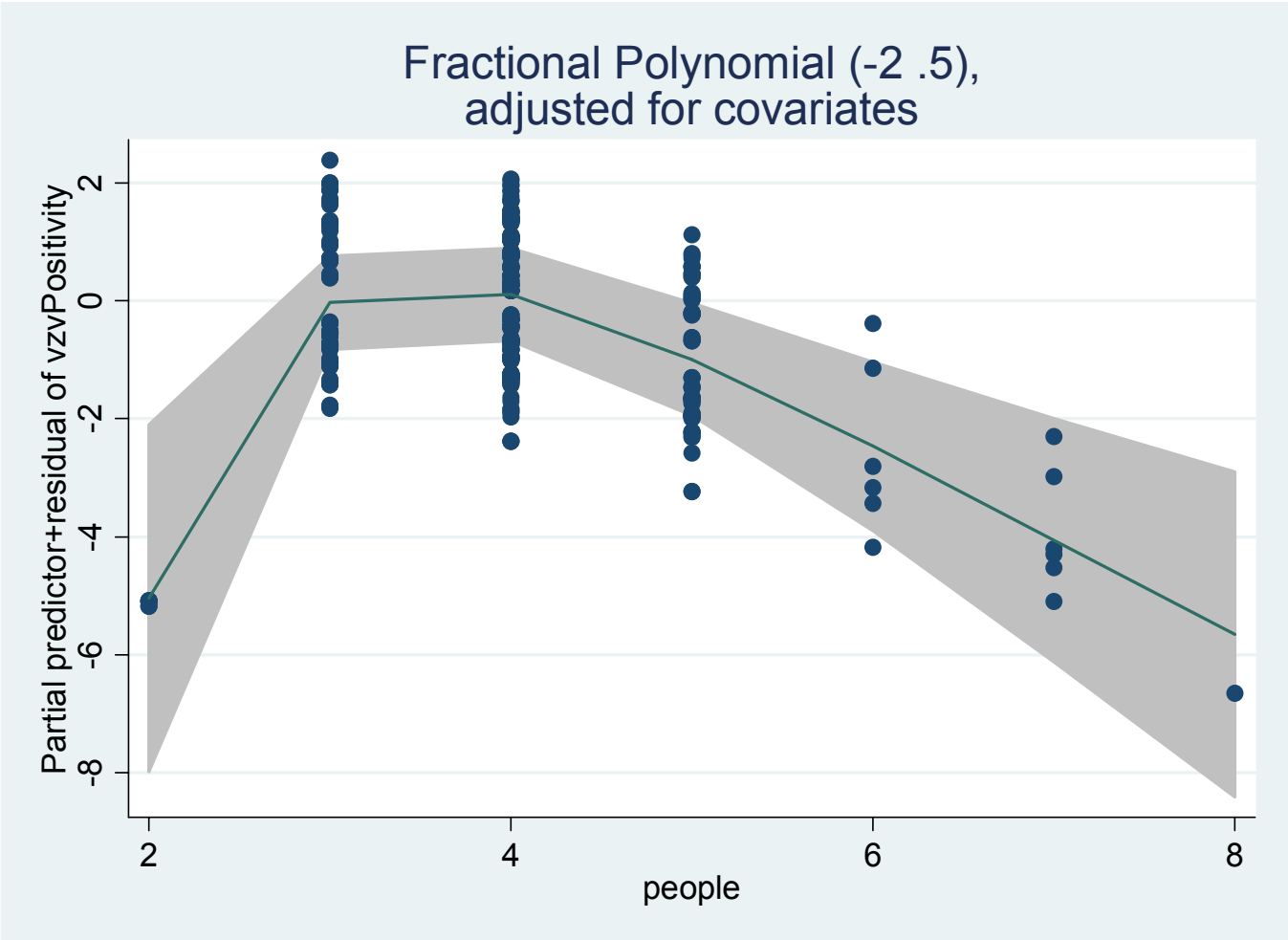
Specific infections

- Norfolk, England in 2002
- Saliva samples measured antibodies for
  - Varicella zoster virus
  - Epstein-Barr virus
- 616 children aged 1-4 years
- Fractional polynomial regression (in Stata)
- Examine risk of virus in association with host, family and community characteristics

Multivariable logistic regression

Significant odds ratios	VZV	EBV
Age	2.15	
Mother smoked year 1	2.31	
Father unemployed		3.62
Older children	2.23	
People	Non-linear	
Day care	0.40	1.58
Migration distance	1.01	

People and VZV



Summary

- Proxies for infection associated with childhood leukaemia
- Proxies are rarely tested for true reflection on infectious disease risk
- Proxy association with risk is not straightforward
  - Pathogen specific
  - Non-linear

Future directions

- Lessons learned
  - Selection bias, participation and ‘adjustment’
  - Comparison diagnostic categories/diseases
- To pursue infections - we need to
  - Measure infections more accurately
    - GP, infection diary, biomarkers for immune function?
    - Relative to radiation metrics/interpolation
  - Relate the infection measurement to proxies

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Supplementary slides

Community: ‘day care’ or ‘child care’

- Large meta-analysis from Uruyama and colleagues
- What does it mean?
- “However there is no evidence to suggest that mothers that stay at home and look after their children in the pre-school years are putting their children at an increased risk of developing leukaemia.” (LRF.org.uk, 2008)

Day care and infections

- Review (Nesti and Goldbaum, 2007) found
  - 2-3 times risk of infection
  - No contradictory results
- Most commonly
  - Upper and lower respiratory tract infections
  - Otitis media
  - Gastrointestinal system and liver
  - CMV, VZV, Bacteria
  - Skin e.g. Herpes simplex

Day care and infections

- Some reports of no association
- For example,
  - Gardner et al., 1984: Some notable lower rates (picornavirus, enterovirus)
  - Hedin et al., 2007: “…daycare infants are visiting a physician and treated with antibiotics in the same way as homecare infants.” (after adjustment for asthma, perception and symptoms are taken into account)

Day care characteristics

- Independent of age, race, socioeconomic status
- Exploration of their environment with their mouths
- Absence of hygiene
- Faecal incontinence
- Immunity not fully acquired

- Larger number/density of children increases risk

- Flow of infection from day care to community

Results – demographic variables

	Eastern region		West Midlands		Non-infectious	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Unadjusted						
Deprivation	1.04	1.03 – 1.05	1.05	1.04 – 1.06	1.01	0.99 – 1.02
Pop Density Low	1.00		1.00		1.00	
Med	1.14	1.05 – 1.24	1.18	1.08 – 1.30	0.99	0.87 – 1.13
High	1.29	1.19 – 1.40	1.44	1.32 – 1.57	0.88	0.78 – 0.99
Adjusted						
Pop Density Low	1.00		1.00		1.00	
Med	1.10	1.01 – 1.19	1.10	1.00 – 1.20	0.95	0.83 – 1.08
High	1.06	0.97 – 1.17	1.15	1.04 – 1.28	0.76	0.66 – 0.89

Childhood residential migration

	Eastern region		West Midlands		Non-infectious	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Unadjusted						
Volume	1.08	0.97 – 1.20	0.79	0.70 – 0.89	1.28	1.08 – 1.50
Diversity	1.20	1.12 – 1.29	1.21	1.12 – 1.30	0.93	0.84 – 1.02
Distance	0.94	0.91 – 0.97	0.86	0.83 – 0.89	1.03	0.98 – 1.09
Adjusted						
Volume	1.02	0.92 – 1.13	0.88	0.78 – 0.98	1.31	1.11 – 1.55
Diversity	1.10	1.04 – 1.19	1.04	0.96 – 1.12	0.90	0.81 – 1.00
Distance	1.00	0.96 – 1.03	0.92	0.88 – 0.96	1.05	0.99 – 1.11

Causal pathway for infections