



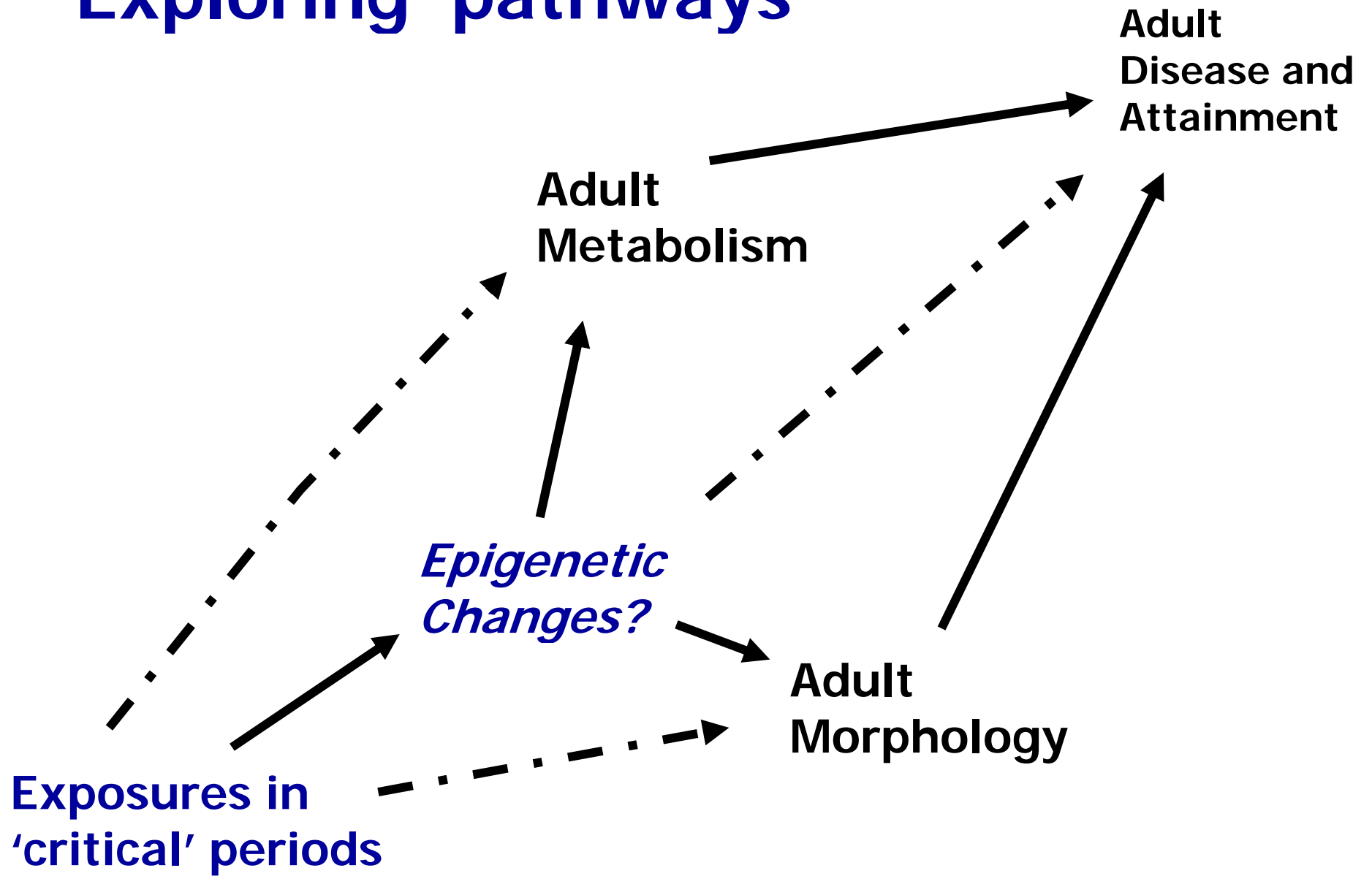
Life course consequences of early life events?

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*Biology, Genetics, and Econometrics of Health and Aging
Conference. University of Chicago, September 16, 2011*

Exploring pathways



Human studies of poor nutrition during development

- Nordic countries 19th century
- Soviet Union 1930s
- WWII 1939-1945
- China 1959-1961
- Seasonal famines 20th century

Dutch Hunger Winter 1944-45

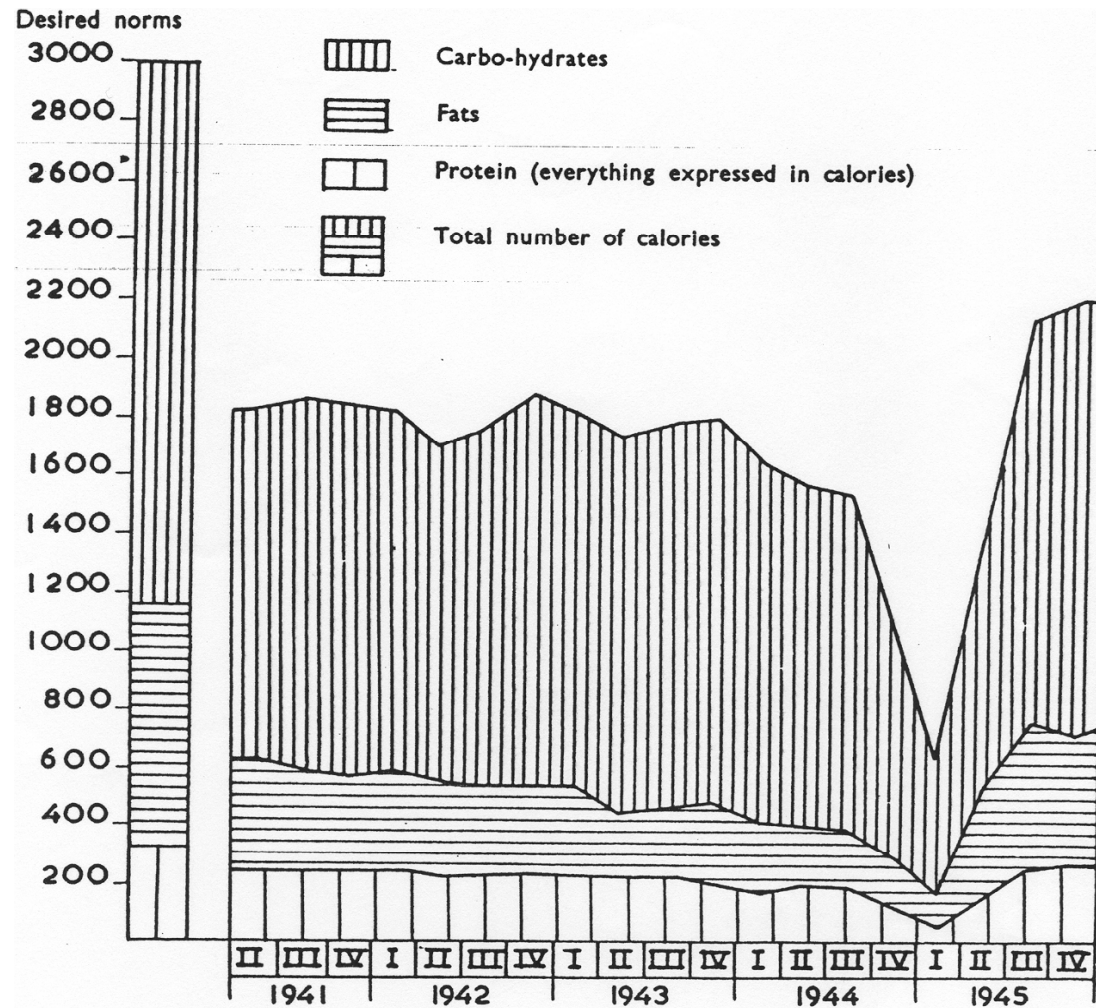


- Transport embargo
 - German response to rail strike in support of advancing Allied troops.
 - Rail strike was continued by Dutch for non-military reasons after failed military advance
- Limited to western Netherlands
- Ended with surrender of the German forces, May 1945

Food rations

Western Netherlands, 1941-1945

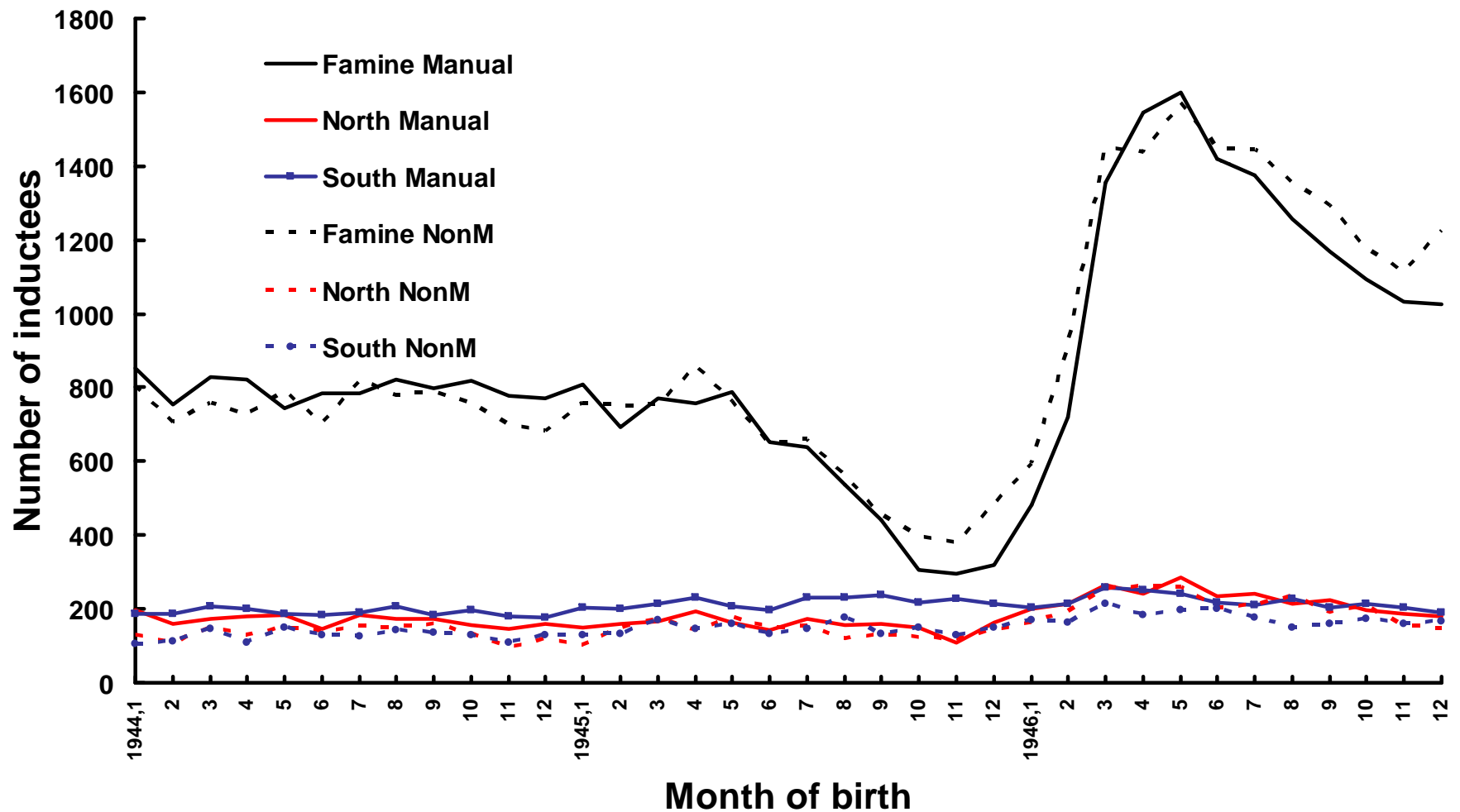
Burger et al, 1948



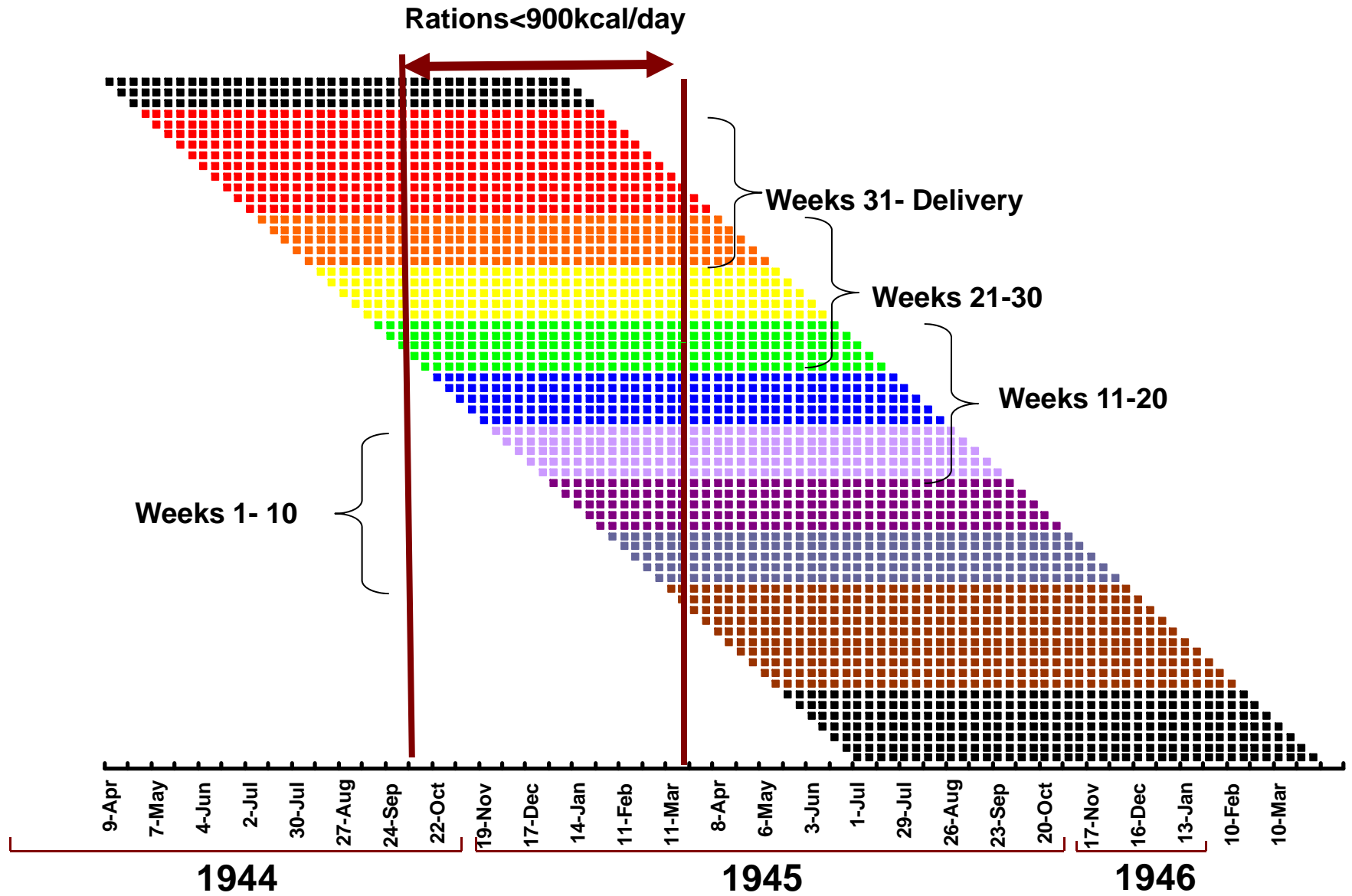
Fertility and social class

Dutch recruits by region of birth

1944-1947



Exposure categories



Hunger winter families study

Lumey et al., Int J Epid, 2007



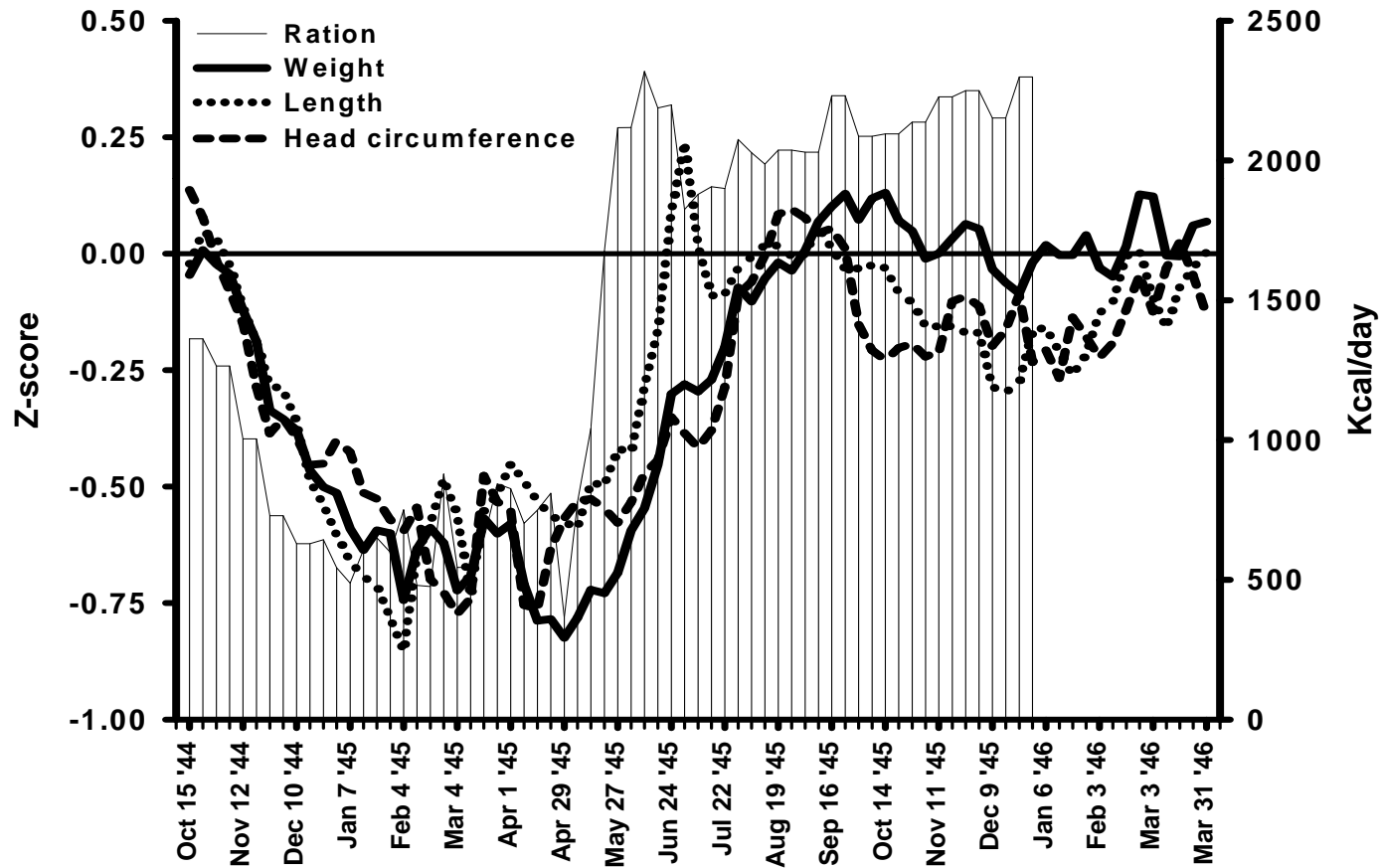
- 3,307 births at three institutions:
 - Amsterdam, Leiden, Rotterdam
 - 1943; Jan 45-Mar 46; 1947
- Tracing through Population Registers
- Recruitment via mail
- **Sibling controls**
- Telephone interviews 2003-2005 at age 59
- Clinical assessments in Leiden at age 59

Funding: RO-1 HL067914

Size at birth

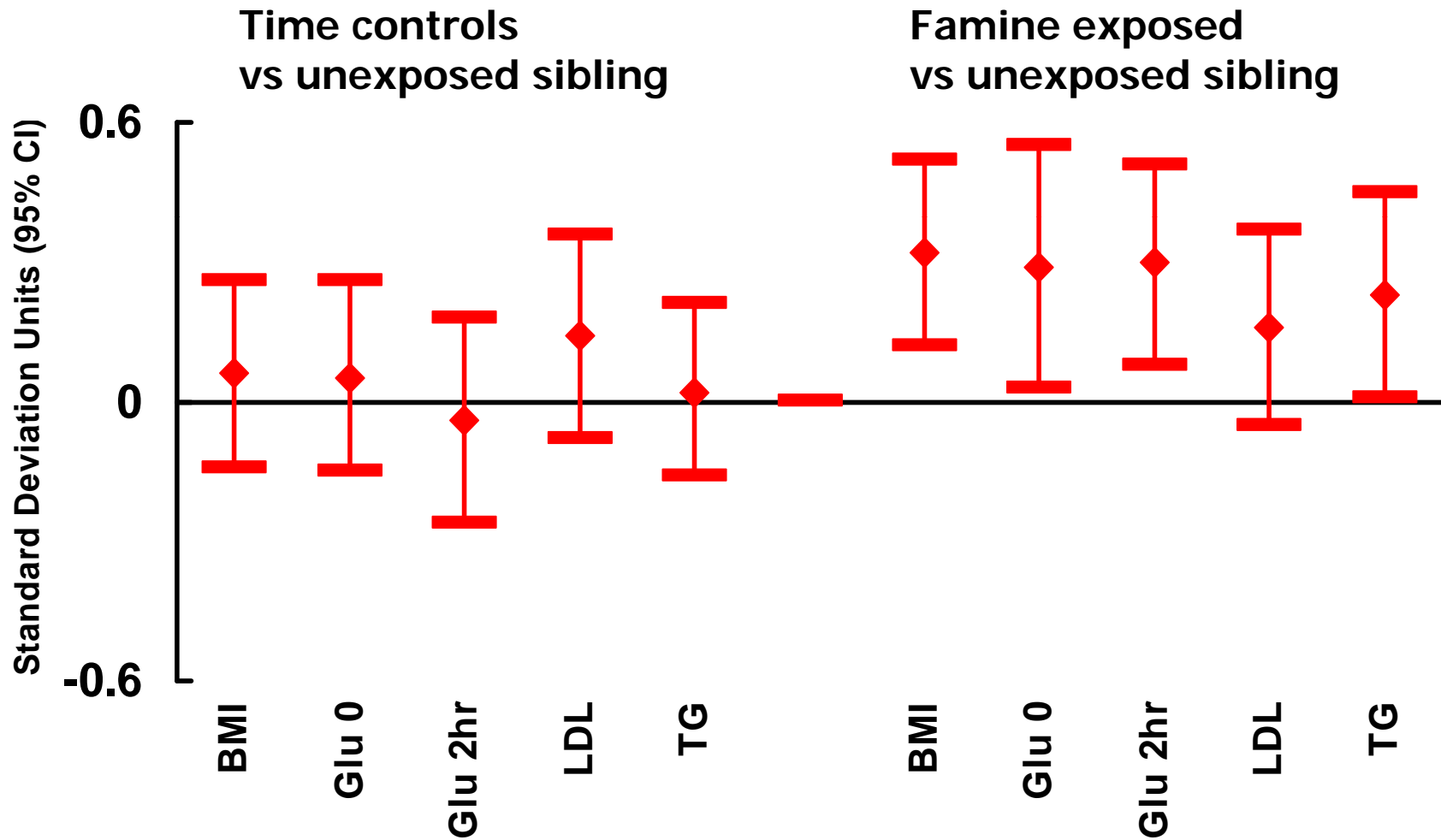
Dutch famine selected clinics

Stein et al., Int J Epi 2006



Outcome differences between siblings

(SD units)



Pre-natal nutrition and methylation

Proof of concept in rodents



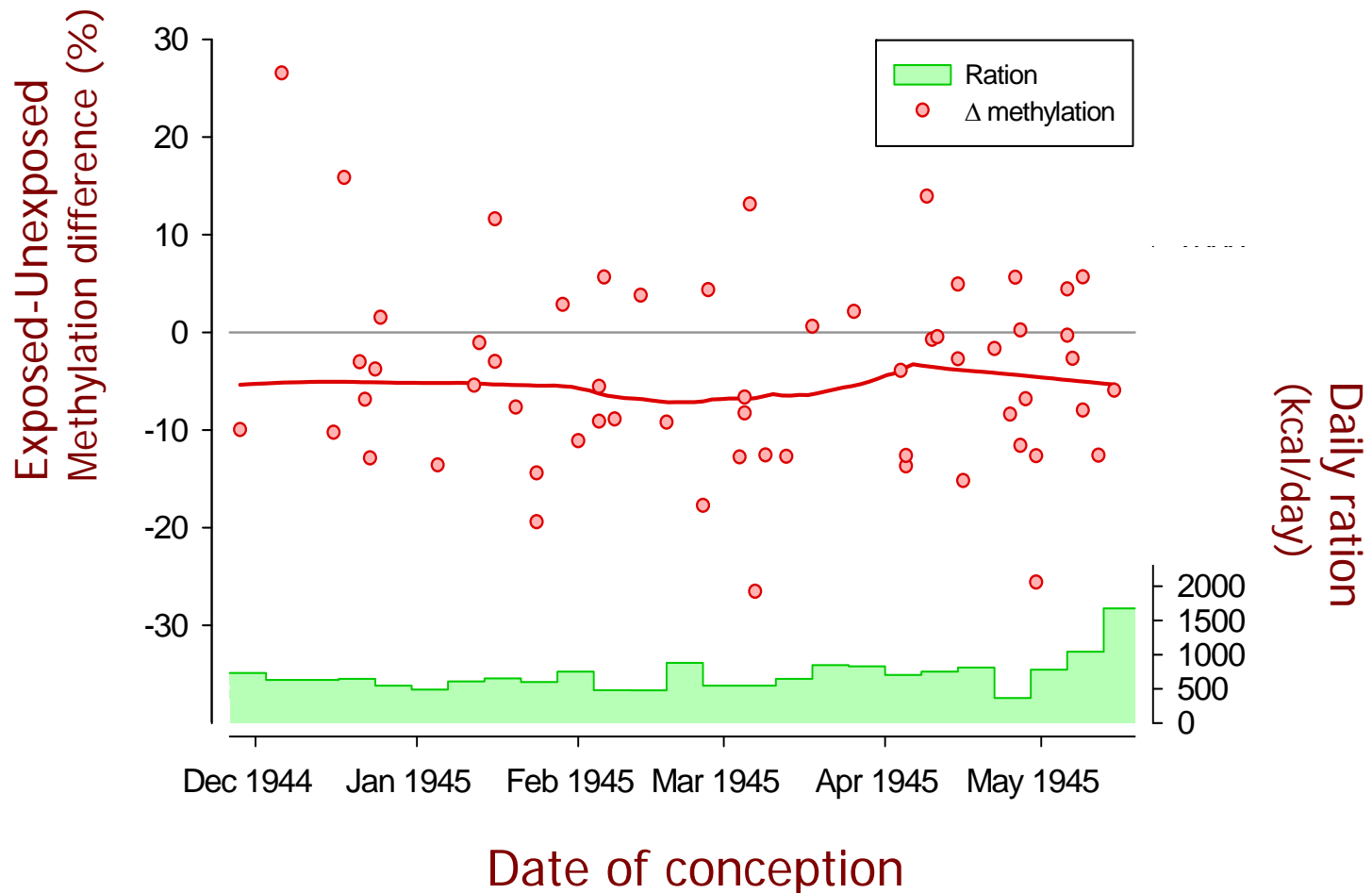
Agouti mice

- Inbred: same DNA sequence
- Methyl supplementation diet pregnant females
- Recorded as higher methylation of *agouti* gene; no production of yellow coat
- Retained into adulthood
- Transmitted across generations, albeit diluted

Waterland and Jirtle. Mol Cell Biol 2003.

Pre-natal nutrition and methylation

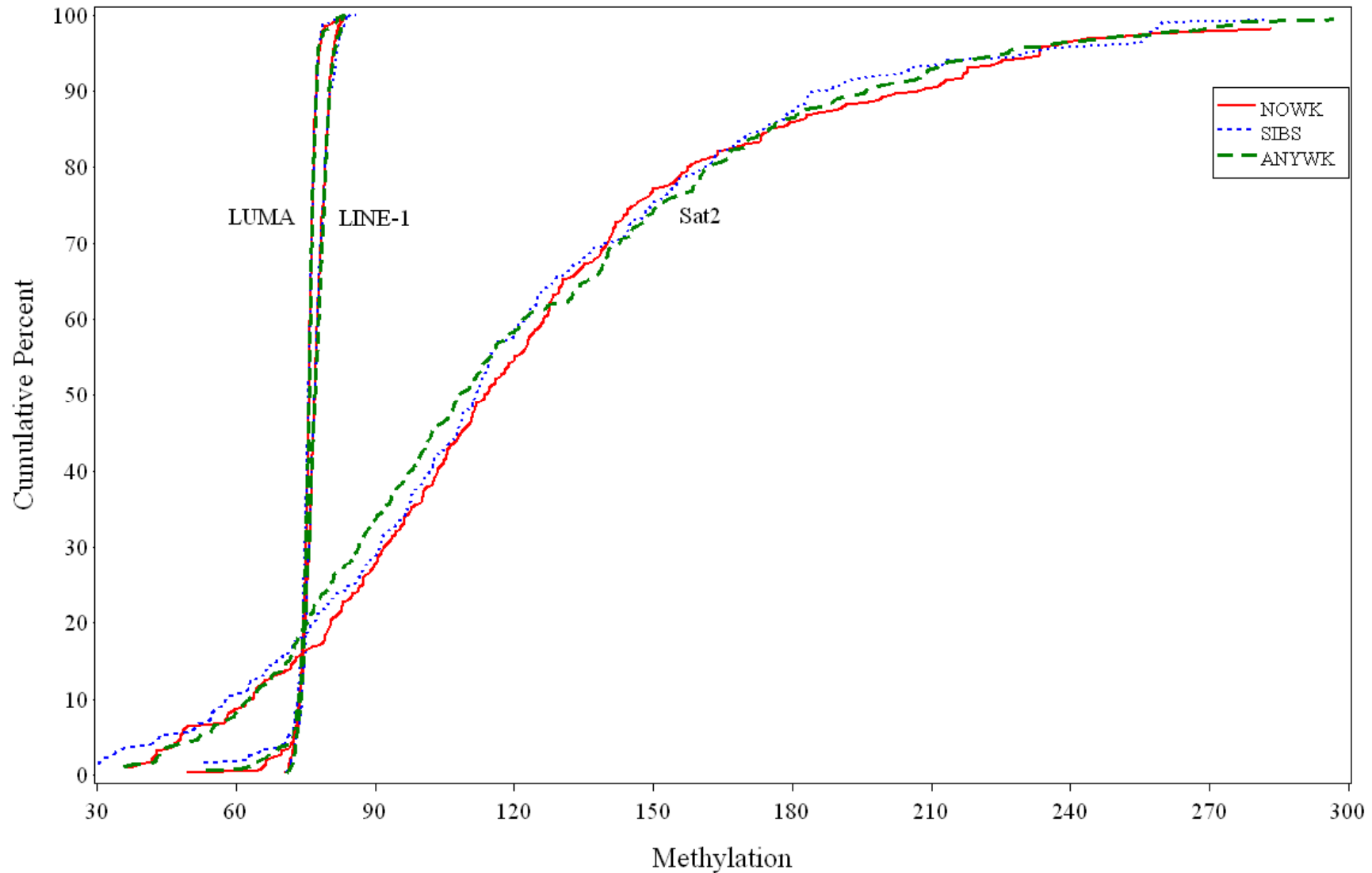
Proof of concept in humans (IgF2)



Heijmans et al., PNAS, 2008

LUMA, LINE-2 and Sat2 global methylation by famine exposure status

Lumey et al., IJE (in press) Funding: RC1-1HD063549



LUMA, LINE-2 and Sat2 global methylation by famine exposure status

	Overall % (s.d)	Famine % (95% CI)	p-value
Sat2	122.2% (56.2)	-0.51% (-7.38 to 6.36)	p=0.88
LUMA	75.2% (4.7)	0.16% (-0.49 to 0.81)	p=0.63
LINE-1	77.1% (2.5)	-0.05% (-0.33 to 0.22)	p=0.70

Mortality and cause of death in Dutch military



with FWA van Poppel, NIDI

Select 25,348 conscripts born in six cities in the West with prenatal famine exposure from 408,015 births 1944-1947

- **Link** military ID with names
- **Match Vital status** at Central Statistical Office (CBS)
- **Match and search** missings by hand at Central Genealogy Office (CBG)
- **Find cause of death** at CBS
- **Compare mortality** with matched time and place controls
- **Compare other outcomes** from administrative health services, social security databases, and income tax records

Funding: R01-AG028593

Dutch recruits born 1943-1947 follow-up 18-62 years, by month of birth

Month / Year of Birth	Alive at age 18 n	Alive at age 62 %	Dead at age 62 %	Not yet found, incl. emigration; %
Jan-Oct 1944	2,565	76.8	10.1	13.1
Nov 1944	1,628	78.8	12.2	9.0
Dec 1944	1,588	80.3	9.5	10.2
Jan 1945	1,718	79.3	10.1	10.7
Feb 1945	1,591	79.4	9.9	10.6
Mar 1945	1,675	76.7	11.8	1.6
Apr 1945	1,780	78.1	10.2	11.7
May 1945	1,704	78.9	10.3	10.8
Jun 1945	1,430	80.7	9.2	10.1
Jul 1945	1,444	81.0	9.6	9.4
Aug 1945	1,223	77.4	11.3	11.4
Sep 1945	999	77.5	11.9	10.6
Oct 1945	803	76.6	9.7	13.7
Nov 1945	744	78.1	9.9	12.0
Dec 1945	891	79.2	9.5	11.2
Jan 1946	1,181	80.5	9.6	9.9
Feb 1946	1,803	80.1	9.3	10.6
Mar 1946	3,081	80.3	9.9	9.8
Apr 46-Dec 47	7,431	80.9	9.8	9.3
Total West	35,279	79.4	10.1	10.5
Total Non-famine	9,758	79.4	9.3	11.3

Potential for future work

Explore linkages of CBS Microdata

- **Cause of death** (ICD 10)
- **Hospital discharge diagnoses** (ICD9-CM)
- **Long term care** (admission to nursing home, psychiatric hospital, long-stay hospital, home for the handicapped, home care)
- **Prescription drug usage**
- **Mental health care** (outpatient and short term admissions)
- **Medical consumption** (Hospital reimbursements; health insurance charges)
- **Employment**
- **Income** (fiscal); social security benefits

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Lumey et al., Ann Rev Publ Hlth, 2011

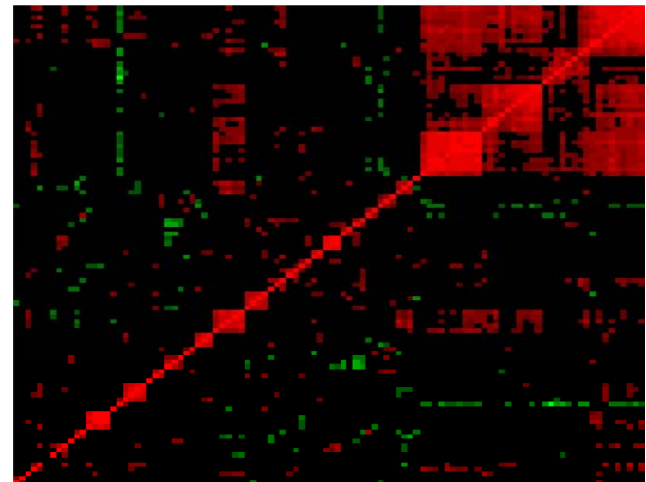
- **Schizophrenia**
- **Body weight**

- **Glucose metabolism and lipid profile?**

- **Epigenetic profiles?**

Recommendations

- Combine studies
- Integrate outcomes
- Evaluate genome
- Changes in offspring?
- Need for explicit hypotheses
- Replicate study findings





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Dutch famine birth cohorts: exposure definitions by date of birth

