Japan's Environment and Children Study– Lessons learned from incorporating HBM in a large-scale birth cohort study

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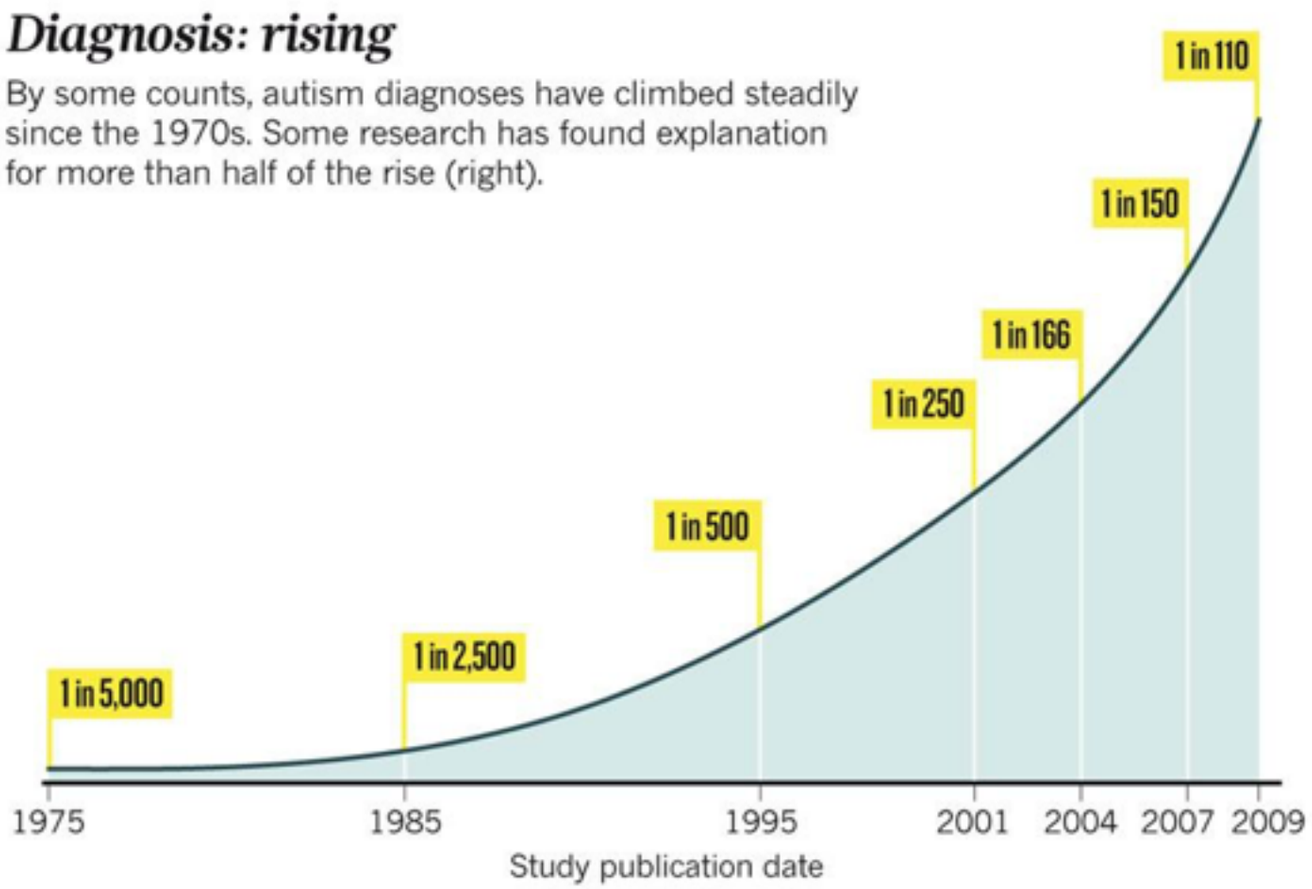
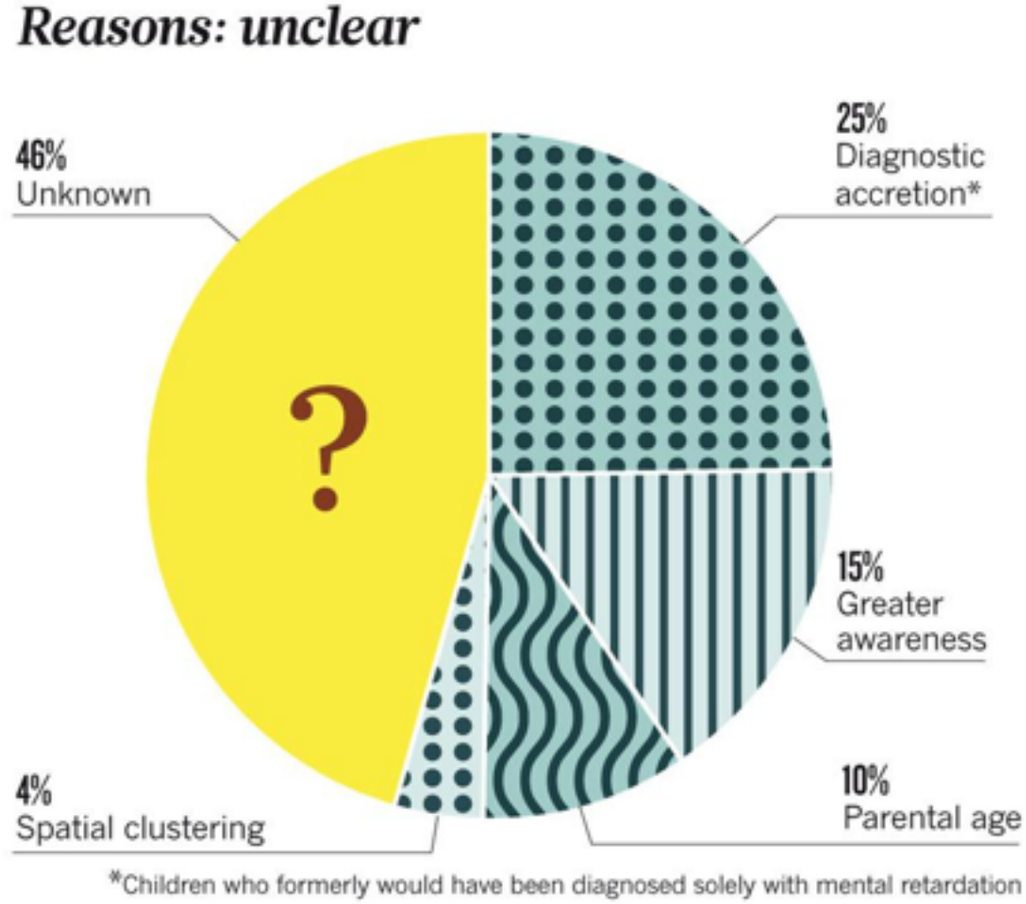
Environment affects children's health





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Japan Environment and Children's Study (JECS)

- JECS is a **longitudinal birth cohort** study involving **100,000** mother-child pairs
- **Main Study** targets all the participants
  - **Biological sample collection** from mothers, children and fathers
  - **Questionnaire administration** during pregnancy, at birth, 1 month, 6 month, and every 6 month after that until children reach **13 years of age**
  - Medical record, resident registry and school record **transcription**
- **Sub-Cohort Study** formed 5,000 sub-cohort within the Main Study
  - Home visit—Indoor and outdoor air quality, particulate matter, house dust, noise, dwelling inspection… at 1.5 and 3 years
  - Psychological development test, physical examination, blood and urine collection at 2 and 4 years
- **Case-cohort** and **nested case-control** studies
- **Adjunct Studies** conducted with extramural funding
- **Pilot Study** to evaluate the feasibility, acceptability and cost of the proposed procedures and processes to be used in the Main Study
- JECS is flexible and learn much from other studies and projects

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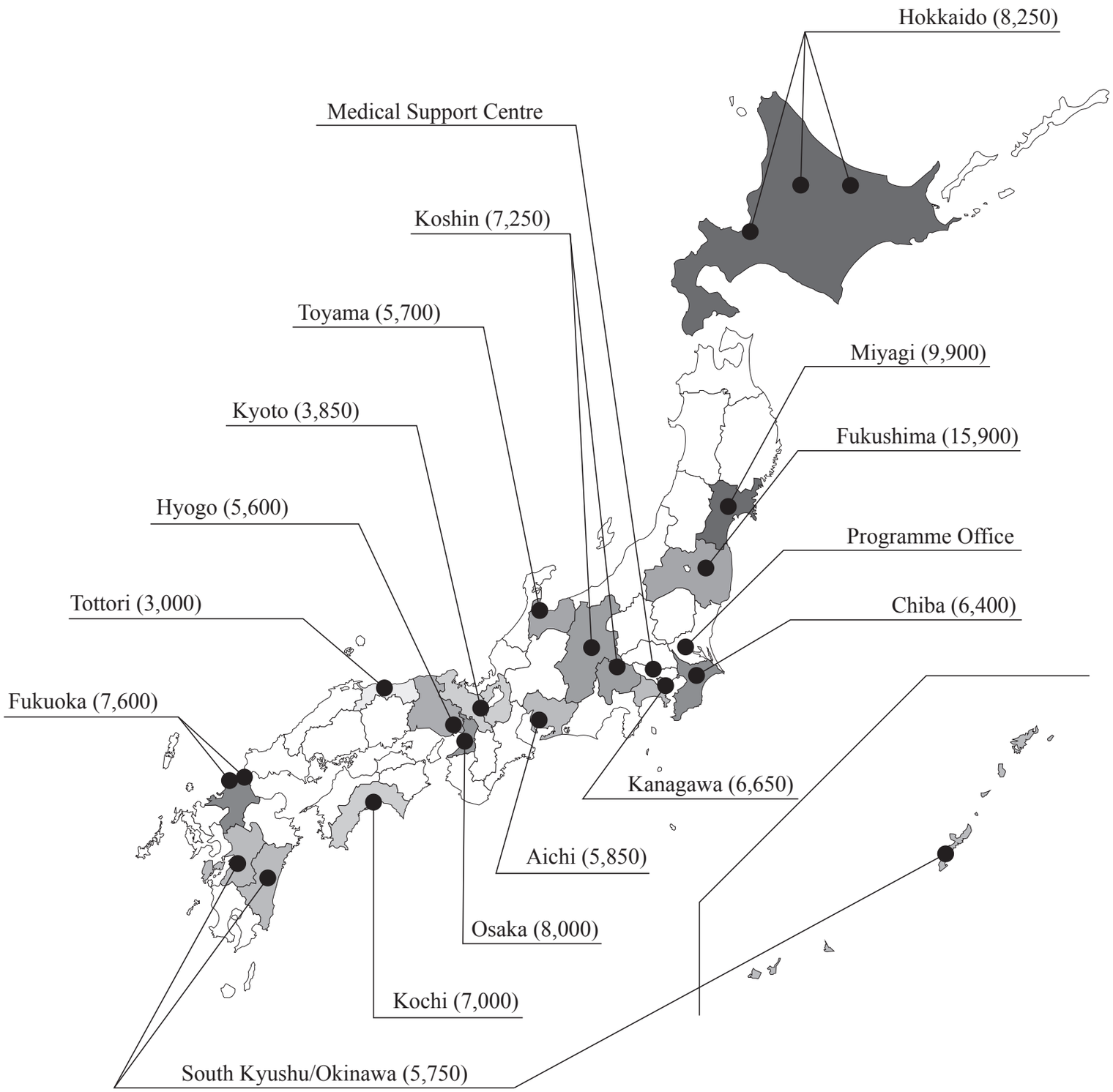
Study areas



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Priority outcomes

Pregnancy/reproduction	Stillbirth, preterm delivery, low birth weight, sex ratio, growth
Congenital anomalies	Cleft lip and palate, ventricular septal defect, hypospadias, cryptorchidism, Down syndrome
Neurodevelopmental disorders	Autism spectrum disorders, learning disability, ADHD
Immunological disorders	Asthma, atopic dermatitis, food allergy, Kawasaki disease
Metabolic disorders	Glucose metabolism disorder, obesity
Cancers	Leukaemia, solid cancers

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Exposures of interest

Chemicals from environment/ occupation	PCBs, PBDEs, PFASs, POPs, pesticides, EDCs, synthetic musk, phthalates, parabens, triclosan, benzophenone, PAHs, cotinine, caffeine, metals, particulate matters
Physical environment	Noise, heat, ionising radiation, housing condition, neighbourhood
Lifestyle	Stress, nutrition, daily rhythm, smoking and alcohol, infections, medications
Socio-economic status	Education, house-hold income, social bonding, community support
Genetics/-omics (when new funding comes)	Genomics, epigenetics, metabolomics, aductomics

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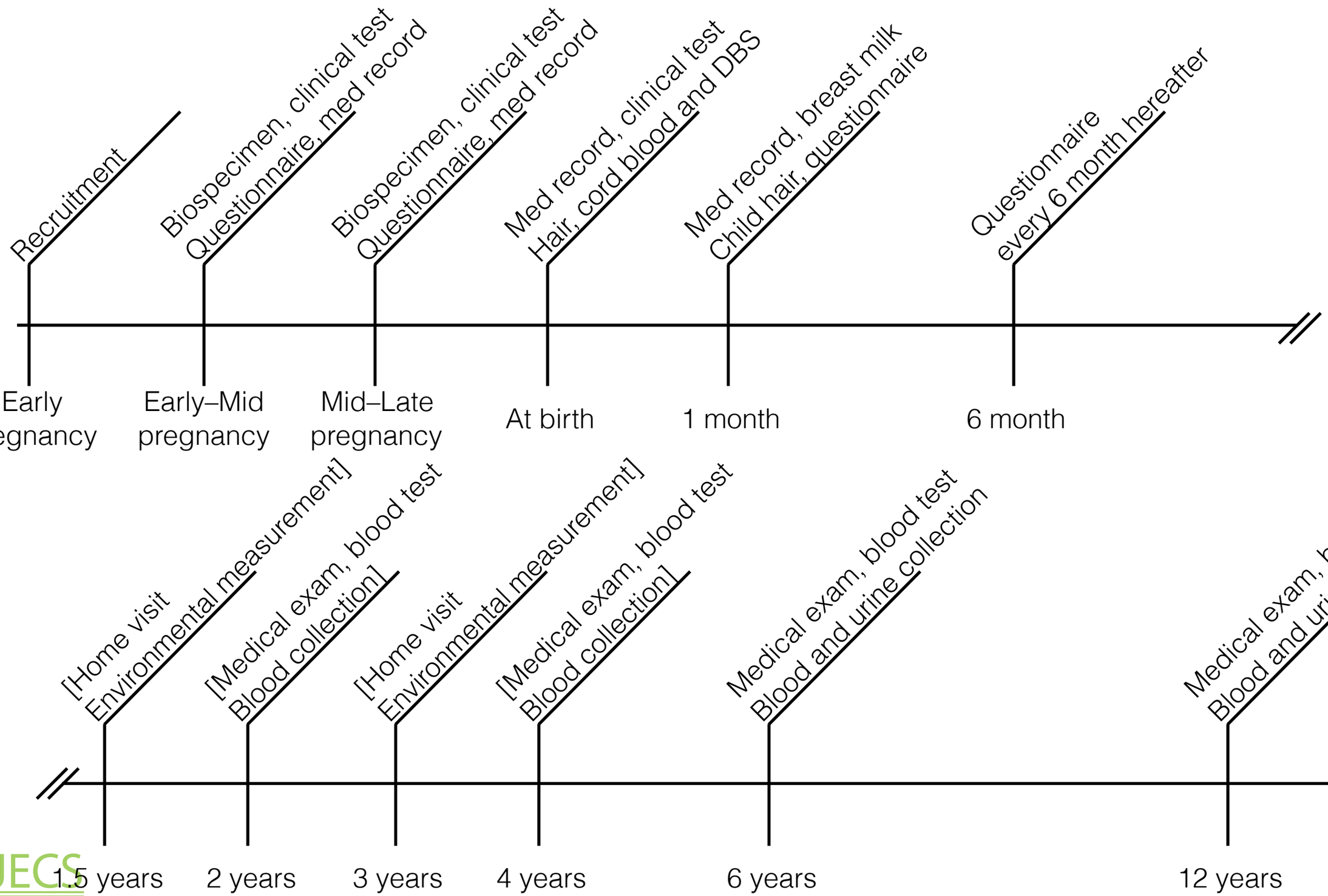
Mile stones



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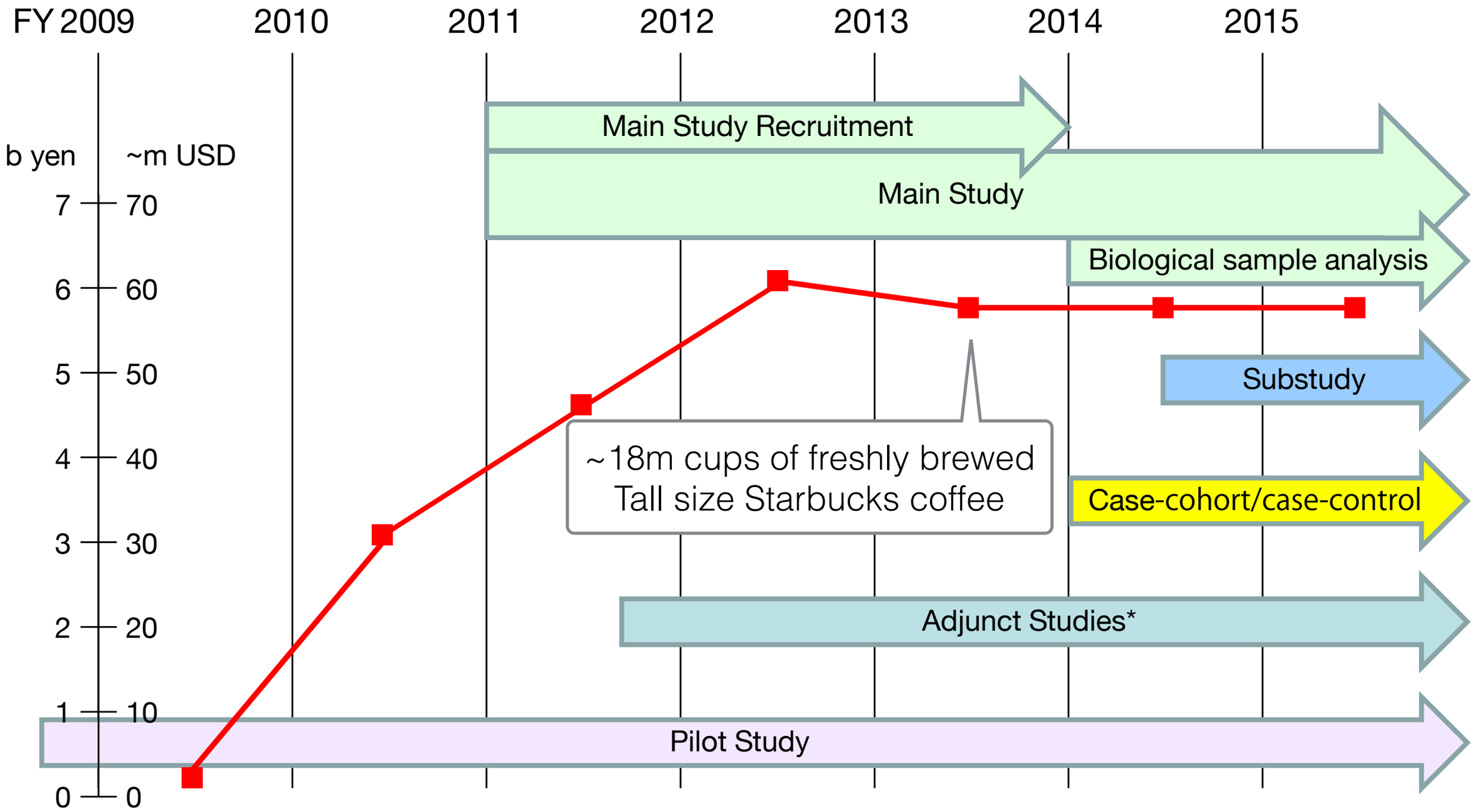
Funding and study structure



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Current status

- Recruitment completed in March 2014
  - Mother: 103,103 (~80% consent rate)
  - Father: 51,913
  - Birth: 100,045
- Questionnaire
  - Through pregnancy to 4.5 years old (every 6 months)
- Biological samples > 5,000,000 aliquots
  - Maternal blood, urine, breast milk, cord blood, hair, blood spots, paternal blood, …
  - Analysed for Hg, Pb, Cd, Mn, Se (> 50,000 blood) and cotinine/8-OHdG (>15,000 urine)
- Sub-Cohort Study (n = 5,000) started in November 2014
  - Home visit (1.5 and 3 y/o): VOCs, aldehyde, PM, house dust, dwelling observation
  - Developmental test, physician's exam, blood and urine collection (2 and 4 y/o)

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HBM method requirements

- High through put, high sensitivity methods
  - Can process > 50,000 samples a year
  - Require < 0.5 mL of samples
  - Are reliable enough to run one-chance samples
- Inexpensive, epidemiologically sound methods
  - Must be < $100 per sample
  - Can measure individual exposure
  - No need to be super precise

- In addition, affordable and portable sampling devices
  - Can be used by citizens scientist
  - Cost < $100 preferably < $5 per device
  - Can be used in developing countries

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New methods developed for JECS

- Metal (Hg, Pb, Cd, Mn, Se)
  - Alkaline dilution of 0.2 mL whole blood
  - No ND so far for Japanese pregnant women's samples
  - > 40,000 per year capacity with 6 ICP–MSs
- Nicotine metabolite (cotinine) and oxidized deoxyguanosine (8-OHdG)
  - Buffer dilution of 50 uL and column switching LC–MS/MS
  - RL = 0.14 ng/L (cotinine), 0.16 ng/L (8-OHdG)
  - Detect cotinine in 80% of non-smoker urine
- Perfluorinated compound (PFASs) in drinking water
  - SPE clean-up of 10 mL drinking water
  - On-line SPE LC–MS/MS
  - RL = ppt levels

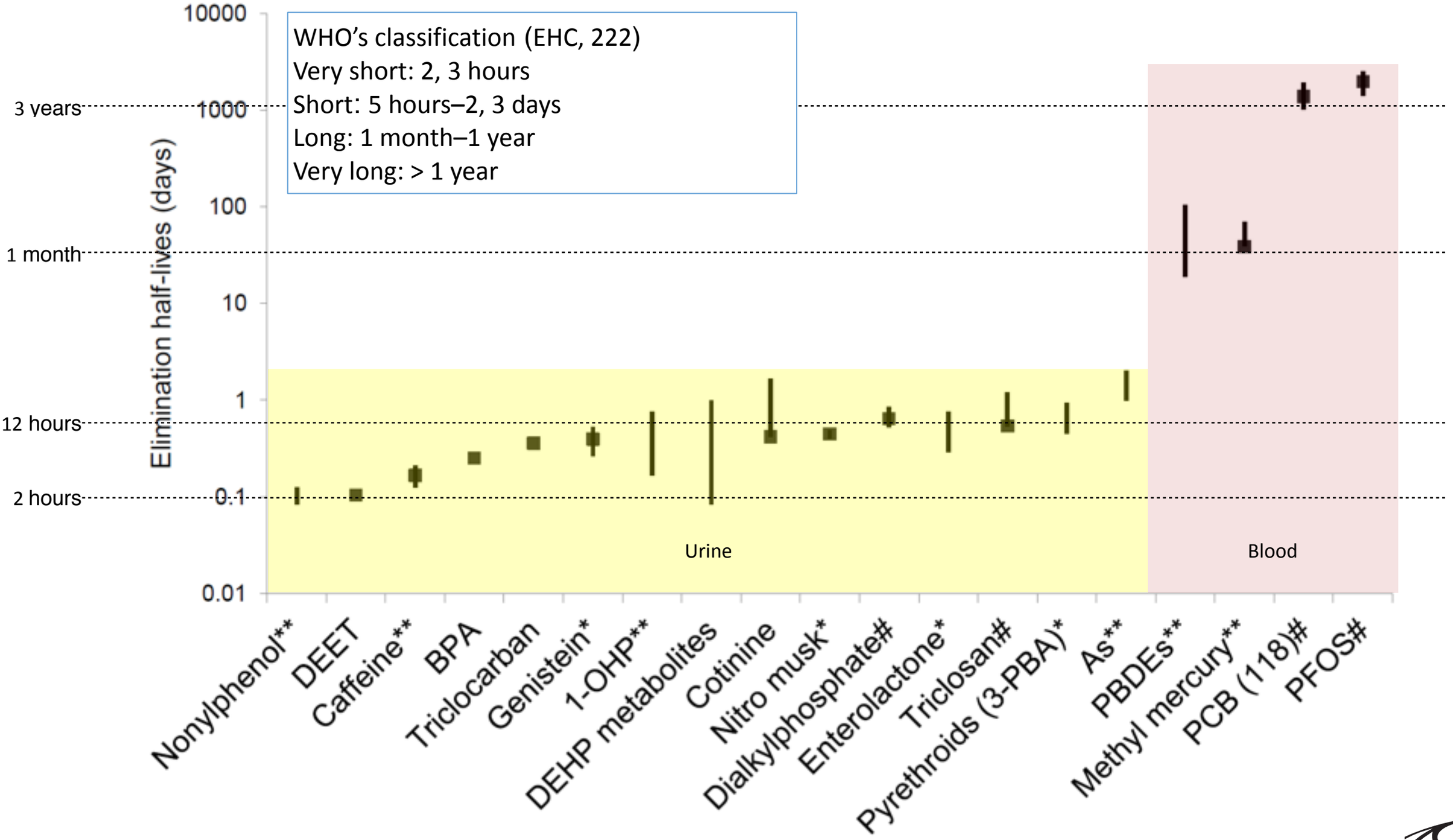
New methods developed for JECS

- Volatile organic compounds (VOCs)
  - Passive sampler for 7 days time-weighted average conc.
  - Benzene, Toluene, Xylene, Styrene, Ethylbenzene, …
  - HS–GC–MS
  - 10,000 samples a year
- Aldehyde
  - Passive sampler for 7 days time-weighted average conc.
  - Formaldehyde, acetaldehyde, other aldehyde, …
  - LC–MS/MS
  - 10,000 samples a year

Methods under development

- Phthalate metabolites
  - Urine 0.1 mL with deconjugation
  - Dilute and shoot to on-line SPE LC–MS/MS
- Parabenes
  - Urine 0.1 mL with deconjugation
  - Dilute and shoot to on-line SPE LC–MS/MS
- PCB-PBDE-DDE screening
  - 4,4’-DDE, PCB 153 and BDE 47 screening
  - Dried blood spot extraction and GC–MS/MS
  - Modification of Dr Reiner’s method (NIST)
- PFASs in blood
  - Dilution
  - Automated extraction and on-line LC–MS/MS

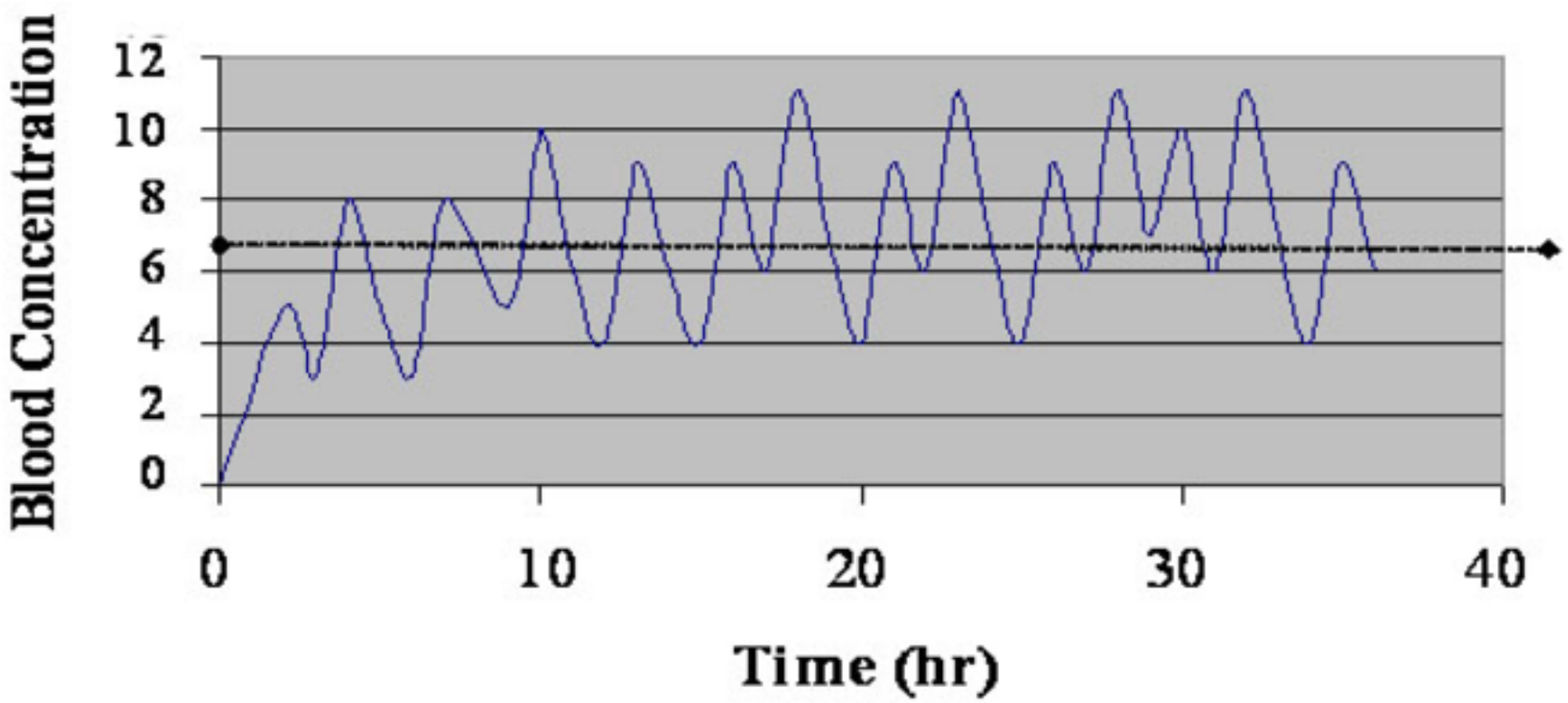
Biological half-lives of JECS target compounds



Dot: Mean half-life, *: Mean with SD, #: Mean with 95% CI, **: Min–Max

“Pseudo-persistent”

- Continual environmental introduction of drugs by sewage effluent makes them “pseudo-persistent” pollutants… (Daugton, 2002) — US EPA
  - PPCPs
  - High volume products (e.g. PVC, PS, PP)



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Low ICCs cause other problems

- Attenuation bias

$$\mathrm{OR}_{\mathrm{true}} = 2.0$$

$$\mathrm{OR}_{\mathrm{obs}} = \left[\mathrm{OR}_{\mathrm{true}}\right]^{\rho_I}$$

ICC (ρ_I)	ORobs
0.1	1.07
0.2	1.15
0.3	1.23
0.4	1.32
0.5	1.41
0.6	1.52
0.7	1.62
0.8	1.74

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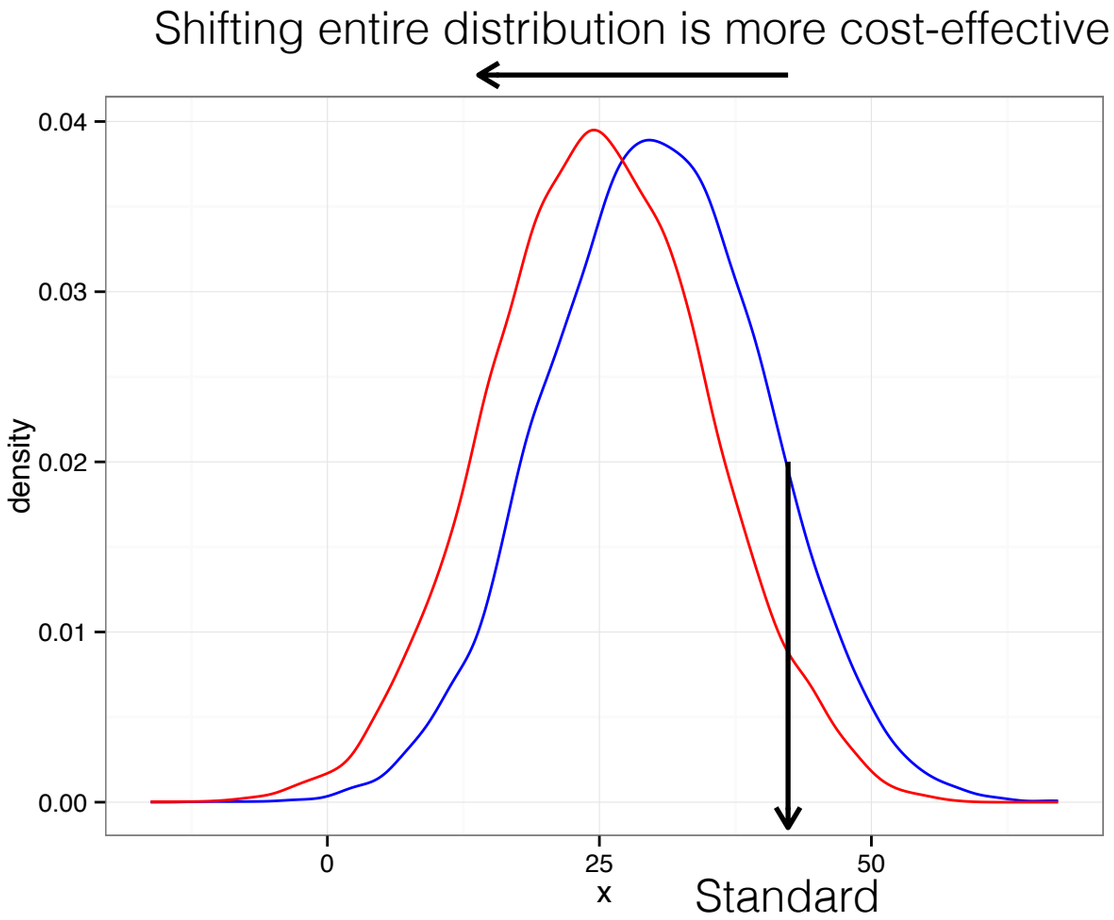
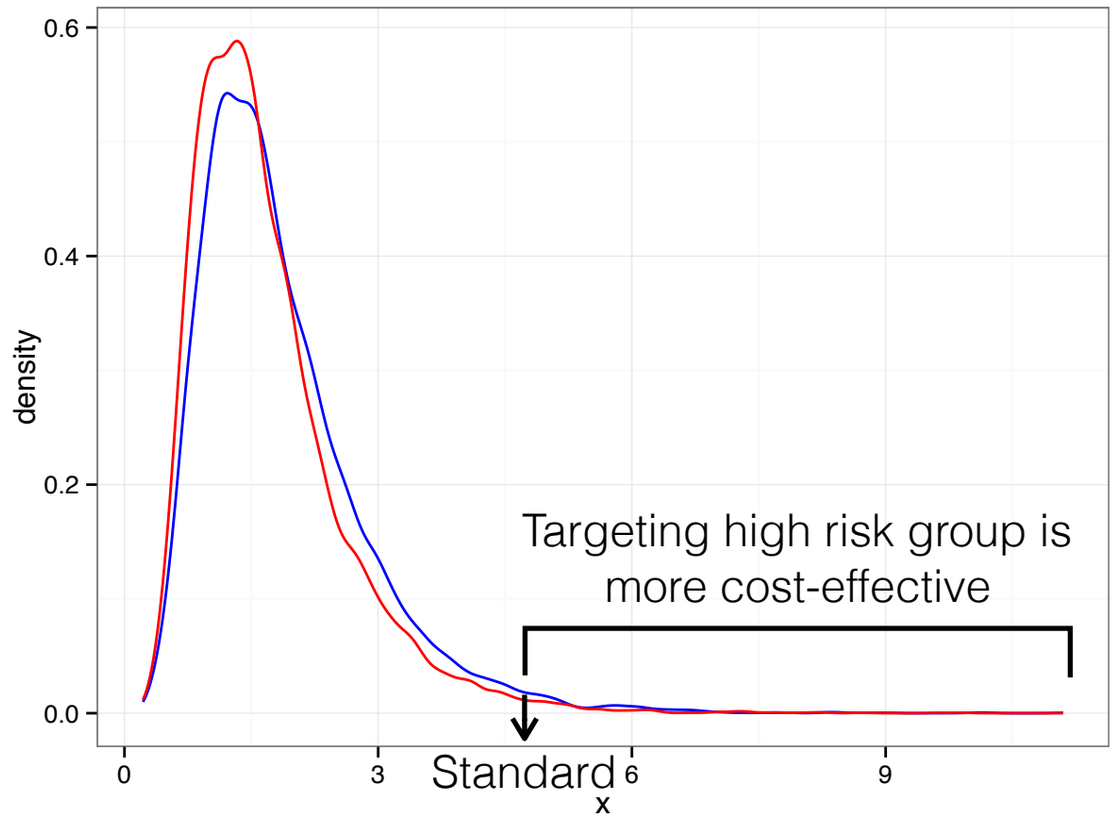
HBM based public health

- Mass personal biomonitoring era will come soon
- Population approach and high risk group approach





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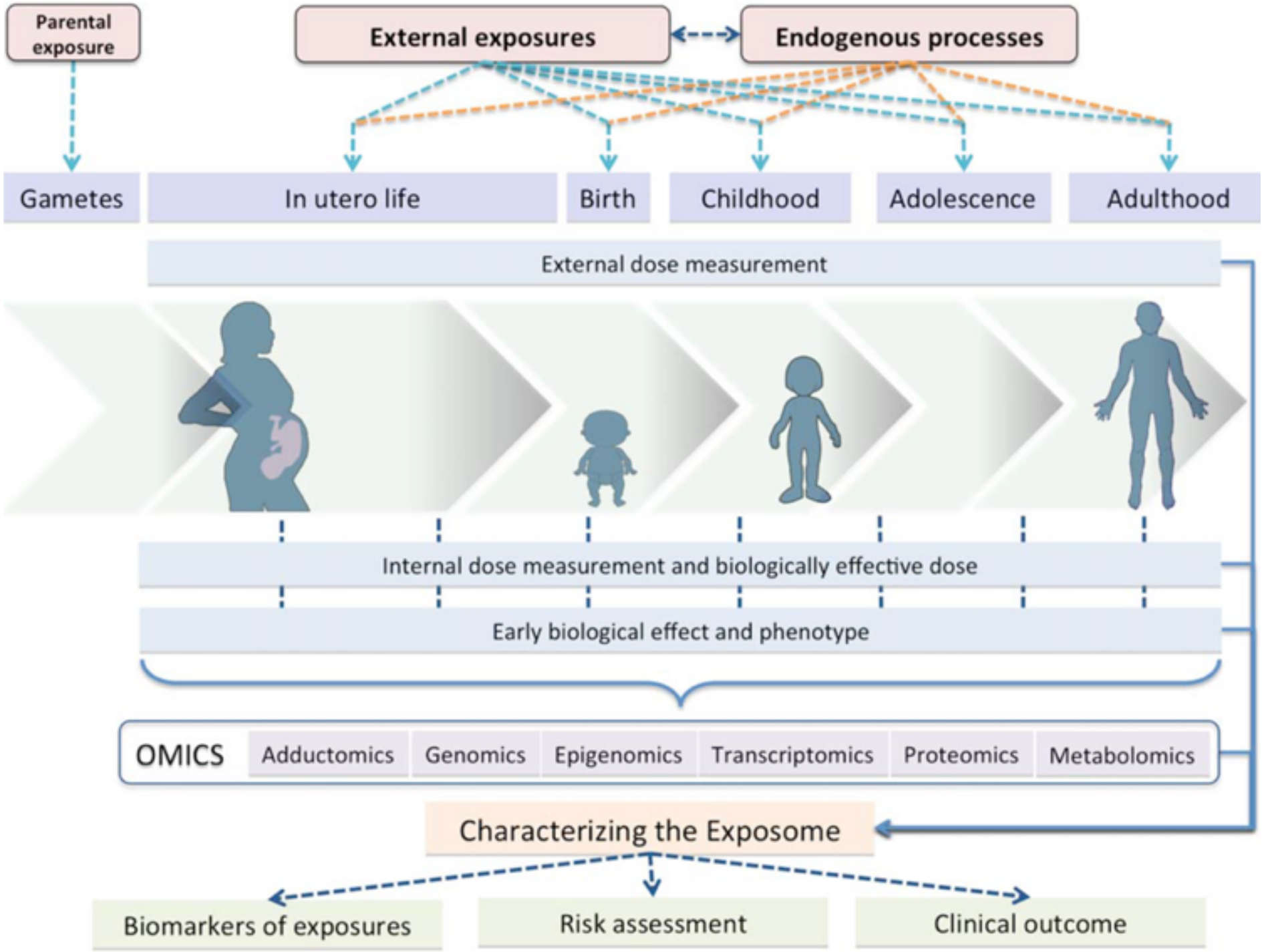
Exposome and life-course epidemiology



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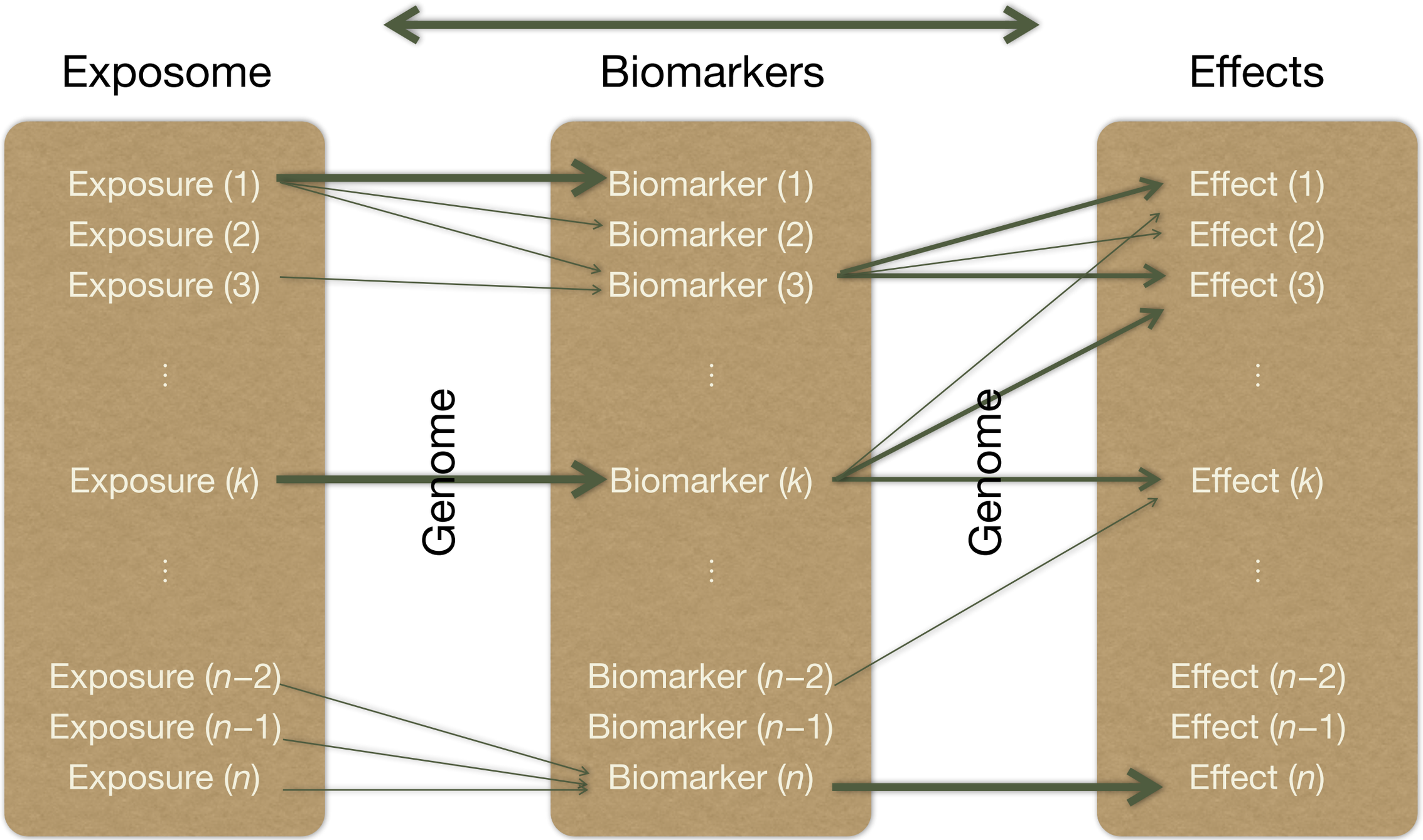
Precision epidemiology



–Omics and pharmacokinetics

Acknowledgement

- Participating families
- Regional Centre staff
- Programme Office staff
- International collaborators
- Taxpayers

The Japan Environment and Children's Study

For the future crew of the Earth

How can we keep the environment healthy and hand it over to the next generations? The Japan Environment and Children's Study (JECS) started in 2011 is to answer such a question by investigating a wide range of environmental factors that could affect children's health and development.

Disclaimer: The findings and conclusions of this presentation are solely the responsibility of the authors and do not represent the official views of the Japanese government

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