How do lifestyle and environment of previous generations impact on the health of our children today?

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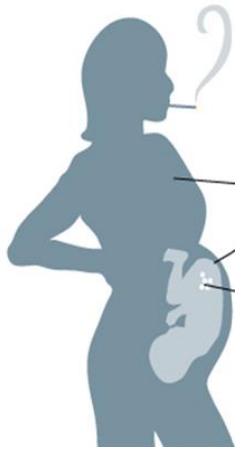
PUBLIC HEALTH SCHWEIZ
SANTE PUBLIQUE SUISSE
SALUTE PUBBLICA SVIZZERA
The Swiss Society for Public Health

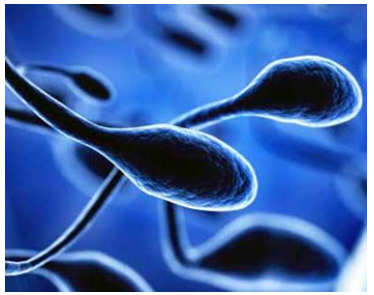
SSPH+ SWISS SCHOOL OF PUBLIC HEALTH

Zurich University of Applied Sciences
zh aw School of Health Professions

When is disease risk established? SUSCEPTIBILITY WINDOWS



- In the **near past** – main health policy focus
- Early life origins - ***in utero*** and **early childhood** – large impact on health policies
- ? Long **before conception**, in previous generations



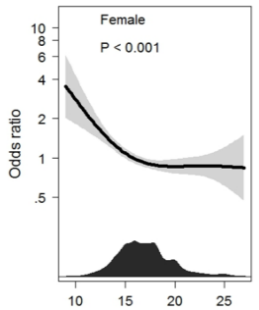
SO WHAT?

Susceptibility windows offer OPPORTUNITY for efficient intervention

Susceptible time windows during life-time

TOBACCO SMOKING

in utero OR 1.6
post-natal OR 1.3



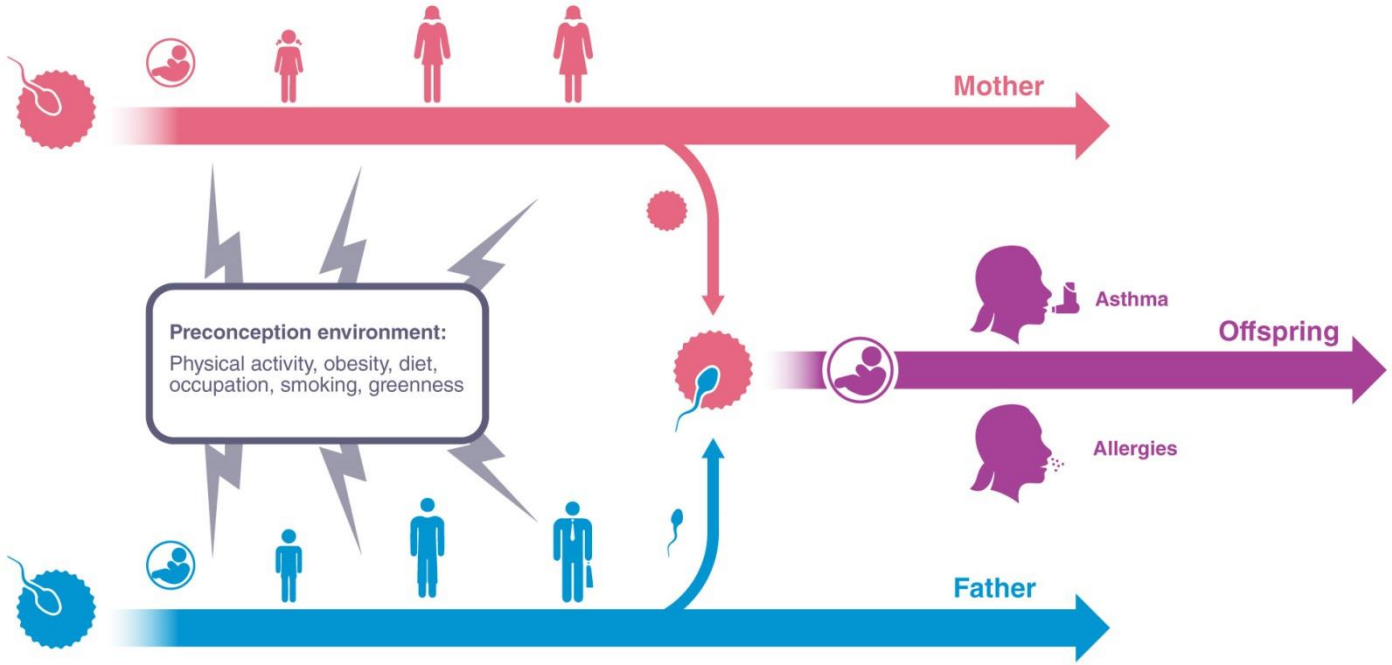
per 10 p.years women OR 1.3
per 10 p.years men OR 1.2

in utero **childhood** **adolescence** **adulthood** **elderly**

RESPIRATORY SYMPTOMS

Erbas B Envir Res 2018

Potential preconception susceptibility windows



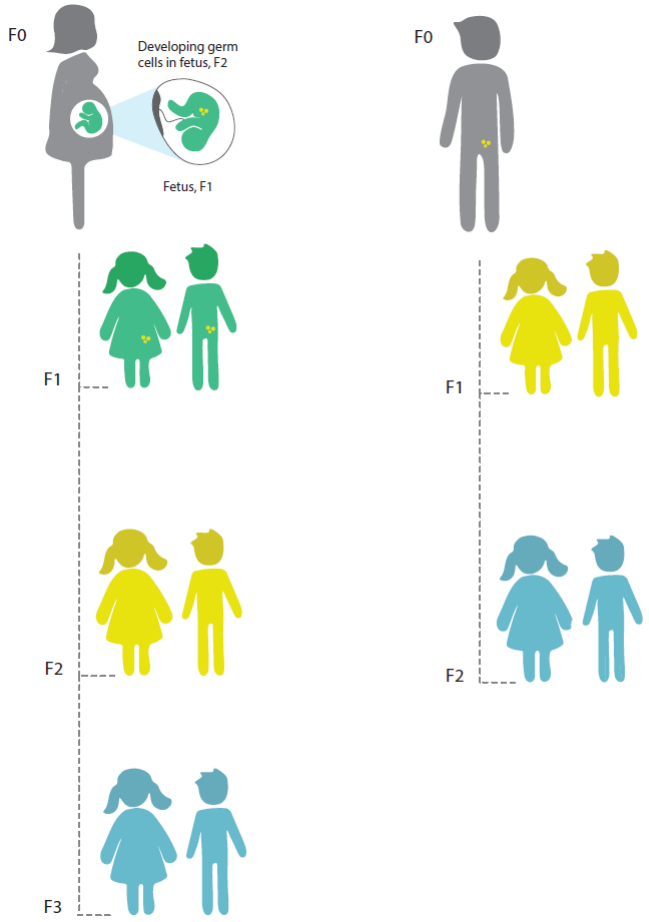
F Gomez Real/ A Villén

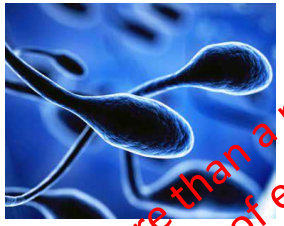
Germ cells undergo extensive epigenetic reprogramming phases - from *in utero* to mature reproductive cells
Male/ female differ

potential susceptibility windows

Lønnebotn M et al Challenges 2018

Inter- & trans-generational pathways for environmental influence on subsequent generations





...more than a pack of DNA...
contain lots of epigenetic information

Morkve Knudsen et al JACI 2018



What do we need to study exposure effects over generations

DATA: preconception exposure data – over parents life-course

METHODS: statistical analyses of multi-generation life-course data

MECHANISTIC MODELS: epigenetics, immunology, animal models

DATA:
The RHINESSA generation study

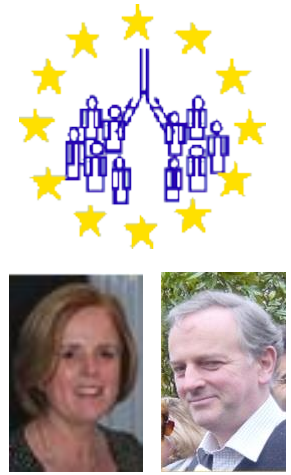
DATA: the parent generation

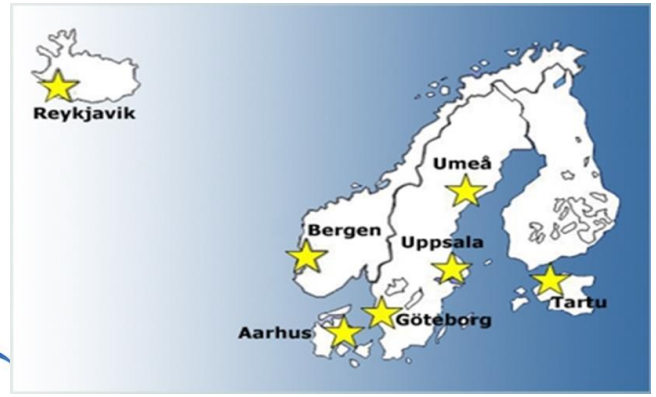
ECRHS The European Community Respiratory Health Survey, www.ecrhs.org

Population-based cohort, adults born 1945-1970

Investigated ~1990, 2000 & 2010

Questionnaire and clinical data





RHINE Respiratory Health In Northern Europe, www.rhine.nu

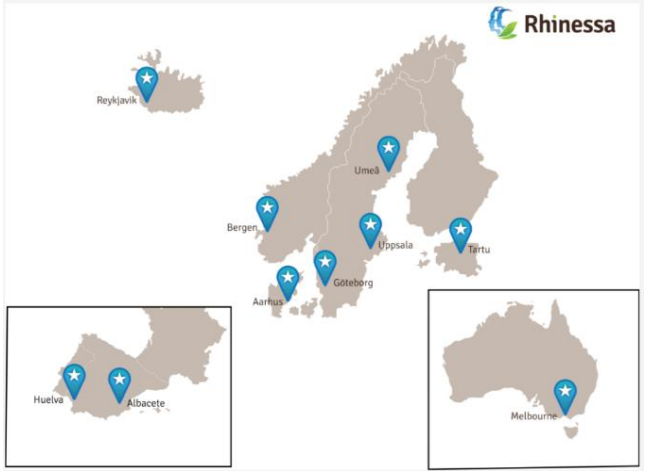
Questionnaire follow-up of ECRHS I stage I in 7 Northern European centres

Born 1945-1973, investigated ~1990, 2000 and 2010

Extensive postal questionnaires

RHINE
Respiratory Health in Nothern Europe

The RHINESSA generation study



Grandparents born 1898-55	**ECRHS/RHINE Parents** born 1945-70 20 yrs follow-up well-characterised	**Offspring** born 1960-2013	**4th generation** born 1978-d.d.

Clinical and questionnaire study ages 4-9, 10-17, 18-50

N= 12 433 questionnaire
N= 2 154 clinical (April 2019)
Registry data in Nordic countries

STATISTICAL METHODS: analyses of multi-generation data

Simone Accordini and Lucia Calciano

University of Verona

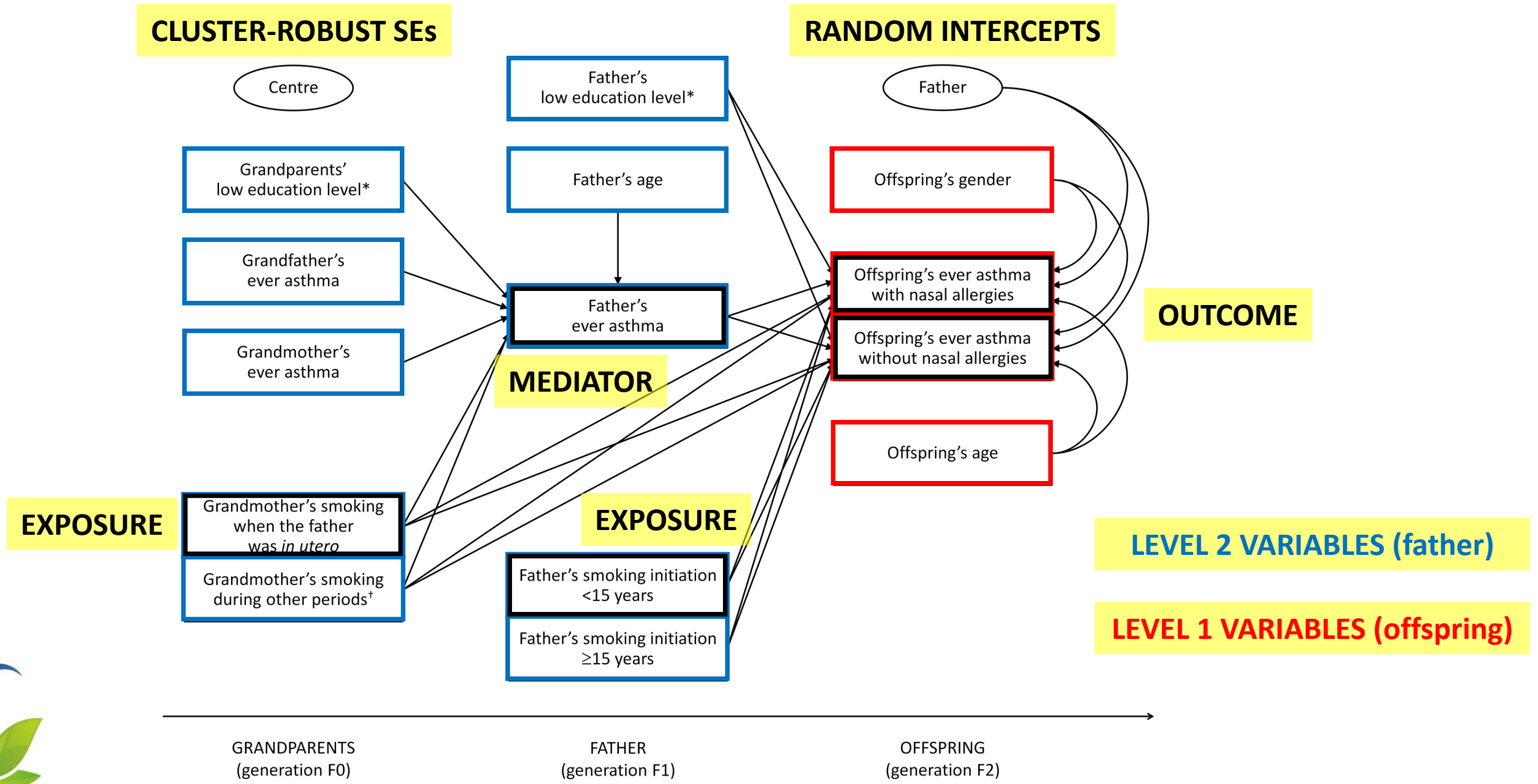
- Individuals' life course and generations ⇒ longitudinal data
- Different exposures ⇒ different pathways
- Individual and ecological exposures ⇒ hierarchical data
- Theory, knowledge, hypothesis ⇒ theoretical models

STATISTICAL METHODS

(PATH ANALYSIS, STRUCTURAL EQUATION MODELING, MULTILEVEL MODELING, …)

(CLUSTERED) TWO-LEVEL 2-2-1 MEDIATION GLMs

THEORETICAL MODEL – Effects of tobacco smoking on asthma across 3 generations (paternal line)



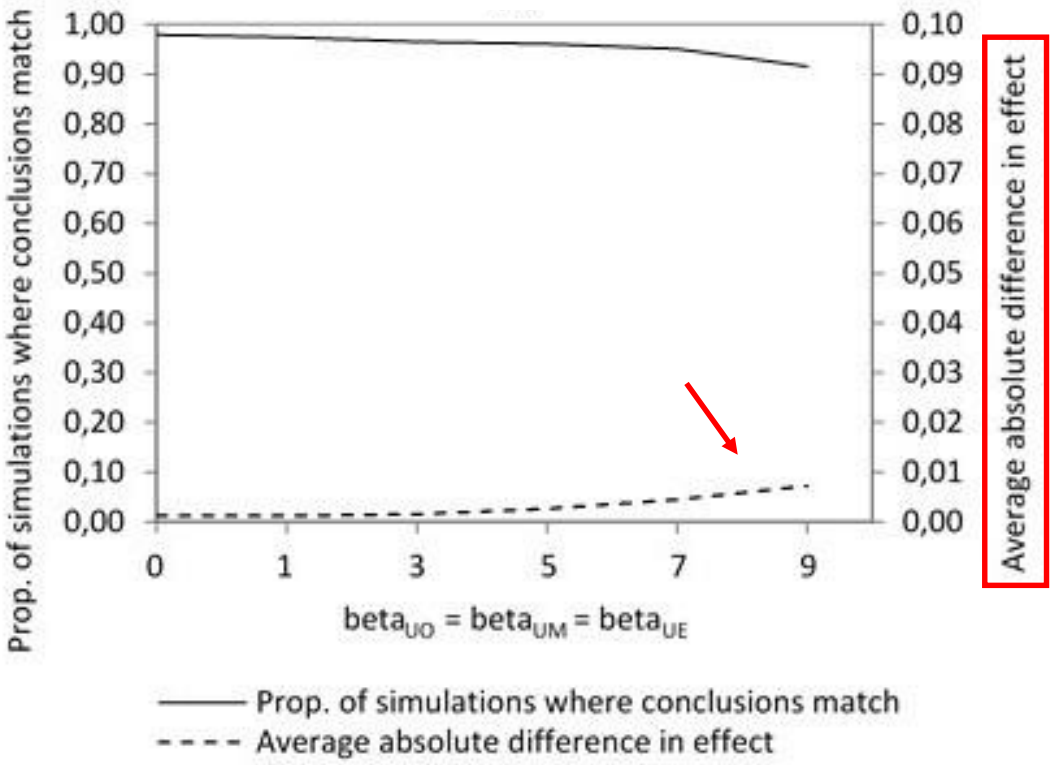
STRENGTHS …

- The temporal ordering among variables can be modelled
- The pattern of associations among all the variables can be evaluated fitting a single model
- The impact of unmeasured confounders on the estimates can be investigated
  → **SENSITIVITY ANALYSES**

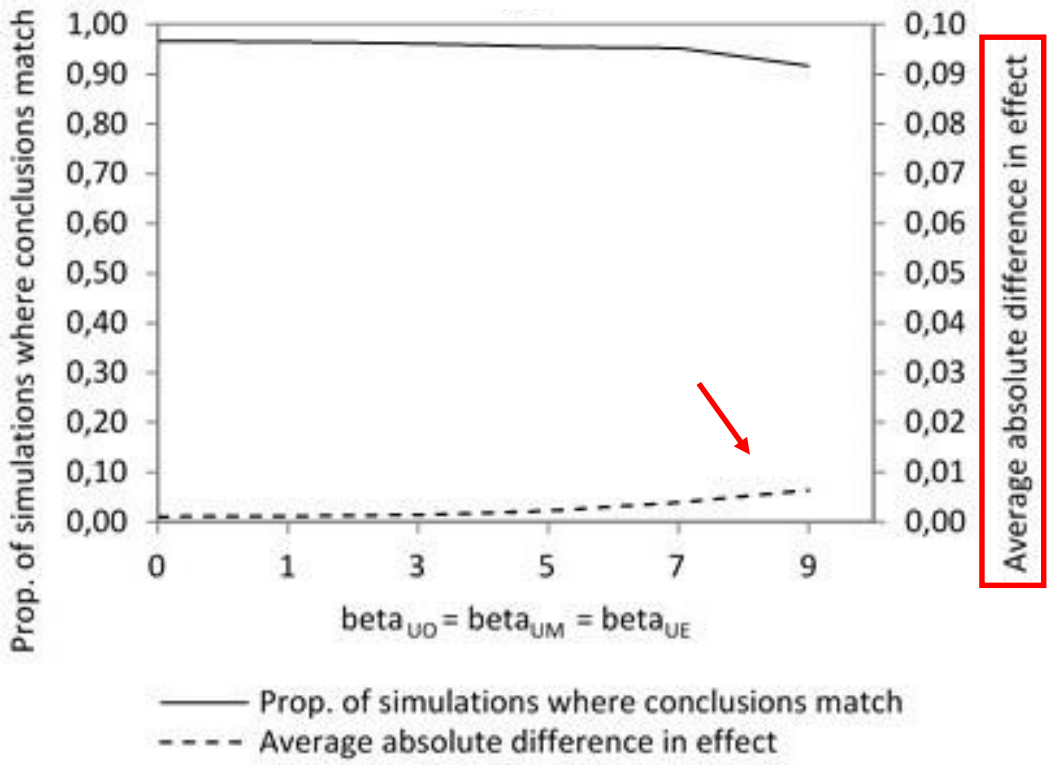
SENSITIVITY ANALYSES

Evaluate the impact of unmeasured confounders on the estimate of the effects
→ SIMULATION ANALYSES (*Umediation package* in R)

paternal line
asthma without nasal allergies

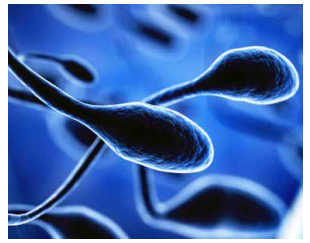


paternal line
asthma with nasal allergies



SOME RESULTS

Exploring effects of **father's smoking** before conception



We asked the following questions:

- Does father's smoking before conception play a role for offspring asthma?
- If yes, which are important:
  - Age of starting smoking
  - Total years of smoking
  - Numbers of cigarettes daily
  - Smoke free time from quitting until conception

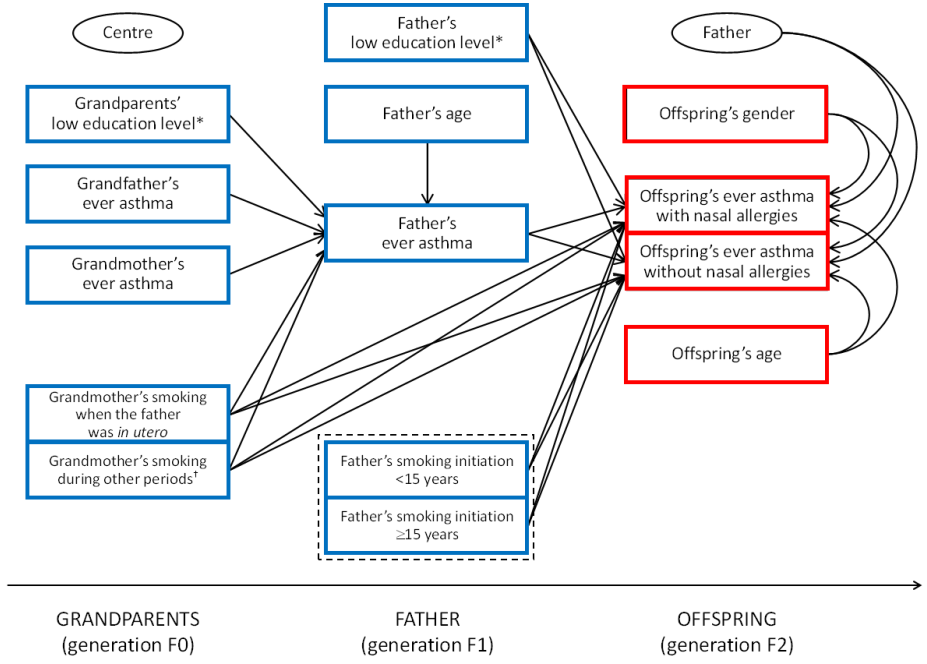
Data from RHINE study, info about 27000 offspring from 16000 parents

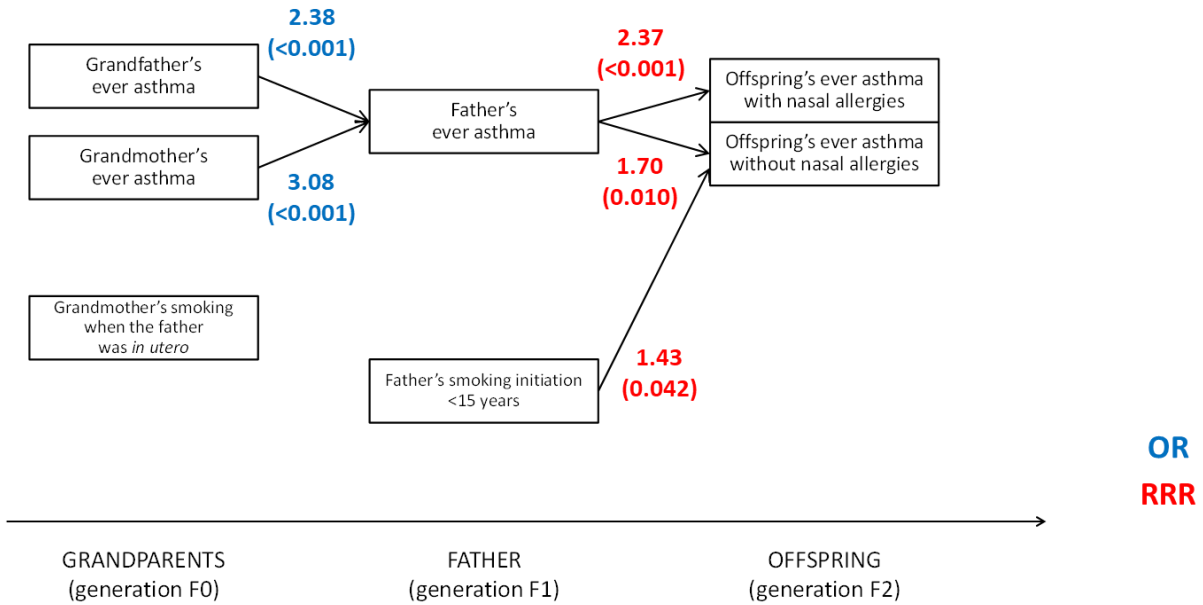
Svanes C et al Int J Epidemiol 2017

Ageing Lungs in European Cohorts

Father's smoking in adolescence and offspring asthma

Findings confirmed in data from ECRHS study on 8588 offspring of 4197 parents





Accordini et al IJE 2018

Funded by European Union's Horizon 2020 research & innovation programme - Grant No 633212. Further funding provided from SERI (Switzerland) and NHMRC (Australia) through reciprocal agreements

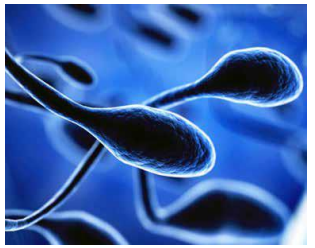
Paternal preconception smoking and offspring asthma - Supporting evidence from Health Survey for England

	All	BIOL parent	N-BIOL parent
Mothers smoking	**n = 27,490**	**n = 27,007**	**n = 451**
Never smoked	1.00	1.00	1.00
Smoked only prior to conception (stopped 2 years before)	1.08 (0.87-1.33)	1.03 (0.83-1.28)	Too few
Smoked around time of birth	**1.21 (1.04-1.40)**	**1.21 (1.04-1.41)**	1.07 (0.33-3.43)
Smoked only after child's birth	1.29 (0.71-2.32)	1.40 (0.76-2.58)	Too few
Father smoking	**n = 27,308**	**n = 25,126**	**n = 2,173**
Never smoked	1.00	1.00	1.00
Smoked only prior to conception^^^ (stopped 2 years before)	**1.20 (1.01-1.44)**	**1.26 (1.05-1.51)**	0.45 (0.17-1.17)
Smoked around time of birth	1.07 (0.94-1.22)	1.06 (0.92-1.22)	1.11 (0.75-1.62)
Smoked only after child's birth	0.69 (0.40-1.16)	**0.29 (0.10-0.90)**	1.02 (0.51-2.06)
Father smoking		**n=25,601**	**n=2153**
Never smoked	1.00	1.00	1.00
Smoked only prior to conception (began 8 - 14 yrs)	**1.58 (1.15-2.17)**	**1.71 (1.23-2.37)**	Too few
Smoked only prior to conception (began 15 - 19 yrs)	1.15 (0.94-1.42)	1.20 (0.97-1.48)	0.60 (0.22-1.62)
Smoked only prior to conception (began >19 yrs)	1.20 (0.82-1.75)	1.25 (0.86-1.83)	Too few
Smoked around time of birth (began 8 - 14 yrs)	**1.22 (1.02-1.46)**	1.18 (0.97-1.44)	1.37 (0.83-2.25)
Smoked around time of birth (15 - 19 yrs)	1.09 (0.94-1.26)	1.11 (0.95-1.29)	0.95 (0.61-1.48)
Smoked around time of birth (began >19 yrs)	0.97 (0.78-1.21)	0.95 (0.75-1.20)	1.24 (0.64-2.41)
Smoked only after child's birth	0.70 (0.41-1.19)	**0.30 (0.10-0.91)**	1.04 (0.51-2.10)

Father's smoking
prior to conception,
in particular starting age 8-14 yrs,
was associated with more asthma
- in biological offspring
- not in non-biological offspring

Jarvis D et al ERS 2018

Father's smoking in early puberty and offspring respiratory health
- consistent in four cohorts -



ECRHS, RHINE *Svanes et al IJE 2017, Accordini et al IJE 2018*

- offspring asthma
- father's smoking starting <15 years
- // maternal grandmother's smoking

RHINESSA+EC *...i et al, ongoing*

- offspring lung functio...
- father's smoking starting <1...

Health Survey for England *Jarvis et al, ongoing*

- offspring asthma
- father's early onset smoking
- comparing biological vs non-biological father

Adolescence in men appears to be an important susceptibility window

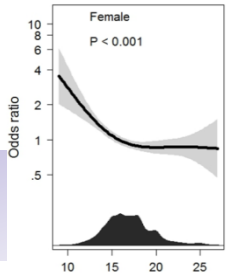
Susceptible time windows in three generations?

TOBACCO SMOKING

grandmother OR 1.4

father <15 years OR 3

in utero OR 1.6
post-natal OR 1.3



per packyear women OR 1.03
per packyear men OR 1.02

grand parents

parents pre-conception

in utero

childhood

adolescence

adulthood

elderly

RESPIRATORY SYMPTOMS

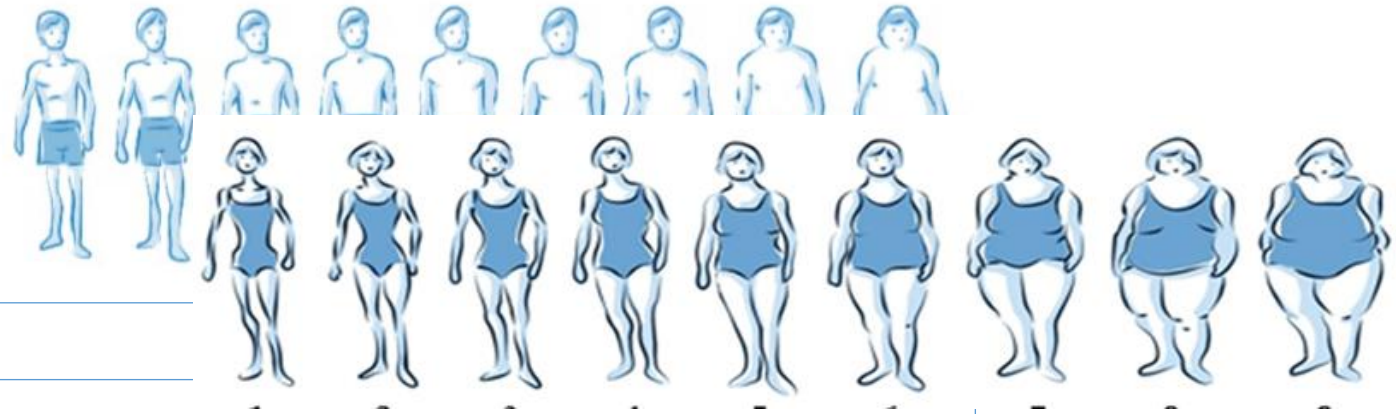
ASTHMA

Which other factors in father's puberty might be important?

OVER/ UNDER WEIGHT

Historic literature suggests grandfathers' low food availability in prepuberty was related to lower cardio-vascular and cancer risk in grand offspring

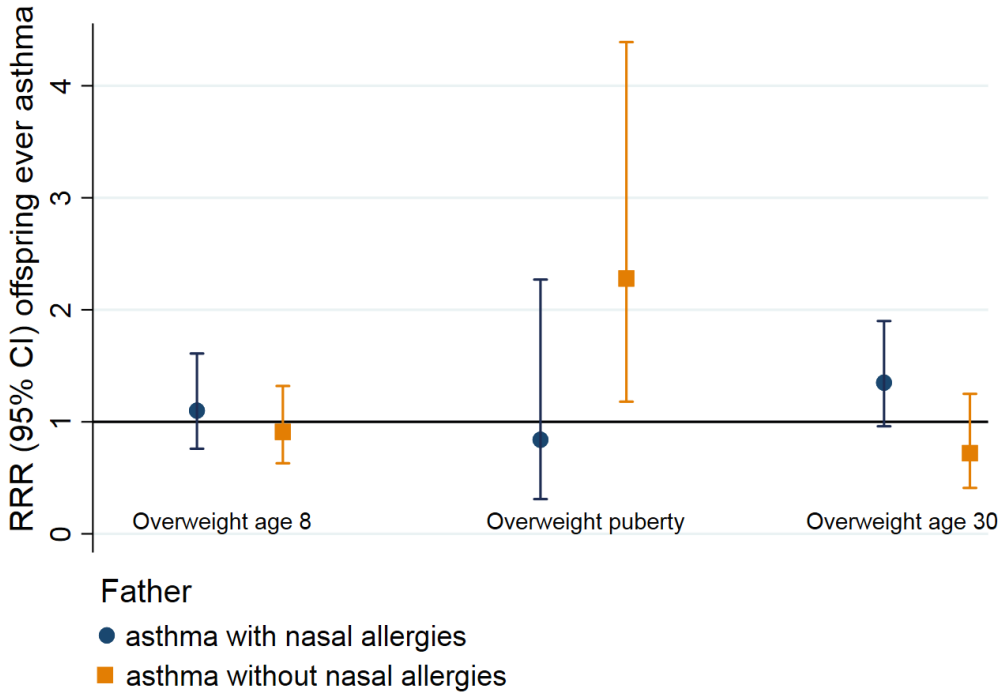
Retrospective body silhouettes – a tool to assess childhood overweight



Body size at age 8
Body size at voice break
Body size at age 30
Body size at age 40

Validated: *Dratva et al 2017* (current BS)
Lønnebotn et al 2018 (past BS)

Father's overweight starting in puberty was associated with asthma in offspring



Johannessen A et al. JACI prov. acc.

Father's weigh gain and offspring asthma

Fathers *with* **change ≥2 body silhouettes** *from:*	*Non-allergic asthma in offspring*		
	Crude OR (95% CI)	**Model 1** Adjusted OR (95% CI)	**Model 2** Adjusted OR (95% CI)
Age 8 to puberty	**1.60 (1.01, 2.55)**	**1.67 (1.05, 2.68)**[1]	**1.70 (1.06, 2.74)**[1]
Puberty to age 30	1.14 (0.83, 1.55)	1.13 (0.83, 1.56)[2]	1.12 (0.81, 1.53)[2]
Age 30 to current age	0.97 (0.73, 1.29)	0.99 (0.74, 1.33)[2]	0.97 (0.72, 1.31)[2]
Fathers *with change* ***≥2 body silhouettes*** *from* ***age 8 to puberty*** + ***overweight* at:***			
Puberty	**3.14 (1.61, 6.13)**	**3.21 (1.63, 6.33)**[1]	**3.45 (1.75, 6.80)**[1]
Age 30	1.49 (0.73, 3.06)	1.60 (0.77, 3.33)[2]	1.56 (0.75, 3.25)[2]
Current	1.30 (0.77, 2.20)	1.37 (0.80, 2.34)[2]	1.37 (0.80, 2.35)[2]

Model 1, [1]adjusted for fathers' asthma. [2]adjusted for fathers' asthma, smoking and education.
Model 2, as model 1+ adjusting for **offspring BMI.**

Lønnebotn et al ERS 2018

Own weigh gain from age 8 to puberty and subsequent asthma

Fathers *with* **change ≥2 body silhouettes** *from:*	*Non-allergic asthma in offspring*		
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Age 30	1.49 (0.73, 3.06)	1.60 (0.77, 3.33)[2]	1.56 (0.75, 3.25)[2]
Current	1.30 (0.77, 2.20)	1.37 (0.80, 2.34)[2]	1.37 (0.80, 2.35)[2]
Offspring *with personal change* ***≥2 body silhouettes*** *from:*	Crude OR (95% CI)	**Model 3** adjusted OR (95% CI)	**Model 4** adjusted OR (95% CI)
Age 8 to puberty	**1.76 (1.16, 2.65)**	**1.75 (1.14, 2.68)**[3]	**1.81 (1.17, 2.82)**[3]
Puberty to current age	0.91 (0.68, 1.22)	0.93 (0.68, 1.27)[3]	0.93 (0.68, 1.27)[3]

Model 1, [1]adjusted for fathers' asthma. [2]adjusted for fathers' asthma, smoking and education.
Model 2, as model 1+ adjusting for **offspring BMI.**
Model 3, [3]adjusted for parents' asthma, smoking and education..
Model 4, as model 3 + adjusting for **fathers change ≥2 body silhouettes from age 8 to puberty.**
*overweight= fathers body silhouette ≥5

Lønnebotn et al ERS 2018

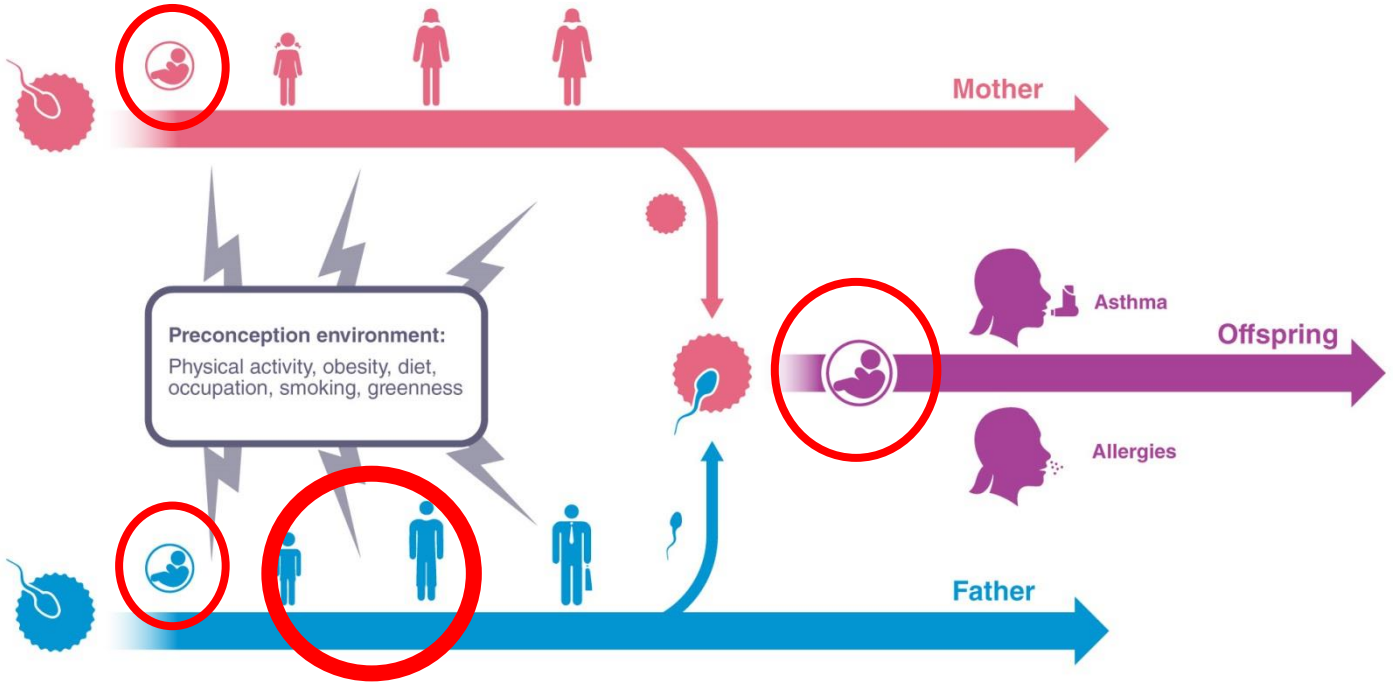
What are possible mechanisms for effects across generations?

- EPIGENETIC MECHANISMS

- IMMUNOLOGIC MECHANISMS

- ANIMAL STUDIES

CONCLUSION



F Gomez Real/ A Villén

PREGNANCY may be important for several generations

FATHERS might be as important as mothers for offspring health

EARLY PUBERTY may be an important susceptibility window – for several generations?

SO WHAT? Susceptibility windows offer OPPORTUNITY for efficient intervention

How lifestyles and behaviours of earlier generations impact on the health of our children today
WHERE NEXT?

PERSONAL HEALTH ACHIEVEMENT *VERSUS* SOCIETAL RESPONSIBILITY

RESEARCH – fo health as well as disease
- Human, animal and l ar research guide each other
- Research in LMIC setting
- Behavioural research – adolesc s, child-raising under new paradigma

POLICY MAKERS – allocate resources to children/adolescents
- public health, school, lifestyle
- the built environment
- regulation of food, tobacco, marketing aimed at this age g

PEOPLE - knowledge of ongoing researh, even though early stage evid

Lønnebotn M et al Challenges 2018

ALEC

Ageing Lungs in European Cohorts

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