The preconception origins of adult asthma and COPD

Föräldramiljö före befruktning och betydelse för lunghälsa som vuxen

Symposium: Lungan genom livet
29. mars 2023

Cecilie Svanes MD PhD
Professor, Centre for International Health, University of Bergen,
Consultant pulmonology, Dept Occupational Medicine, HUS hospital,
Bergen, Norway

Haukeland University Hospital

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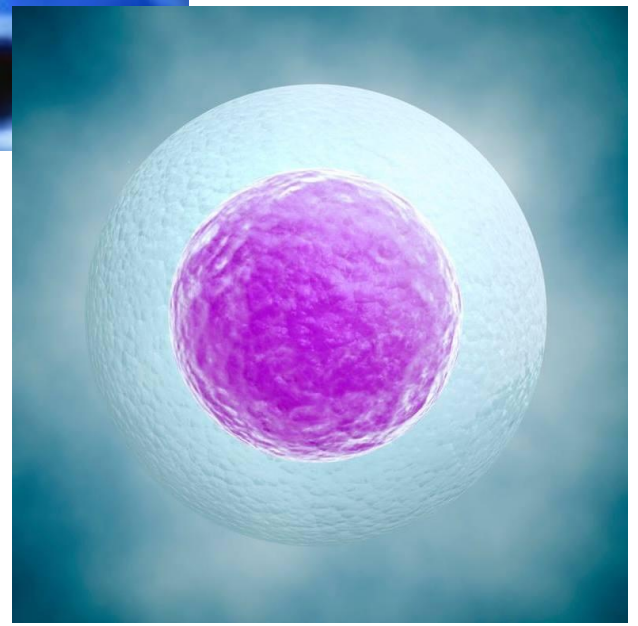
The beginning of life

Before the beginning



Early life origins of health and disease

Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease?

Forsdahl A. Br J Prev Soc Med. 1977.

Sir David Barker

Forsdahl-Barker hypothesis:

The early life origins/ developmental origins of health and disease (DOHaD)

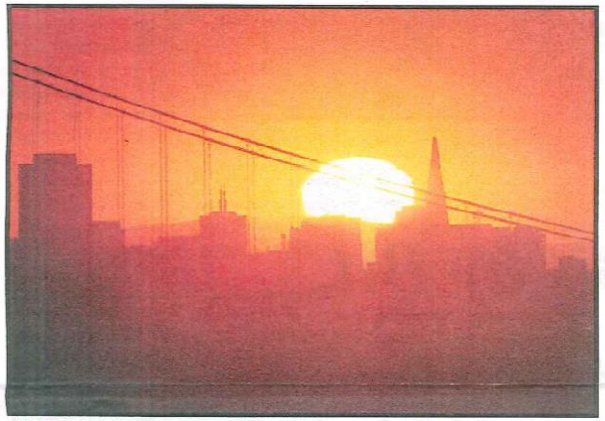
SUNDAY, MAY 18, 1997

ALA/ATS DAILY BULLETIN

San Francisco, CA
MAY 16–21 • 1997

THE OFFICIAL NEWSPAPER OF THE AMERICAN LUNG ASSOCIATION/AMERICAN THORACIC SOCIETY 1997 INTERNATIONAL CONFERENCE

Welcome to San Francisco and the ALA/ATS 1997 International Conference



"No city invites the heart to come to life as San Francisco does. Arrival in San Francisco is an experience in living."

—William Saroyan

More than 12,000 health care profes- sionals from around the world are gathe- ing in San Francisco this week for th 90th International Conference of t American Lung Association and Ame i- can Thoracic Society.

This is the world's largest lung-rela ed conference, featuring some of the la est and most significant developments in clinical and basic research and pu lic educations. More than 300 scientific nd clinical symposia have been plann d, addressing such topics as asthma, toba o control, tuberculosis, environmen al health, critical care medicine, manag d care and cost containment, and mu more.

In addition, the conference offers a unique opportunity to meet and network with colleagues and friends from around the world in one of the world's most beautiful cities — San Francisco.

Low birth weight shown to be an indicator for obstructive lung disease

Researchers from Norway have shown a strong and significant association between low birth weight and a susceptibility for obstructive lung disease in young adults.

Cecilie Svanes, MD, PhD, and her colleagues from the Department of Thoracic Medicine at Haukeland University Hospital, Bergen, Norway, looked at respiratory symptoms recorded in a popu- lation-based questionnaire survey conducted in Norway from 1991-1993. Records of study sub- jects born in 1967 or later were matched with the Norwegian Medical Birth Registry.

"We analyzed the association between number of asthma-like symptoms and birth weight by poly- chotomous logistic regression, adjusting for smok- ing habits, hay fever, age, sex and body mass," Dr. Svanes reported.

Birth weight was found to be related to a number of asthma-like symptoms, according to Dr. Svanes, and the odds for having more symptoms decreased significantly for each 500g increase in birth weight.

"The association was strong and significant in women, but weaker and not significant in men," Dr Svanes said. "Thus, birth weight, reflecting intra terine conditions, is related to obstructive l ng isease in young adults in Norway."

he study will be reported in a poster di cussion sessi at 1:30 p.m. and 4:15 p.m. tod y in Room 301 of th Moscone Convention C nter.

Visit us online

New ALA president to focus on building revenue base

More autonomy for ATS is goal of incoming president

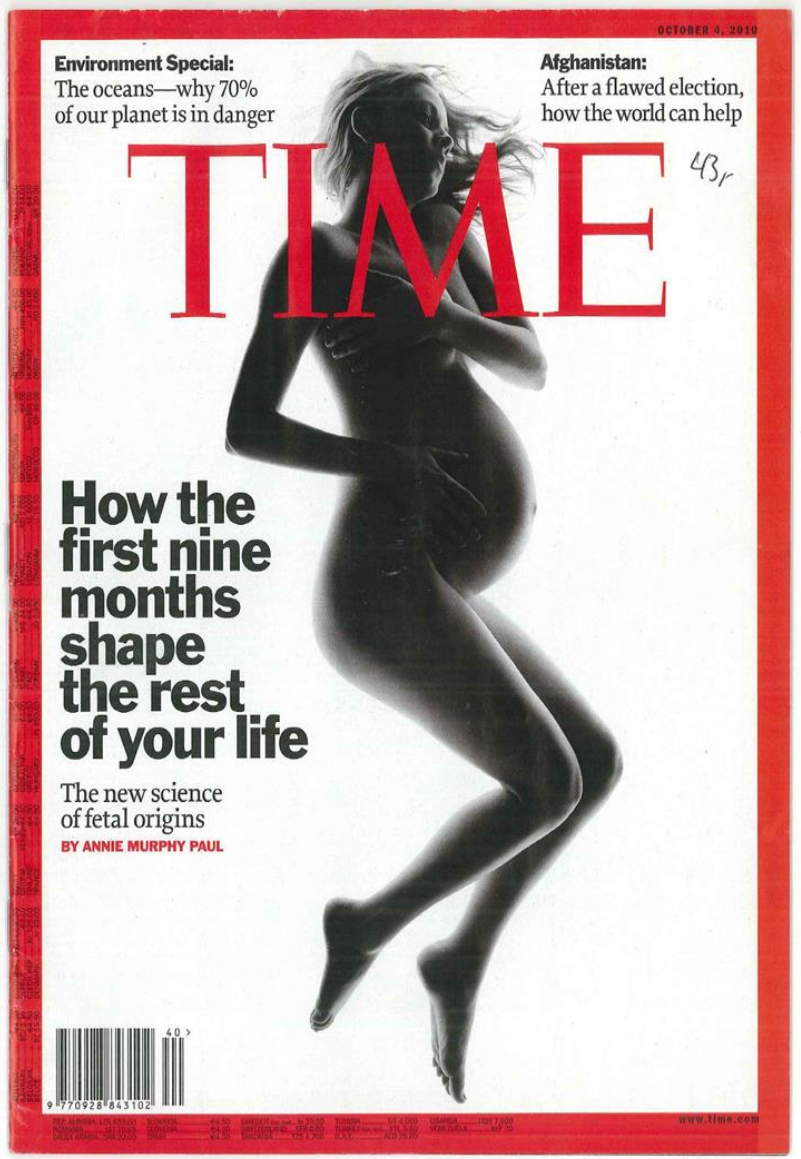
CNN news ++

Svanes et al ERJ 1998

The early life origins of lung health and disease

Asthma, COPD, lung function and lung function decline related to early life factors

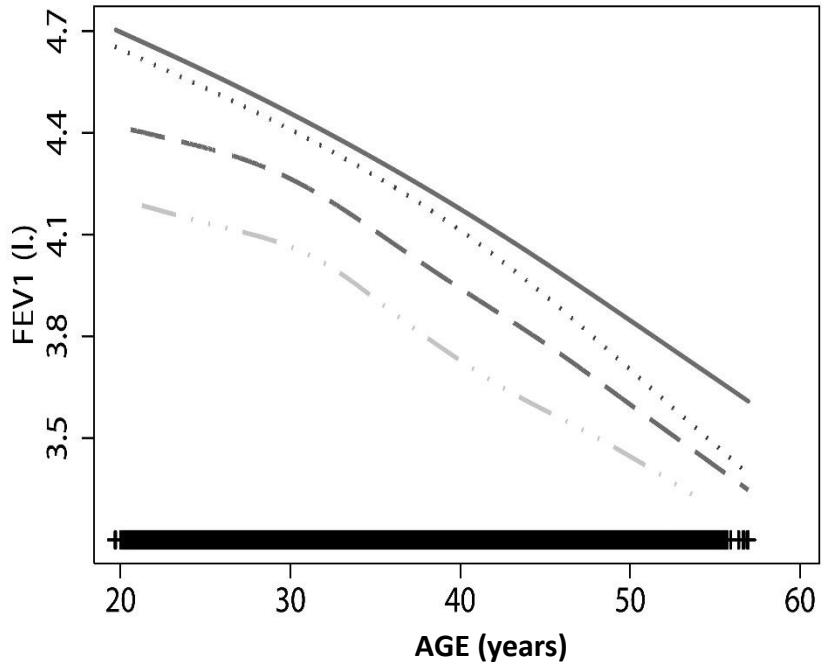
- Birth weight, birth characteristics, reproductive factors
- Childhood infections
- Mother's smoking
- Siblings and pets – *the hygiene hypothesis (the microbial diversity hypothesis)*



Svanes et al. ERJ 1998; Respir Med 1998; JACI 1999, 2006; Thorax 2002, 2004, 2005, 2010. Dratva 2016. Dharmage ERJ 2009

Early life origins of lung function

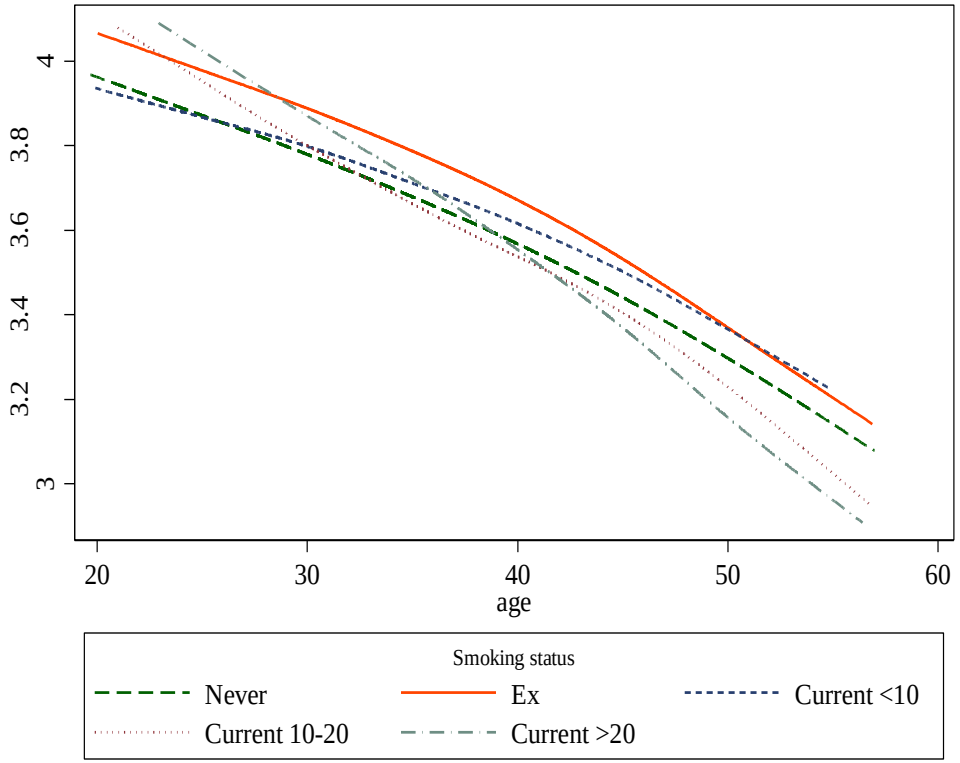
Childhood disadvantage



1, 2 and 3-4 childhood disadvantage factors
>40% of the population

(mother smoking, early life infections,childhood asthma, mother/father asthma)

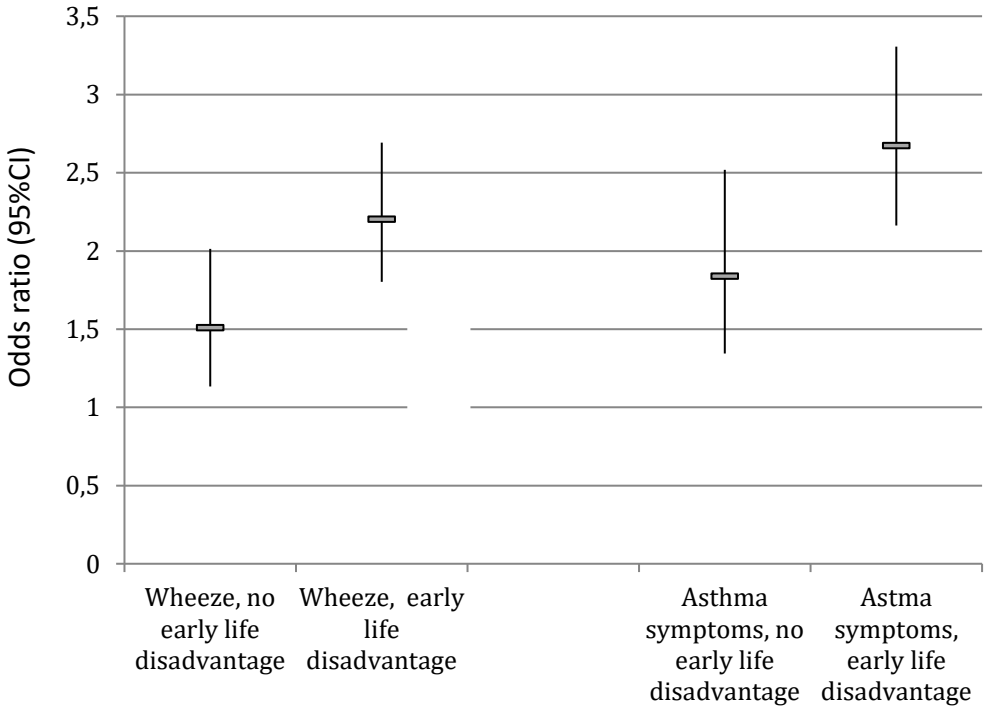
Smoking – *for comparison*



Svanes et al Thorax 2010

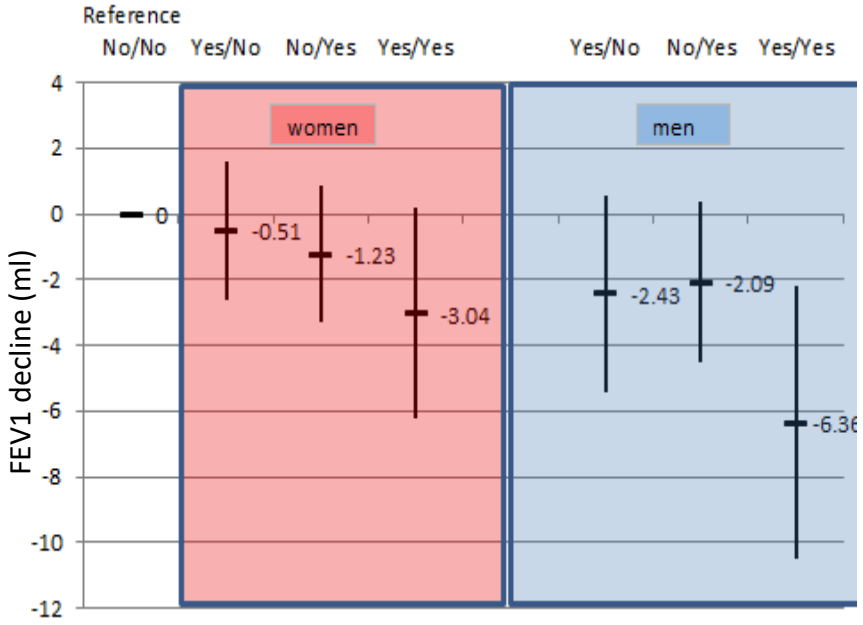
Does early life disadvantage influence susceptibility to adult hazards?

Occupational cleaning – more increased asthma risk if early life disadvantage



Svanes Ø et al 2015

Smoking – more accelerated lung function decline if mother smoked

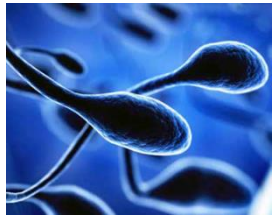


Dratva J et al 2016

Why are susceptible time windows relevant?

ADULTHOOD: mature organs

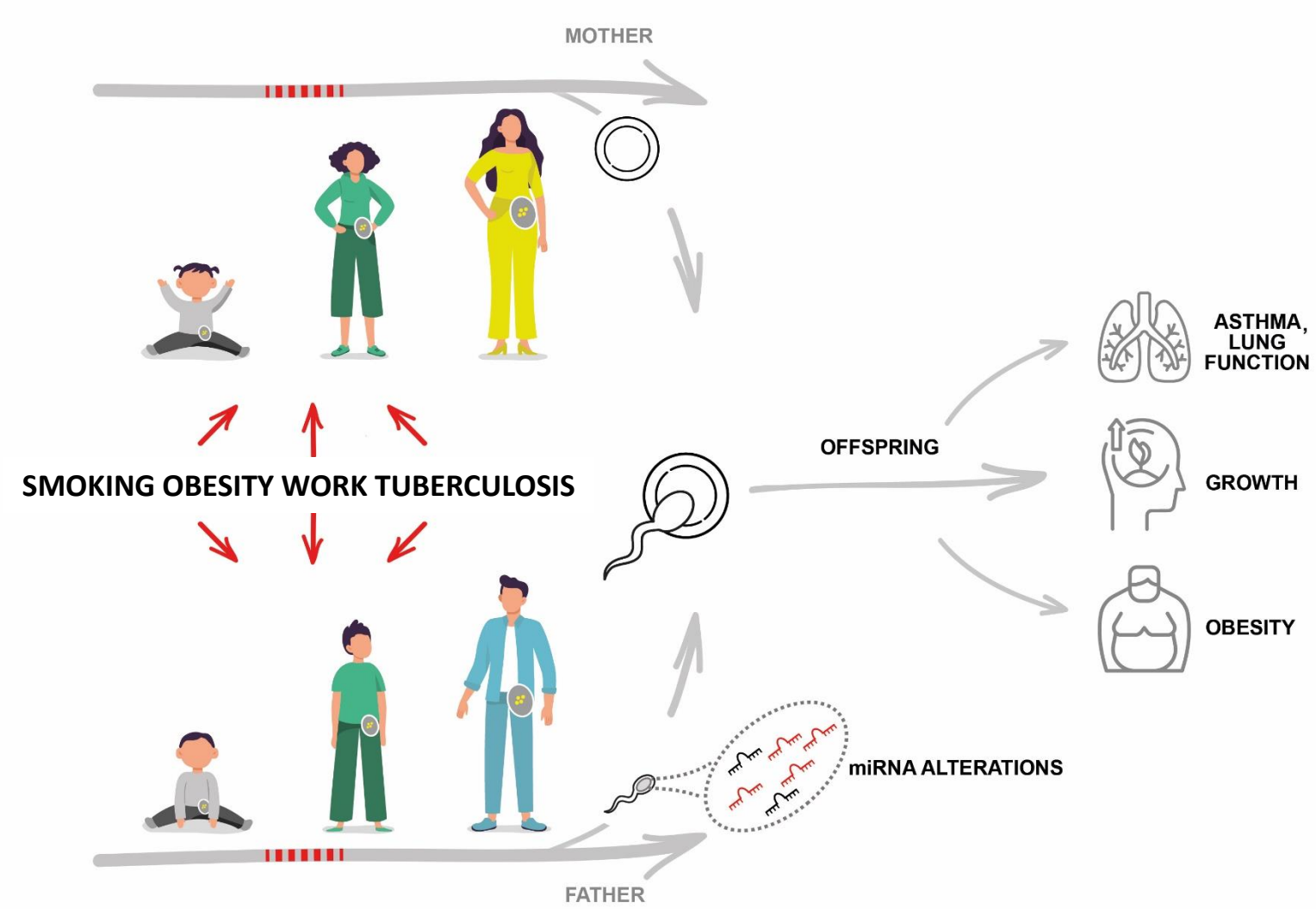
IN UTERO/EARLY CHILDHOOD: organ development, growth



BEFORE CONCEPTION: germ cell development

Opportunity for efficient intervention

The preconception origins of asthma and respiratory health



Reviews: Lopez-Cervantes JP et al IJTLD 2022; Svanes C et al Biol. Reprod. 2021; Svanes C et al JIM 2023

How can we study the preconception origins of adult disease?

ECRHS

Europe+

Population-based

Clinical follow-up over 30 years of 21.000 young adults

RHINE

North Europe ECRHS-linked study

Questionnaire follow-up 30 years of 21.000 young adults

RHINESSA

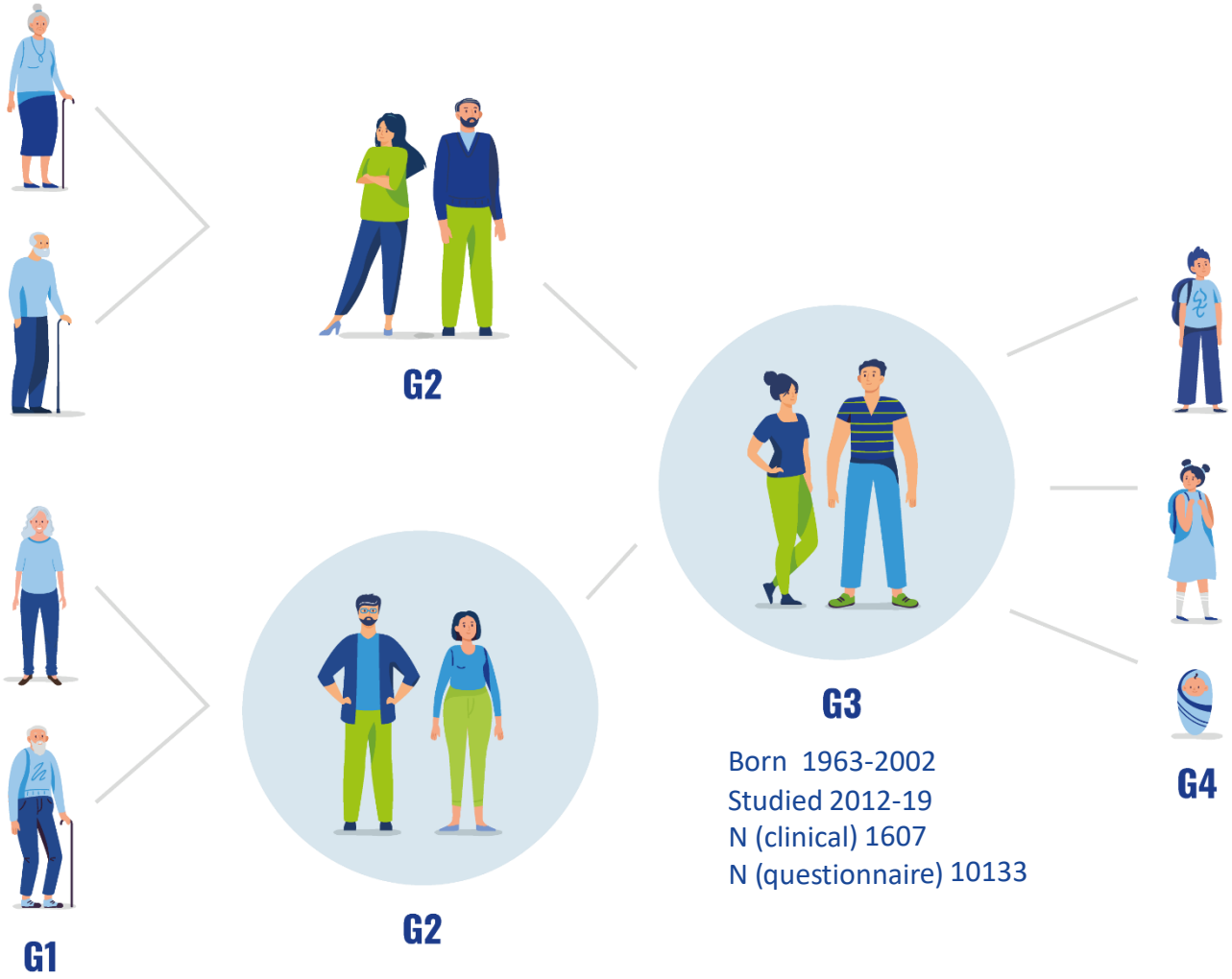
Offspring of ECRHS /RHINE

Clinical/ questionnaire

10.000 offspring with data on parent

MULTIGENERATIONAL STUDY RHINESSA

- designed to study preconception exposures



G1

G2

Born 1945-73
Studied 1991-2014 + ongoing
N (clinical, ECRHS) 7000
N (questionnaire, RHINE) 21000

G3

Born 1963-2002
Studied 2012-19
N (clinical) 1607
N (questionnaire) 10133

G4

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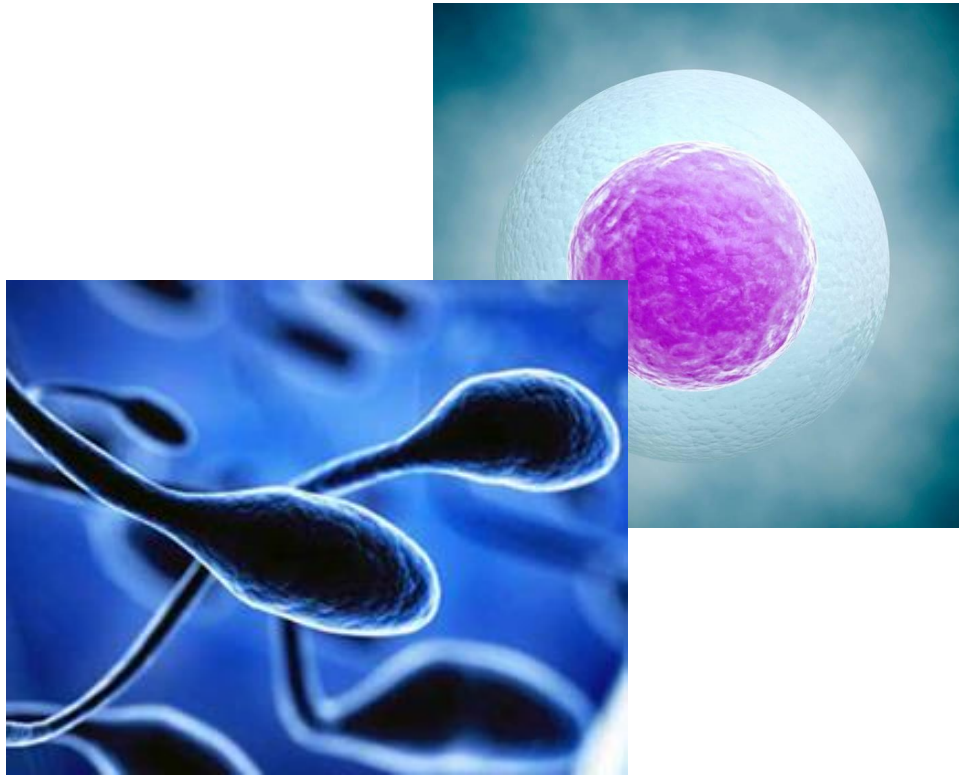
N >35.000 persons, born 1918-2018, from 4 generations www.rhinessa.net

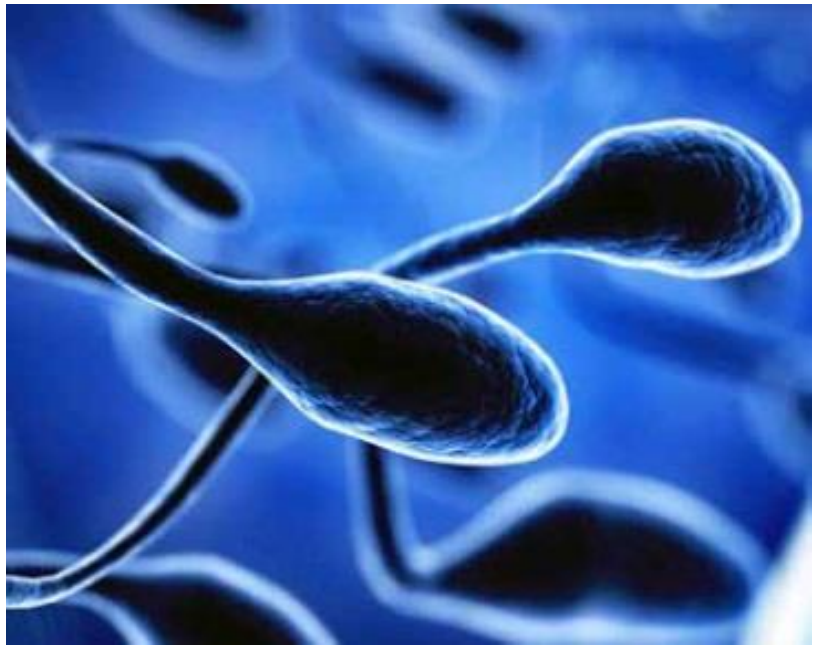
Cohort profile paper: Svanes C et al BMJOpen 2022

The beginning of life

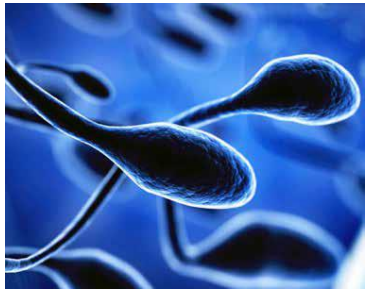
Before the beginning



the MALE line



Is father's smoking *before conception* important for asthma in future offspring?



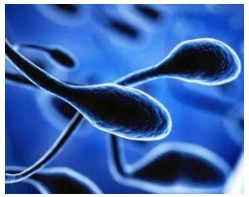
Is offspring asthma associated with father's smoking

- only preconception? **YES** **OR 1.4** [95%CI 1.01-1.86] p=0.044
- total years of smoking (10 years)? **YES** **OR 1.5** [95%CI 1.1-2.0], p=0.016
- smoke free time from quitting until conception? **NO**
- age of starting smoking? **YES – a lot** **OR 3.2** [95%CI 1.7-6.3], p=0.001

For comparison: mother smoking
-only before conception OR **1.1**
-around pregnancy OR **1.5**

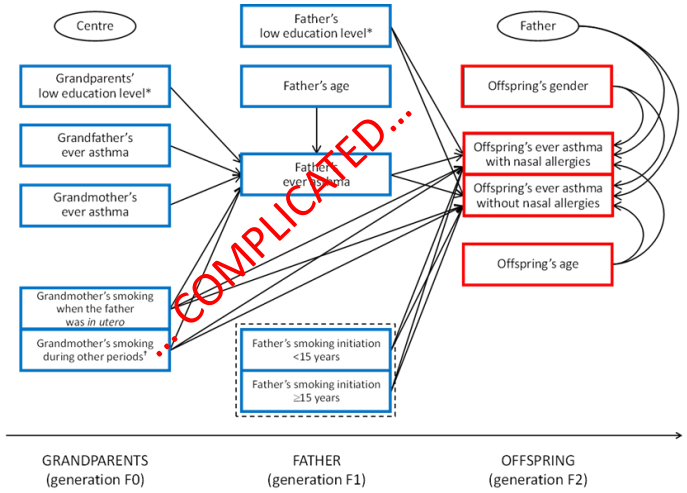
Svanes C et al IJE 2017

Father's preconception smoking and offspring asthma – supporting evidence



Epidemiological studies

- different cohorts RHINESSA/RHINE/ECRHS, UK cohort, Australian TAHS
- different asthma definitions, lung function
- other chemical exposures – father's welding, parents air pollution
- simple and advanced statistical models, causal inference approaches



Murine studies

Epigenetic analyses

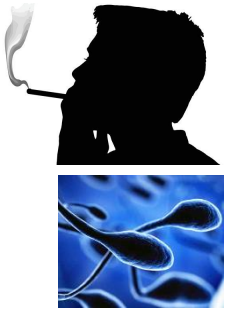
International Journal of Obesity
https://doi.org/10.1038/s41366-021-00798-2

Preconceptional smoking alters spermatozoal miRNAs of murine fathers and affects offspring's body weight Hammer B et al

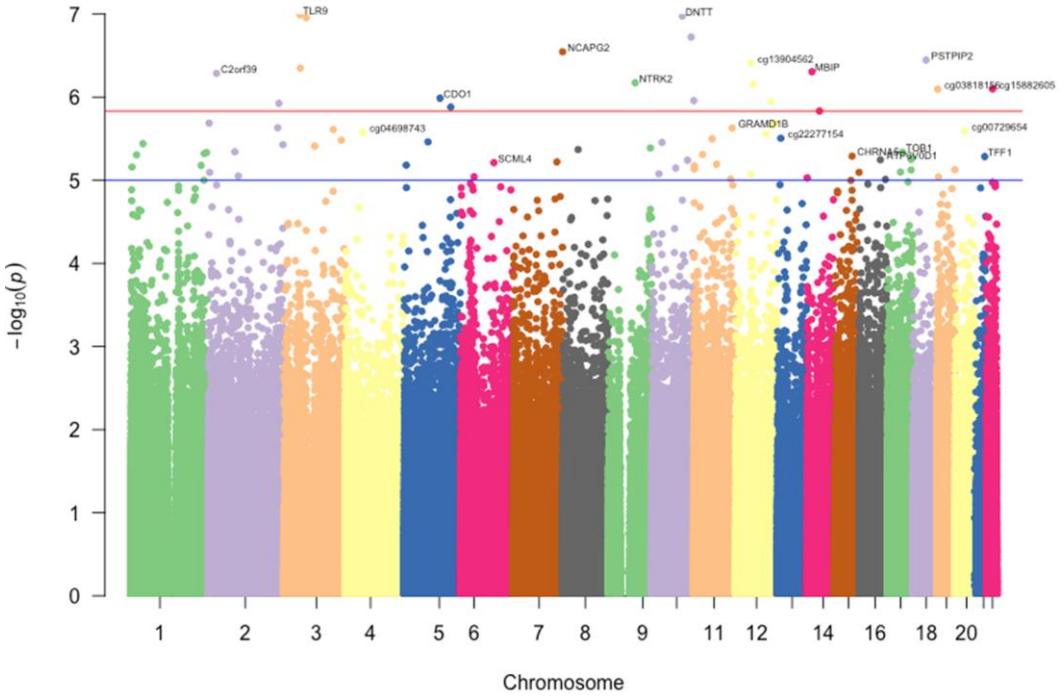
112-2023-MARK

Ref. smoking: Accordini S 2018, 2021, Svanes C 2017, Knudsen GTM 2018, 2021, Kitaba N submitted, Hammer B 2021, Jarvis D, Liu 2022. Ref. other chemical: Kuiper I 2020, Pape K 2020, Tjalvin G 2021.

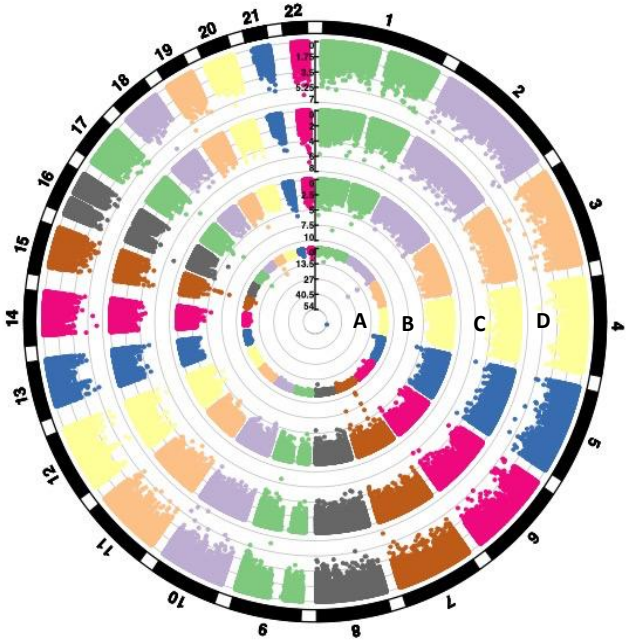
DNA methylation in offspring blood as related to father's smoking



RHINESSA/ECRHS 875 offspring/parent pairs, EWAS, EPIC 850k CpG sites



CpG sites associated with father's smoking <age 15



A: EWAS personal smoking
B: EWAS mother smoking
(both agree with other studies)
C: EWAS father smoking
D: EWAS father smoking <15 years

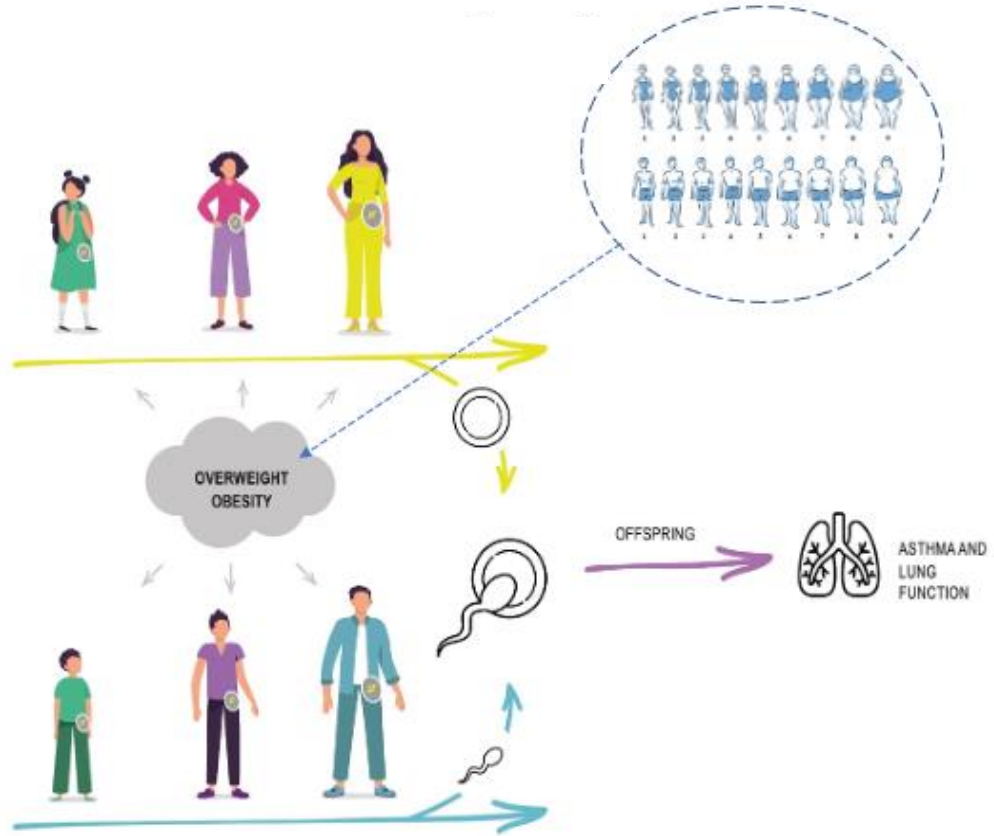
We identify epigenetic signals related to father's smoking,
more if father started smoking early

Signals differ from those of personal and mother smoking

Signals suggesting functional importance, related to innate immunity+++

Kitaba N et al In revision

Can parents' overweight influence future offsprings' health?

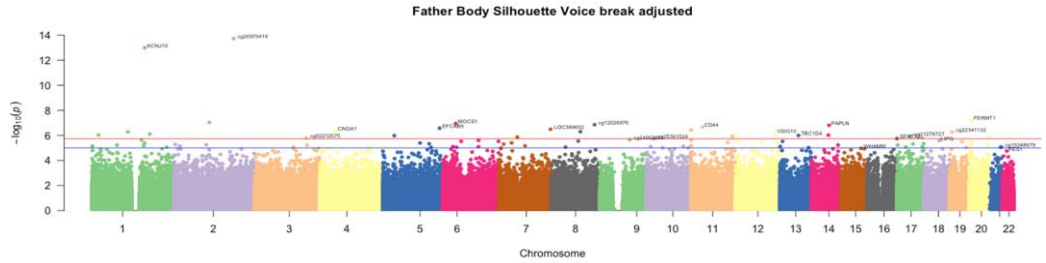


Fathers' overweight starting before puberty was associated with

- more asthma in offspring
- lower lung function in offspring
- lower adult height in sons

consistent in three cohorts

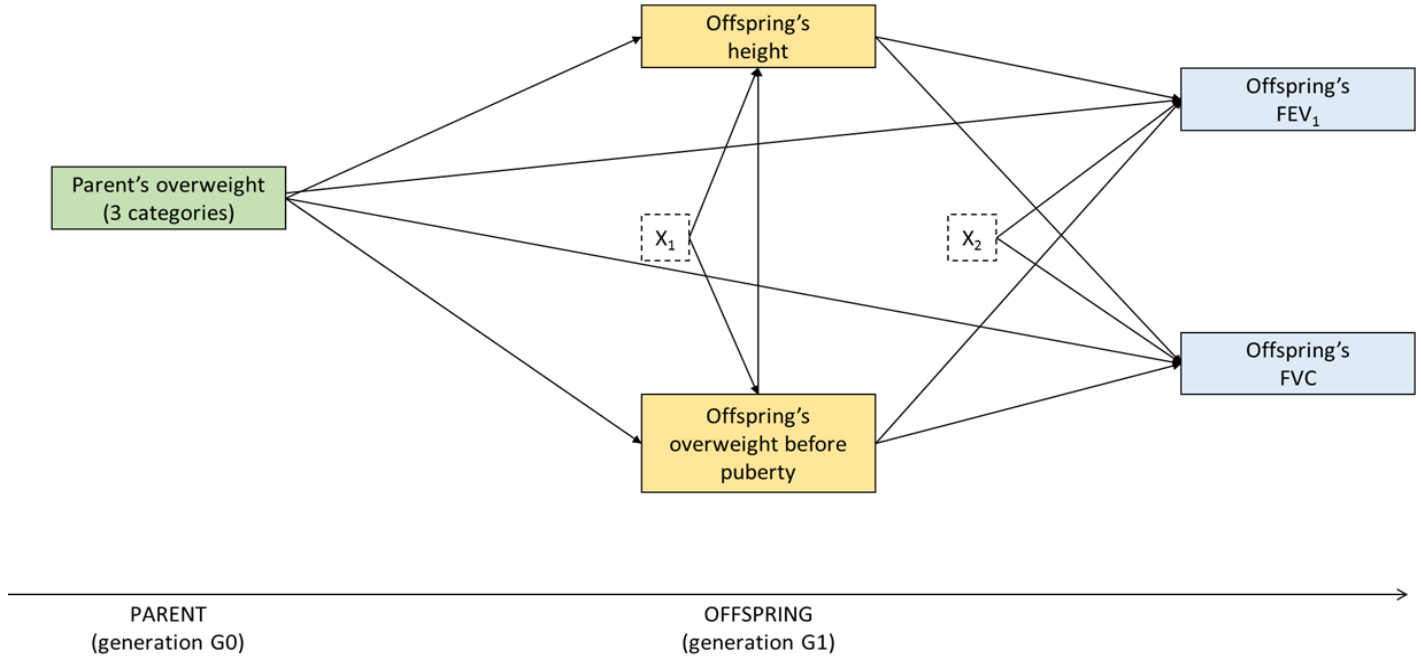
Causal inference models



Johannessen, Lønnebotn, Calciano JACI 2020; Lønnebotn, Calciano 2022, Bowatte 2022. Kitaba, ongoing.

Father prepuberty overweight and lung function in offspring

RHINESSA/ECRHS 929 offspring-parent pairs, causal models



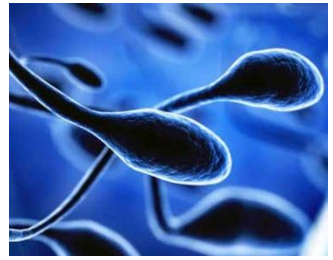
Graphical representation of the path model for FEV_1 and FVC in sons or daugthers within the paternal or maternal lines. The green box represents the exposure of interest, the yellow boxes the mediators and the blue boxes the outcomes. The dotted boxes represent the set of potential confounders and adjusting variables of the mediators (X_1: parent's low education level) and of the outcomes (X_2: parent's low education level and offspring's age and smoking).

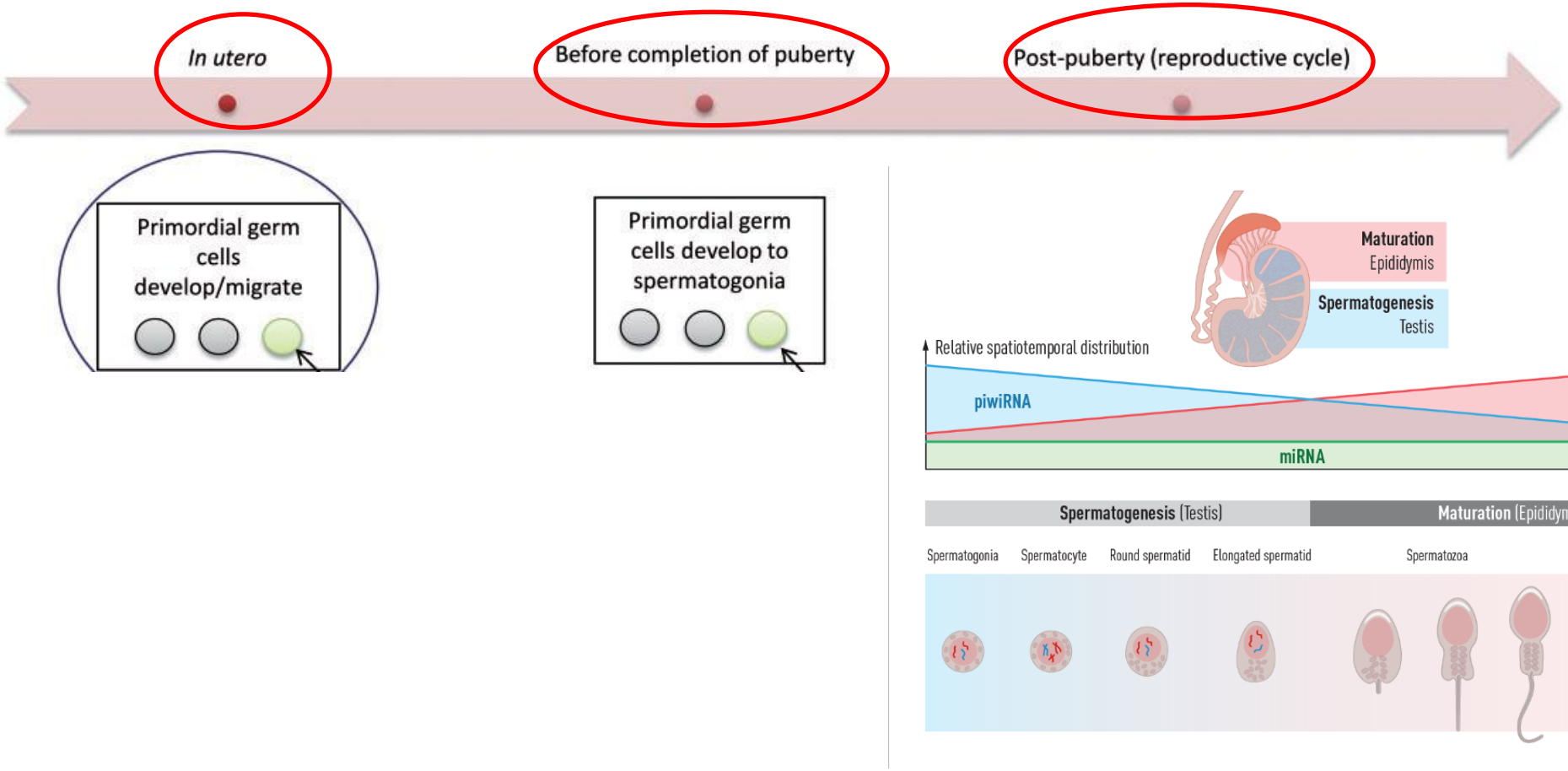
Lønnebotn M et al Nutrients 2022

Father's overweight starting befor voice break led to

- lower adult lung function in sons – 262ml lower FVC/unit higher body silhouette
- lower adult height in sons – 3.42 cm lower stature/unit higher body silhouette

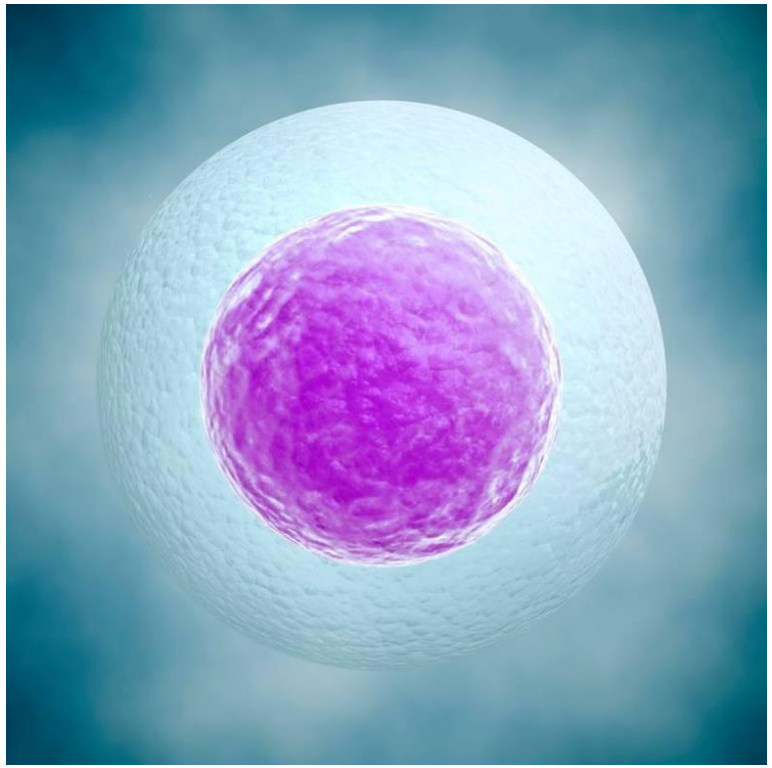
Can susceptible windows in sperm development explain our findings?





Hammer B 2021, Bertelsen RJ 2017, Svanes C 2017, 2021, Accordini S 2018, 2021, Knudsen GTM 2018, 2021, Johannessen A 2020, Kuiper I 2020, Pape K 2020, Tjalvin G 2021, Lønnebotn M 2018, 2022, Kitaba N ongoing, López-Cervantes JP 2021.
Illustrations adapted from Soubry A, and from Svanes C JIM 2023.

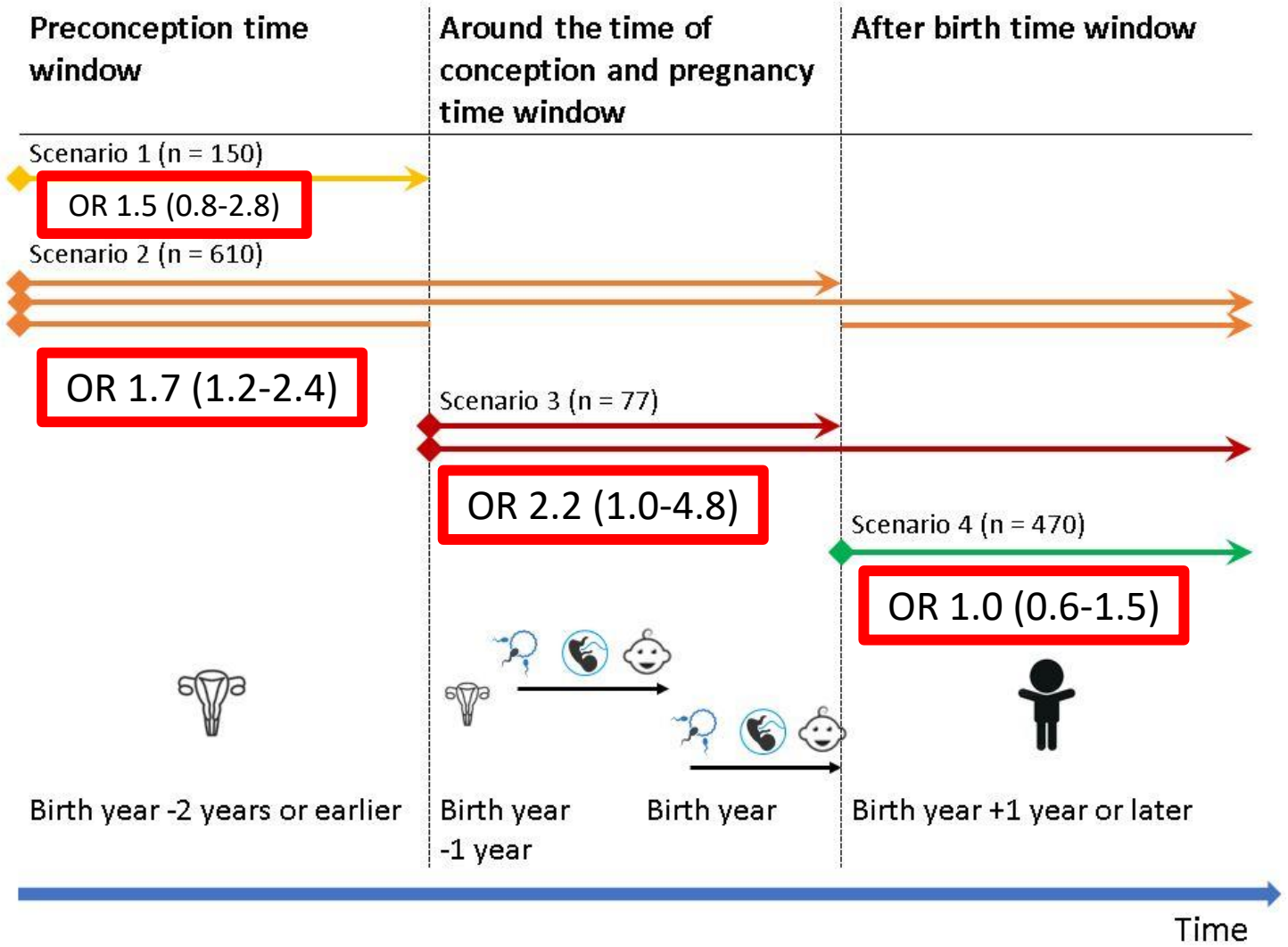
the FEMALE line



Some jobs using “cleaning agents and disinfectants”

Mother's job with cleaning agents/ disinfectants before conception associated with asthma in offspring

RHINESSA/RHINE, 3318 mother-offspring pairs

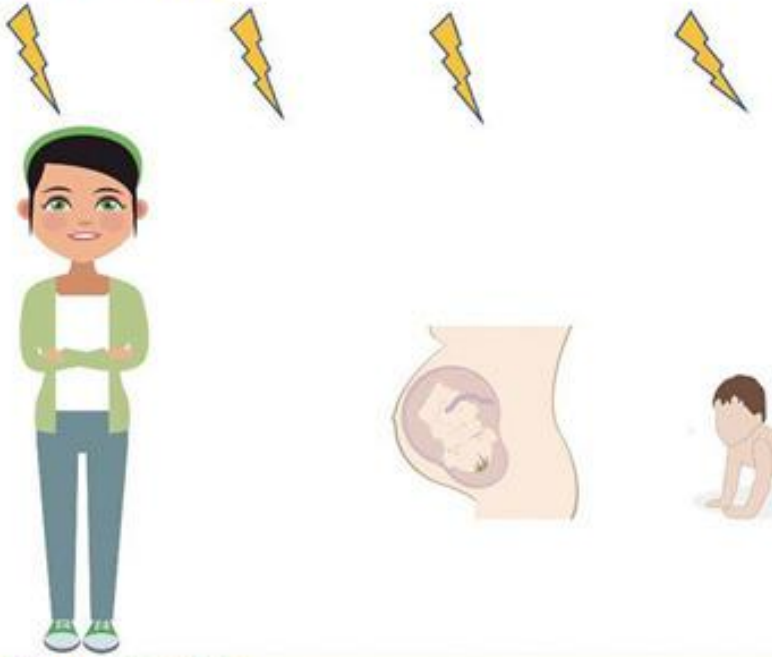


Tjalvin G et al JACI 2021

Maternal preconception occupational exposure to cleaning products and disinfectants and offspring asthma

Maternal occupational exposure (defined by maternal occupational history AND an occupational asthma-specific job-exposure matrix)

This hypothesis-generating, multi-center, two-generation study, comprising 3318 mother-offspring pairs, raises concern for adverse health effects of cleaning agents, revealing more asthma after mother's preconception exposure, and supports the paradigm that preconception exposures may impact offspring health in humans.



Offspring childhood asthma and/or wheeze

Time of exposure

Starting preconception	OR 1.71 (1.19-2.44)
Starting around conception and pregnancy	OR 2.25 (1.03-4.91)
Starting after birth	OR 1.08 (0.69-1.67)

Tjalvin G et al JACI 2022

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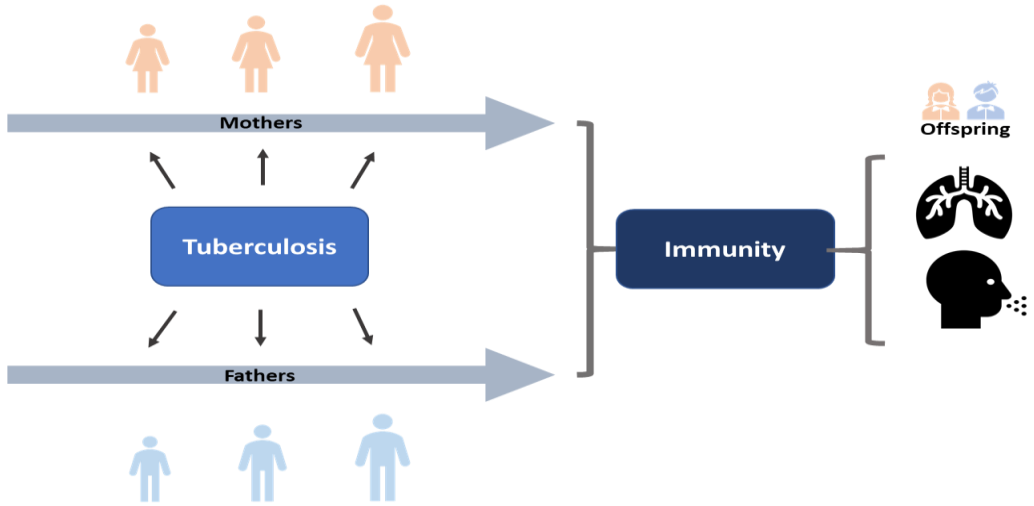
Can infections influence offspring immunity?

Mice studies suggest infections may influence germ cells and next generations' stem cells and immunity

We find in humans

Parental *Toxocara* (a helminth) associated with much more offspring allergies

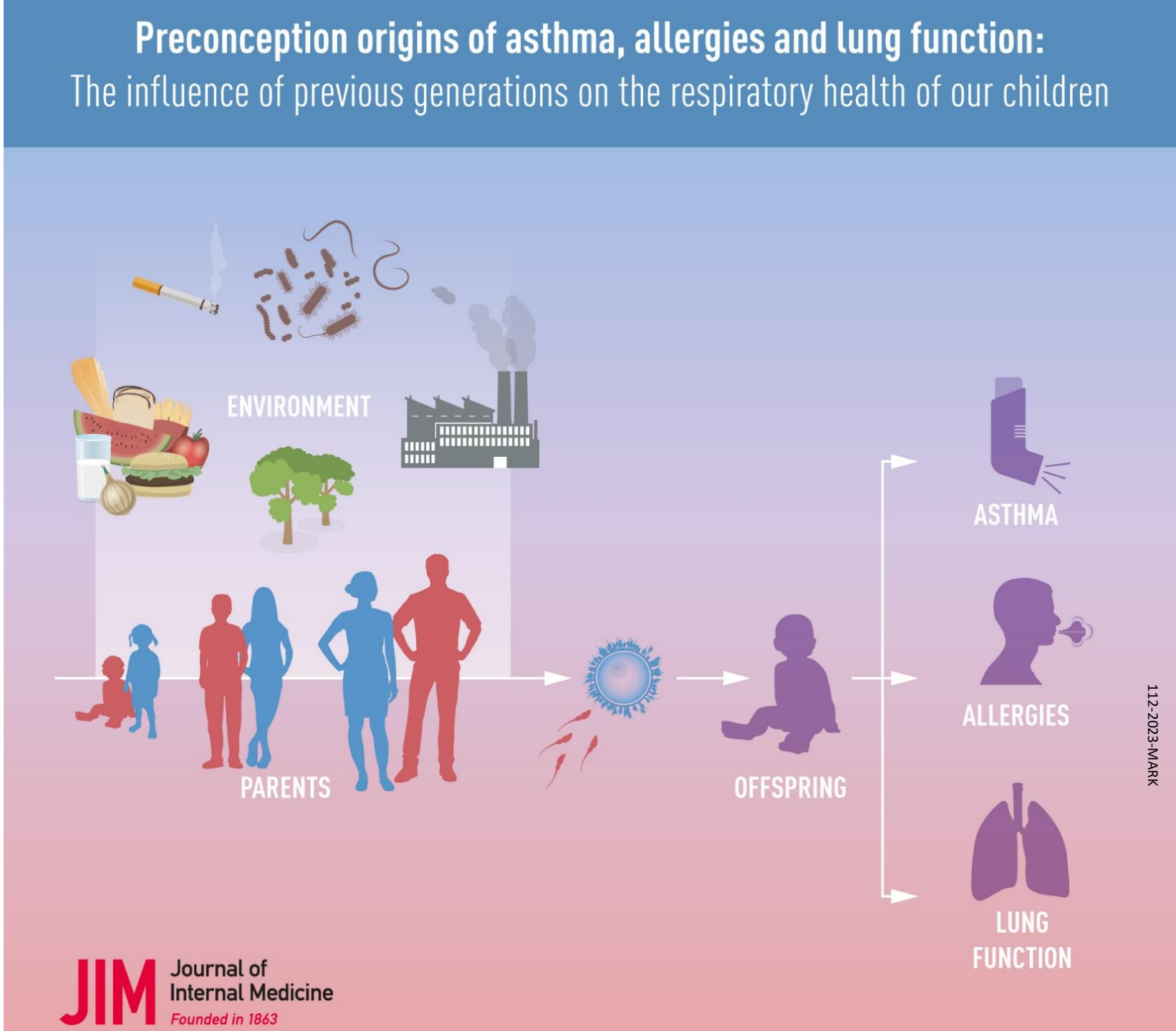
Parental tuberculosis associated with more offspring asthma



Jögi O et al. CEA 2017, JACI 2022, ongoing; López-Cervantes JP et al. IUTLD 2022; Gyawali S et al. submitted

CONCLUSION

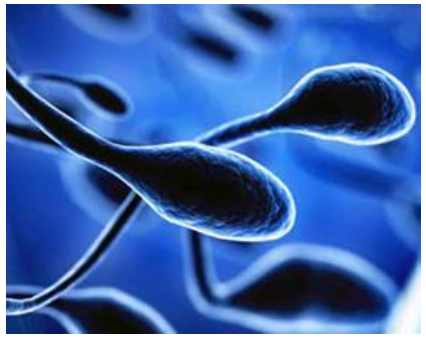
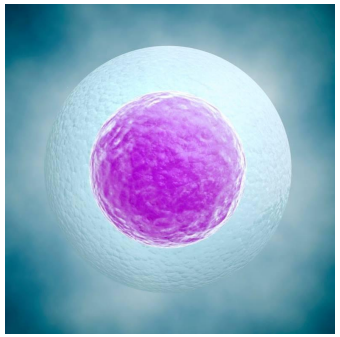
Reviews: Svanes Biol Reprod 2021, Lopez-Cervantes IJERPH 2021, Svanes et al JIM 2023



IMPACT

The concept that our lifestyles and behaviors may influence the health of our future children represents a new paradigm.

- harmful exposures - concerns for future health in decades to come
- can preventive strategies improve health in multiple generations?
- reverse the imprint of our parents and forefathers?
- knowledge to break the vicious circle of propagation of health inequalities across generations?


Svanes et al JIM 2023

Acknowledgements

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