Do the effects of orenatal famine exposure pass down generations? An epigenitic study.

Published: 01-07-2008
Last updated: 07-05-2024

Objective: We aim to assess whether [1] epigenetic alterations are responsible for the detrimental effects of maternal undernutrition during gestation on the offspring*s (F1) cardiovascular health, and [2] these epigenetic alterations pass down...

Ethical review	Approved WMO
Status	Pending
Health condition type	Coronary artery disorders
Study type	Observational non invasive

Summary

ID

NL-OMON31890

Source
ToetsingOnline

Brief title
Transgenerational effects of the Dutch Famine. An epigenetic study.

Condition

- Coronary artery disorders
- Glucose metabolism disorders (incl diabetes mellitus)
- Personality disorders and disturbances in behaviour

Synonym
cardiovascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: cardiovascular disease, genes, nutrition, pregnancy

Outcome measures

Primary outcome

Primary outcome: % methylation of the CpG regions of 4 candidategenes.

Secondary outcome

Secondary outcome: health of F2.

Study description

Background summary

Background: Poor nutrition during fetal development can permanently alter growth, cardiovascular physiology and metabolic function. These alterations are detrimental for cardiovascular health in later life. Animal studies consistently find that prenatal undernutrition leads to hypertension, dyslipidaemia and disturbed glucose tolerance as well as reduced lifespan. Supported by 2 previous NHS grants, we have provided the first evidence in humans that maternal undernutrition during gestation leads to a striking 2-fold increase in cardiovascular disease in the offspring, in the Dutch famine birth cohort.
Animal studies have recently started to unravel the underlying molecular mechanisms. Poor intrauterine nutrition leads to persistent alterations to the epigenetic regulation of specific genes, which give rise to altered expression of a range of genes which may raise cardiovascular risk. Epigenetic alterations have recently been identified to feature in cardiovascular disease, and are thus likely to underlie many of the permanent effects of maternal undernutrition on the offspring's health. Moreover, animal studies have demonstrated that epigenetic alterations can be transmitted to subsequent generations even when female offspring of the F1 generation were not exposed to nutritional constraint during pregnancy and, importantly, that these alterations are linked to a phenotype with increased cardiovascular risk.
The Dutch famine birth cohort presents a unique opportunity to resolve the question of whether differences in the epigenetic regulation of genes are induced by variations in maternal diet during pregnancy and whether these epigenetic marks are associated with differential risk of cardiovascular

disease in future generations. Preliminary evidence from our study suggests that the increase in cardiovascular disease may be conveyed to the offspring of men and women who were exposed to famine in utero.

Study objective

Objective: We aim to assess whether [1] epigenetic alterations are responsible for the detrimental effects of maternal undernutrition during gestation on the offspring*s (F1) cardiovascular health, and [2] these epigenetic alterations pass down generations through epigenetic inheritance and are associated with excess cardiovascular risk (F2).

Study design

Design and study population: To address aim 1, we will study the methylation status of specific candidate genes in 793 members of the Dutch famine birth cohort (F1). We will assess whether famine exposure in utero can induce alterations in gene methylation status. Aim 2 will be addressed by carrying out a study among 3 generations: women (F0) who were pregnant around the time of the Dutch famine 1944-45 who delivered in the Wilhelmina Gasthuis Amsterdam, their children (F1) and their grandchildren (F2). We will assess DNA methylation as well as gene expression of the candidate genes in 80 grandmother-parent-child sets. Additionally, we will investigate the cardiovascular risk profile in the F2 in order to study the intergenerational effects of famine exposure on a functional level.
This study will test the hypothesis that epigenetic alterations, induced by maternal undernutrition during gestation, are associated with a rise in cardiovascular disease risk.

Study burden and risks

The burden for the participants consists of a buccal swab and completing a questionnaire (estimated time 1 hour). Both procedures are safe and pain free.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Men and women born at the time of the Dutch Famine 1944-1945 in the Wilhelmina Gasthuis in Amsterdam, their mothers(F0) and children(F2).

Exclusion criteria

NVT

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2008
Enrollment:	2580
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL21803.018.08