The Dutch famine birth cohort study: consequences of a suboptimal start in life

Published: 09-12-2011
Last updated: 28-04-2024

Primary Objective: To assess whether ageing across body systems is accelerated by sub-optimal early life circumstances.Secondary Objective: To asses underlying mechanisms of the potential association between sub-optimal early life circumstances and…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON35232

Source
ToetsingOnline

Brief title
Dutch famine birth cohort study

Condition

- Other condition
- Cardiac disorders, signs and symptoms NEC
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
ageing

Health condition

veroudering incl cognitieve achteruitgang

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: EU

Intervention

Keyword: ageing, famine, pregnancy

Outcome measures

Primary outcome

- cognitive decline

- incidence of white matter hyperintensities and cerebral microbleeds

- cerebrovascular function

- endothelial function

- incidence of stroke

- incidence of fractures

- grip strength and physical performance

- visual acuity

- incidence of cataract operations

- hearing

- mortality.

Secondary outcome

cerebrovascular function

- cellular ageing (quantified by telomere length)

- oxidative stress (quantified by a comet assay)

basal inflammation (quantified by the inflammatory factors C-reactive protein

(CRP) and total leukocyte count).

Study description

Background summary

The Dutch population, as most of the populations worldwide, is *greying*: the proportion of people aged over 60 years is growing faster than any other age group. At the individual level, there is increased ageing across diverse body systems. Alzheimer*s disease, cardiovascular disease, metabolic disorders and osteoporosis are just a few examples of many age-related conditions where the prevalences are expected to rise even further in the coming decades. This not only puts a major burden on our social and health care systems, it also greatly affects the independence and quality of life of older people, their families and caregivers.

Although ageing is an inevitable biological process, the health with which old age is reached can be optimised. Healthy lifestyles are known to increase life expectancy. An important lifestyle factor influencing the ageing process is nutrition. Dietary restriction is one of the most extensively studied ways to elongate lifespan. However, when diet is restricted in early life, the effects seem to be reversed completely. Early life malnutrition may even be more important for the ageing process than later life over nutrition. This was elegantly shown by studies in which mice received either a normal or a 20% protein restricted diet during gestation and/ or lactation followed by either a normal or a high fat cafeteria diet (1). A normal diet during the whole period resulted in a lifespan of on average 765 days, a postnatal cafeteria diet resulted in a lifespan of 715 days, while a prenatally restricted diet resulted in a lifespan of 568 days which was even lowered to 517 days when combined with a postnatal cafeteria diet. Evidence for an effect of suboptimal nutritional circumstance in utero on the ageing process in humans does not exist.

Previous studies in the Dutch famine birth cohort suggest that prenatal exposure to undernutrition may lead to accelerated ageing. We have shown that exposure to famine during early gestation is associated with age-related disorders including a more atherogenic lipid profile, decreased glucose tolerance and a doubled prevalence of coronary artery disease (CAD) (2). However, of particular interest for the proposed study is our finding that people conceived during the famine were on average 3 years younger at the time of CAD diagnosis (3). Another indication that prenatal famine exposure may lead to accelerated ageing is our finding that those exposed to famine in early gestation performed worse on a selective attention task, a cognitive ability that usually declines with age (4). Results of- as yet unpublished- analyses in the cohort also seem to suggest a shorter lifespan: analyses on mortality up to

the age of 63 years show that women conceived during the famine have an increased risk of all cause mortality, cancer related mortality and cardiovascular related mortality (van Abeelen et al., under revision). Other evidence that prenatal undernutrition may lead to accelerated ageing mainly comes from animal experiments. A restriction of the pre or perinatal diet in rats and mice has been shown to lead to several age-related changes and a decreased lifespan (1;5-11). There is also some indirect evidence based on studies investigating surrogate indirect measures for a suboptimal nutritional early environment. Low birth weight and low weight at one year of age have been associated with markers of ageing in a number of different body systems, including the eye, ear, muscle and bone (12;13). We propose to use the unique opportunity provided by the Dutch famine birth cohort to investigate whether the ageing process is affected by a suboptimal early environment and how this may come about.

With the proposed study we intend to investigate in humans whether the ageing process is affected by nutritional environmental factors operating in the very earliest stages of life. We will use the Dutch famine birth cohort to study the effects of prenatal exposure to undernutrition on ageing across body systems, mortality and on possible underlying mechanisms. Based on animal experiments and on the previous findings in the Dutch famine birth cohort, we expect to find increased markers of ageing in the group of people who experienced a suboptimal environment in prenatal life. Those who have been exposed to famine during gestation will show more cognitive decline, decreased vascular function, increased incidence of fracture, decreased grip strength and physical performance, and decreased vision, hearing and physical performance. Furthermore, those exposed to undernutrition in utero will show increased mortality up to the age of 67 years. In studying underlying mechanisms, we expect to find that those exposed to famine during gestation will have increased cerebrovacular tone, a decreased telomere length, increased oxidative stress and increased basal inflammation.

The proposed study will be the first to establish in humans whether ageing across systems is affected by prenatal undernutrition and what the underlying biological ageing processes may be. These findings will shed light on the pathophysiology of the ageing process. Furthermore, the findings may also be of importance from a future public health point of view. Data of the proposed study may provide evidence that suboptimal circumstances during early life can affect the ageing process. Although severe malnutrition such as the shortages that occurred during the famine are uncommon in the Western world today, still many babies have a suboptimal nutritional start in life due to factors such as dieting of the mother (1 in 4 women of reproductive age diet at any given moment in time) and complication of the pregnancy by placental insufficiency. Also, worrying data from the UK suggest that only 3% of the women who get pregnant abide with the healthy diet guideline of less than 7 units of alcohol a week and taking enough folic acid, let alone taking fruits and vegetables daily (14). Placed in a broader perspective, a poor start in life may also be

experienced by those whose mothers suffer from pre-eclampsia or hyperemesis gravidarum, those who are born pre-term and possibly those who are conceived by in vitro fertilization. There is potentially a lot to be gained by improving the prenatal environment.

Study objective

Primary Objective: To assess whether ageing across body systems is accelerated by sub-optimal early life circumstances.

Secondary Objective: To asses underlying mechanisms of the potential association between sub-optimal early life circumstances and ageing.

We hypothesize that a suboptimal start in life as quantified by prenatal exposure to the Dutch famine is associated with accelerated ageing across body systems including the brain, the vascular system, bone, muscle, the eye and the ear. Increased cerebrovascular tone, cellular ageing, oxidative stress and basal inflammation are biological mechanisms underlying these associations.

We will investigate this research question in the Dutch famine birth cohort. Ageing markers as well as possible underlying mechanisms will be compared between cohort members who have been exposed to famine during early, mid or late gestation and cohort members who have not been exposed to the famine during pregnancy.

Study design

Cohort study

Study burden and risks

all measurements are minimally invasive and safe. Participation in the study will not be of benefit nor be of harm to participants

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 as term singletons around the time of the Dutch famine in the Wilhelmina Gasthuis, Amsterdan, the Netherlands, between 1 november 1943 and 28 february 1947

Exclusion criteria

na

Study design

Design

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

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-11-2012
Enrollment:	500
Type:	Actual

Ethics review

Approved WMO

Date:	09-12-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC

Not approved

Date:	31-01-2013
Application type:	Amendment
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	NL37731.018.11