

Investigating the link between early life stress and multiple long-term health conditions

Submission date 29/06/2020	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 15/07/2020	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 26/06/2024	Condition category Other	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

Background and study aims

Stress experienced in the early stages of life – from pregnancy to adolescence – is common and pervasive, affecting up to 75% of pregnant women (and the unborn baby) and nearly 50% of children, with long-term consequences for development and health. The aim of this study is to find out whether early life stress, a well-established risk factor for depressive, cardiovascular (heart) and metabolic disorders individually, is a cause of multiple long-term health conditions (multi-morbidity) in these disorders.

Who can participate?

Children and adults participating in the included population studies:

1. Population-based samples of children
2. Adults aged over 55 years
3. Adults aged over 18 years with depression or anxiety

What does the study involve?

Data from a set of human population studies are used to examine the relationship between early life stress and multi-morbidity across the lifespan, identify potential biological markers and quantify the role of modifiable lifestyle factors (e.g. exercise, diet, sleep, smoking, alcohol use).

What are the possible benefits and risks of participating?

In terms of benefits, this study will increase the health literacy of the participants by making them aware of the negative effects of early life stress on health and disease. This is an observational study with no interventions, so there are no risks for the participants.

Where is the study run from?

Rotterdam and Amsterdam (Netherlands), Oulu (Finland) and Bristol (UK)

When is the study starting and how long is it expected to run for?

September 2019 to June 2024

Who is funding the study?

European Commission

Who is the main contact?

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Study website

<https://earlycause.eu/>

Contact information

Type(s)

Scientific

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Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

EarlyCause funding 848158

Study information

Scientific Title

EarlyCause - causative mechanisms & integrative models linking early life stress to psycho-cardio-metabolic multi-morbidity

Acronym

EarlyCause

Study objectives

EarlyCause will investigate the hypothesis that early-life-stress (ELS), as a risk factor for depressive, cardiovascular and metabolic disorders individually, is linked to multi-morbidity between these conditions. From a biological point of view, the main hypothesis is that ELS activates a chain of events leading to cellular, molecular, epigenetic and microbial changes which result in dysregulations of processes across tissues. This causative chain would ultimately trigger specific cellular and tissue phenotypes and comorbid pathological traits in the mental, cardiovascular and metabolic domains.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 30/11/2019, European Commission (Directorate-General for Research and Innovation, European Commission, Brussels; Tel: not provided; david.canovas-jorda@ec.europa.eu), no ref provided

Study design

Observational study that will leverage existing data from a large set of population research studies (e.g. Generation R, ALSPAC, NFBC, Rotterdam, NESDA)

Primary study design

Observational

Secondary study design

Epidemiological study

Study setting(s)

Other

Study type(s)

Other

Participant information sheet

Not applicable

Health condition(s) or problem(s) studied

Multi-morbidity between unipolar depression, type 2 diabetes, and coronary heart disease

Interventions

The EarlyCause study will leverage harmonised data from a set of human population studies to examine the relationship between ELS and multi-morbidity across the lifespan, identify potential molecular markers and quantify the protective vs. exacerbating role of modifiable lifestyle factors. These datasets together span from pregnancy to old age, including the well-known Avon Longitudinal Study of Parents and Children (ALSPAC), Generation R Study (GenR), Northern Finland Birth Cohorts (NFBC 1966 and NFBC 1986), Rotterdam Study, and the Netherlands Study of Depression and Anxiety (NESDA). The researchers will make use of correlational multivariate analyses as well as novel latent modelling techniques to model the shared versus unique contribution of ELS on multi-morbid outcomes. The researchers will apply Mendelian randomisation to infer causality using population-based human genetic data., and to establish the molecular mediation of biological markers (DNA methylation, cortisol, inflammation, microbiome) linking ELS exposure to later multi-morbidity. The researchers will also quantify the protective or exacerbating role of modifiable lifestyle factors (e.g. exercise, diet, sleep, smoking, alcohol use) in the relationships of ELS with biological markers and multi-morbidity.

Intervention Type

Other

Primary outcome measure

Current primary outcome measures as of 28/12/2023:

1. Depression assessed using the DSM-IV scale at each round of data collection (every 2-5 years depending on the dataset)
2. Diabetes type 2 assessed using the glycated hemoglobin test at each round of data collection (every 2-5 years depending on the dataset)
3. Coronary heart disease assessed using standard cardiovascular exams (biomarkers, imaging, ECG) at each round of data collection (every 2-5 years depending on the dataset)
4. In NFBC, depressive symptoms were measured using Youth self report (YSR) scale at 16 years in NFBC1986 and using Hopkins Symptoms checklist (HSCL) at 31 and 46 years in NFBC1966

Previous primary outcome measures:

1. Depression assessed using the DSM-IV scale at each round of data collection (every 2-5 years depending on the dataset)
2. Diabetes type 2 assessed using the glycated hemoglobin test at each round of data collection (every 2-5 years depending on the dataset)
3. Coronary heart disease assessed using standard cardiovascular exams (biomarkers, imaging, ECG) at each round of data collection (every 2-5 years depending on the dataset)

Secondary outcome measures

Current secondary outcome measures as of 28/12/2023:

EarlyCause will re-use the outcomes already measured by the Generation R, ALSPAC, NFBC, Rotterdam and NESDA studies at each round of data collection (every 2-5 years depending on the study):

1. Depressive symptoms assessed using the Centre for Epidemiological Studies Depression Scale (CESD) at each round of data collection (every 2-5 years depending on the dataset)
2. Metabolic health-related measures such as obesity and glycemic traits

3. Hypertension assessed using blood pressure test (mmHg) at each round of data collection (every 2-5 years depending on the dataset)

Previous secondary outcome measures: EarlyCause will re-use the outcomes already measured by the Generation R, ALSPAC, NFBC, Rotterdam and NESDA studies at each round of data collection (every 2-5 years depending on the study):

1. Depressive symptoms assessed using the Centre for Epidemiological Studies Depression Scale (CESD) at each round of data collection (every 2-5 years depending on the dataset)
2. Glucose level assessed using glycated hemoglobin test at each round of data collection (every 2-5 years depending on the dataset)
3. Hypertension assessed using blood pressure test (mmHg) at each round of data collection (every 2-5 years depending on the dataset)

Overall study start date

04/09/2019

Completion date

30/06/2024

Eligibility

Key inclusion criteria

Current inclusion criteria as of 28/12/2023:

The inclusion criteria are the same as those of the population studies included in EarlyCause:

1. Generation R: Population-based sample of children
2. ALSPAC: Born of a mother resident in former Avon health authority, expected date of delivery between 1st April 1991 and 31st December 1992
3. NFBCs: Pregnant mothers living in the two northernmost province of Finland (Oulu and Lapland). NFBC-1966 included all mothers with expected date of delivery between 1st of January to 31st December 1966 and their offspring with data at birth, 31 and 46 years of age. NFBC-1986 included mothers with expected date of delivery between July 1985 to June 1986 and their offspring with data at birth and 16 years of age.
4. Rotterdam Study: Adults >55 years
5. NESDA: Adults >18 years with DSM-IV diagnosis of depression (minor or major depression, dysthymia) or anxiety

Previous inclusion criteria:

The inclusion criteria are the same as those of the population studies included in EarlyCause:

1. Generation R, ALSPAC, NFBC: Healthy children at birth
2. Rotterdam: Adults > 55
3. NESDA: Adults > 18 with DSM-IV diagnosis of depression (minor or major depression, dysthymia) or anxiety

Participant type(s)

Mixed

Age group

Mixed

Sex

Both

Target number of participants

70,000

Key exclusion criteria

For NESDA, severe mental health (e.g. psychosis, bipolar disorder, obsessive-compulsive disorder, or severe addiction) or disability

Date of first enrolment

01/01/1966

Date of final enrolment

30/05/2020

Locations**Countries of recruitment**

England

Finland

Netherlands

United Kingdom

Study participating centre**Erasmus Medical Centre Rotterdam**

Doctor Molewaterplein 40

Rotterdam

Netherlands

3015 GD

Study participating centre**University of Oulu**

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Study participating centre**VU University Medical Center Amsterdam**

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Organisation
European Commission

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Sponsor type
Government

Website
http://ec.europa.eu/index_en.htm

ROR
<https://ror.org/00k4n6c32>

Funder(s)

Funder type
Government

Funder Name
Horizon 2020 Framework Programme

Alternative Name(s)

EU Framework Programme for Research and Innovation H2020, Horizon 2020, Rahmenprogramm Horizont 2020, Programa Marco Horizonte 2020, Programme-cadre Horizon 2020, Programma quadro Orizzonte 2020, Program ramowy Horyzont 2020, Horizont 2020, Horizonte 2020, Orizzonte 2020, Horyzont 2020, Horizon 2020 Framework Programme (H2020), H2020

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

Results and Publications

Publication and dissemination plan

Peer-reviewed international journals such as:
1. Journal of Developmental Origins of Health and Disease
2. International Journal of Epidemiology

Intention to publish date

30/06/2025

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to legal issues, consents and data policies of the included population studies.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file			07/08/2020	No	No
Protocol file			07/08/2020	No	No
Protocol article		21/01/2021	26/06/2024	Yes	No
Results article	Arterial Thickness, Stiffness, and Blood Pressure With Brain Morphology	09/11/2023	26/06/2024	Yes	No
Results article	Depression, cardiometabolic disease, and their co-occurrence after childhood maltreatment	13/03/2023	26/06/2024	Yes	No
Results article	Obesity	21/08/2023	26/06/2024	Yes	No
Results article	anorexia nervosa	01/11/2022	26/06/2024	Yes	No
Results article	depression prediction	03/04/2024	26/06/2024	Yes	No

Results article	early-life stress and adolescent psycho-physical health	01/05/2024	26/06/2024	Yes	No
Results article	maternal glycemic dysregulation during pregnancy and neonatal blood dna methylation	04/03/2022	26/06/2024	Yes	No
Results article	metabolic Syndrome	20/11/2023	26/06/2024	Yes	No
Results article	psycho-cardiometabolic multimorbidity	30/06/2023	26/06/2024	Yes	No