ISRCTN44060592 https://doi.org/10.1186/ISRCTN44060592

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

Submission date	Recruitment status	[_] Prospectively registered
29/06/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
15/07/2020	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
26/06/2024	Other	

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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Scientific

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Additional identifiers

Protocol serial number
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

Primary study design
Observational

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)

Study type(s)
Other

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(s)
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

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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)

Key secondary outcome(s)
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)

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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)

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 data 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

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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

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

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
United Kingdom

England

Finland

Netherlands

Study participating centre
Erasmus Medical Centre Rotterdam
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Study participating centre
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Sponsor information

Organisation
European Commission

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, Horizon 2020 Framework Programme (H2020), Rahmenprogramm Horizont 2020, Horizont 2020, Programa Marco Horizonte 2020, Horizonte 2020, Programme-cadre Horizon 2020, Orizzonte 2020, Programma quadro Orizzonte 2020, H2020

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

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?
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	maternal glycemic dysregulation during pregnancy and neonatal blood dna methylation	04/03	26/06	Yes	No

article		/2022	/2024		
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
Protocol article		21/01 /2021	26/06 /2024	Yes	No
Protocol file			07/08 /2020	No	No
Protocol file			07/08 /2020	No	No
Study website	Study website	11/11 /2025	11/11 /2025	No	Yes