Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	**Finanziato dall'Unione europea** NextGenerationEU
Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

1 - General information

Project code: PNRR-MAD-2022-12376416	**Project topic:** C1) Malattie croniche non trasmissibili, ad alto impatto sui sistemi sanitari e socio-assistenziali: fattori di rischio e prevenzione
	Applicant Institution: Lazio
PI / Coordinator: Cesaroni Giulia	**Istitution that perform as UO for UO1:** Department of Epidemiology-Regional Health Service, ASL Roma 1

Call section: Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e socio-assistenziali

Proposal title: Socio-Economic position and Multimorbidity in longitudinal studies: the mediation role of lifestyles, blood biomarkers and Microbiota (SEMM)

Duration in months: 24

MDC primary: Oncologia

MDC secondary: Cardiologia-Pneumologia

Project Classification IRG: Population Sciences and Epidemiology

Project Classification SS: Social Sciences and Population Studies - SSPS

Project Keyword 1: Mortality, health, functioning and disability; differentials, trends and projections for individuals, groups and populations; studies of perinatal, infants, child, adult and elderly health and mortality; interrelationships with demographic, social, economic, behavioral, and biobehavioral processes; health economics.

Project Request: **Animals:** ☐   **Humans:** ☒   **Clinical trial:** ☐

Project total financing request to the MOH: €   901.482

Free keywords: Multimorbidity, Socioeconomic Position, Microbiome, Longitudinal Studies, Mechanisms of Health inequality

Declarations

In case of a Synergy grant application 'Principal Investigator'(PI) means 'corresponding Principal Investigator on behalf of all Principal Investigators', and 'Host Institution' means 'corresponding Host Institution'.

1) The Principal Investigator declares to have the written consent of all participants on their participation and on the content of this proposal, as well as of any researcher mentioned in the proposal as participating in the project (either as other PI, team member or collaborator).	☒
2) The Principal Investigator declares that the information contained in this proposal is correct and complete.	☒
3) The Principal Investigator declares that all parts of this proposal comply with ethical principles (including the highest standards of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity — and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct).	☒
4) The Principal Investigator is only responsible for the correctness of the information relating to his/her own organisation. Each applicant remains responsible for the correctness of the information related to him and declared above.	☒

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Personal data protection

The assessment of your grant application will involve the collection and processing of personal data (such as your name, address and CV), which will be performed pursuant to Regulation (EC) No 45/2001 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data. Unless indicated otherwise, your replies to the questions in this form and any personal data requested are required to assess your grant application in accordance with the specifications of the call for proposals and will be processed solely for that purpose. Details concerning the purposes and means of the processing of your personal data as well as information on how to exercise your rights are available in the privacy statement. Applicants may lodge a complaint about the processing of their personal data with the European Data Protection Supervisor at any time.

Abstract

Life expectancy is increasing globally, but healthy life expectancy has not kept the same growing trend. Such a discrepancy is mainly attributable to the increased prevalence of chronic conditions and multimorbidity dramatically affecting the quality of life in the elderly.

Recent evidence highlights social inequalities in health, describing a clear gradient in the association of socioeconomic position (SEP) with chronic diseases, general health status, and mortality. However, the relationship between SEP and multimorbidity has not been fully characterised. Specifically, few studies have investigated the effect of SEP on multimorbidity using different SEP indicators and even less investigated the mediating role of lifestyle and -omic biomarkers. Recent theories of social to biological embedding suggest that social inequalities in health begin in early life; however, they become evident in older age when most diseases appear. The use of -omic biomarkers in epidemiological studies has been successfully applied for the stratification of individuals at high-risk years before the occurrence of the critical period. In this context, DNA methylation, gut microbiome, and gut metaproteome constitute optimal candidates because their changes reflect the effect of long-term exposure to lifestyle and environmental risk factors. Indeed, different measures of SEP have been associated with changes in DNA methylation and epigenetic biomarkers of biological ageing (epigenetic clocks) as well as gut microbiome composition, which are, in turn, associated with morbidity.

This project aims to provide a comprehensive characterisation of the association of SEP with multimorbidity, using different SEP indicators and lifestyle and -omic biomarkers as mediators. Specifically, we will investigate the role of different individual, area-based, and time-varying indicators of SEP in the development of multimorbidity. Further, we will investigate the role of occupational exposure in the relationship between SEP and multimorbidity, and socioeconomic factors associated with multimorbidity severity via survival analyses. At the same time, we will investigate the mediation role of lifestyle factors, epigenetic clocks, and changes in the gut microbiome and metaproteomic profiles to identify molecular/biological mechanisms behind the social gradient in multimorbidity and propose biomarkers for individual risk stratification.

We will use data from: 1) the Lazio Region Longitudinal Study, which includes all 5.5 million residents followed from the 2011 census of the population to 2022. The follow-up is conducted through record-linkage procedures with administrative databases (Health Information System with mortality, hospital discharges, pharmaceutical prescriptions, chronic conditions co-payment exemptions registries); and 2) the EPIC-Turin cohort, which includes 10,604 participants aged 35-65 recruited between 1993 and 1998. Study participants completed questionnaires on anthropometric measurement, diet, lifestyle and medical history at baseline and blood samples were collected and stored in liquid nitrogen containers. For the project about 500 EPIC subjects will be recalled and asked to provide a stool sample. EPIC-Turin has more than 20 years of follow up for cancer, diabetes, cardio and cerebrovascular diseases, and mortality. Further, the EPIC dataset is very rich in available biomarkers, including DNA methylation, blood biomarkers of inflammation, and metabolomic.

In order to best review your application, do you agree that the above non-confidential proposal title and abstract can be used, without disclosing your identity, when contacting potential reviewers? Yes

2 - Participants & contacts

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Operative Units

Institution that perform as UO	CF Institution	Department / Division / Laboratory	Role in the project	Southern Italy	SSN
1 - Department of Epidemiology-Regional Health Service, ASL Roma 1	13664791004	Department of Epidemiology-Regional Health Service	PI/CoPI/UO1		X
2 - University of Turin	80088230018	Dept. of Clinical and Biological Sciences, centre for biostatistics, epidemiology, and public health	UO2		
3 - Azienda Ospedaliera di Sassari	02268260904	Struttura Complessa Microbiologia e Virologia	UO3	X	X

Principal Research Collaborators

Key Personnel Name	Operative Unit	Role in the project
1 - AGABITI NERA	Department of Epidemiology-Regional Health Service, ASL Roma 1	CoPI
2 - Badaloni Chiara	Department of Epidemiology-Regional Health Service, ASL Roma 1	Research collaborator UO 1
3 - Uzzau Sergio	Azienda Ospedaliera di Sassari	UO 3 coordinator
4 - Ricceri Fulvio	University of Turin	UO 2 coordinator
5 - GIACHINO CLAUDIA	University of Turin	Research collaborator UO 2
6 Under 40 - Civra Andrea	University of Turin	Research collaborator UO 2
7 Under 40 - RONCHI GIULIA	University of Turin	Research collaborator UO 2

Key Personnel Name	Co-PI	Resp. CE	Resp. Animal	Birth Date	Gender
1 - AGABITI NERA	X			07/11/1959	F
2 - Badaloni Chiara				25/05/1977	F
3 - Uzzau Sergio				27/05/1967	M
4 - Ricceri Fulvio				26/11/1980	M
5 - GIACHINO CLAUDIA				04/11/1964	F
6 Under 40 - Civra Andrea				09/10/1984	M
7 Under 40 - RONCHI GIULIA				27/11/1982	F

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Additional research collaborators under 40 to hire

Key Personnel Name	Operative Unit	Birth Date	Gender	Role in the project	Degree	Actual Pos. and Inst.
0 - Abbondio Marcello	Azienda Ospedaliera di Sassari	17/11/1985	M	To sequence and analyze the microbiota samples	PhD	Post Doc, University of Sassari
1 - FIORITO GIOVANNI	Azienda Ospedaliera di Sassari	25/01/1985	M	Statistical analyses of epigenetic data, pre-processing and normalisation, differential analyses and dissemination of the results.	PhD	Fixed-term researcher (RTDa), University of Sassari

2.1 Administrative data of participating

Operative Unit Number 1:

Address: Dipartimento di Epidemiologia del Servizio Sanitario Regionale
ASL Roma 1
Via Cristoforo Colombo 112
00147 Roma
Italia

PEC: dir_dep@pec.deplazio.it

Operative Unit Number 2:

Address: Dipartimento di Scienze Cliniche e Biologiche - Centro di Biostatistica, Epidemiologia e Sanità Pubblica
Università di Torino
Regione Gonzole 10
10043 Orbassano (TO)
Italy
PEC: dscb@pec.unito.it

Operative Unit Number 3:

Address: Struttura Complessa Microbiologia e Virologia
Azienda Ospedaliera di Sassari
Viale San Pietro, 18
07100 Sassari
Italy
PEC: protocollo@pec.aou.ss.it

Operative Unit Number 4:

Address:

PEC:

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Operative Unit Number 5 (self financing):

Address:

PEC:

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.2 Principal Investigator (PI) Profile

Last Name: Cesaroni	**Last name at birth:**
First Name: Giulia	**Gender:** F

Title: Principal investigator   **Country of residence:** ITALY

Nationality: Italiana   **Country of Birth:** ITALY

Date of birth: 10/11/1965   **Place of Birth:** Roma

Official H index (Scopus or Web of Science): 43.0

Scopus Author Id:6602328018   **ORCID ID:**0000-0001-7361-9072   **RESEARCH ID:**K-1500-2016

Contact address

Current organisation name: Department of Epidemiology-Regional Health Service, ASL Roma 1

Current Department / Faculty / Institute / Laboratory name: Department of Epidemiology- Regional Health Service

Street: Via Cristoforo Colombo 112

Postcode / Cedex: 00147   **Town:** Roma

Phone:+393476455995   **Phone 2:**3476455995

Education / training

Educational institution and location	Degree	Field of study	From year	To year
London School of Hygiene and Tropical Medicine	Master's Degree / Laurea Magistrale	Epidemiology	2003	2004
Sapienza University of Rome	Specialization / Specializzazione	Medical Statistics	1995	1996
Sapienza University of Rome	Master's Degree / Laurea Magistrale	Mathematics	1987	1992

Personal Statement:

The project will study the association between socioeconomic position and multimorbidity and will investigate the mediation role of lifestyles, blood biomarkers and microbiome. As PI, she will have the responsibility of the distribution of the work and funds, the coordination of activities, the collection of results from all contributors and the release of intermediate and final reports. With a strong experience in analyzing cohort studies in the field of social and environmental epidemiology, she will be in charge of the analyses of the Lazio Region Longitudinal Study and of coordinating the work in UO 1.

Positions and honors

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Positions

Institution	Division / Research group	Location	Position	From year	To year
ASL Roma 1, Department of Epidemiology RHS	Health Status of Population	Rome	Epidemiologist	2019	2022
ASL Roma 1, Department of Epidemiology RHS	Etiological and Occupational Epidemiology	Rome	Epidemiologist	2006	2018
ASL Roma 1, Department of Epidemiology RHS	Clinical Epidemiology	Rome	Epidemiologist	2000	2005
Lazio Regional Health Authority	Health Information Systems	Rome	Research Fellow	1993	2000

Other awards and honors

2019 Commendatore della Repubblica Italiana (N 1451 Serie VI)

2018 Highly Cited Researcher (Web of Science)

2009 Best Paper Award, Circulation, for the paper: Effect of the Italian smoking ban on population rates of acute coronary events. Circulation. 2008; 1183-1188

2016-2018 Board of the Italian Association of Epidemiology

Other CV informations

She started her career as epidemiologist in the field of social epidemiology, then she moved to the field of environmental epidemiology, for going back to social epidemiology in recent years. She implemented, for the Lazio Region, the Rome Longitudinal Study, the cohort of residents in Rome followed from 2001 census through administrative databases. The study that became the Lazio Region Longitudinal Study and, since 2012 it is part of the National Statistical Programme. She has experience in international and national projects and in creating productive collaborations. She recently coordinated the UO 7 of the project COVID-2020-12371675

Selected peer-reviewed publications of the PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
An Italian network of population-based birth cohorts to evaluate social and environmental risk factors on pregnancy outcomes: The LEAP study	Article	NOT_FOUND	17	2020	10.3390/ijerph17103614	32455694	2	L
Air pollution and occurrence of type 2 diabetes in a large cohort study	Article	68-76	112	2018	10.1016/j.envint.2017.12.007	29253730	74	L
Mortality inequalities by occupational status and type of job in men and women: Results from the Rome Longitudinal Study	Article	NOT_FOUND	10	2020	10.1136/bmjopen-2019-033776	32499259	6	L
A cohort study on long-Term exposure to air pollution and incidence of liver cirrhosis	Article	NOT_FOUND	4	2020	10.1097/EE9.0000000000000109	NOT_FOUND	3	L
Exposure to residential greenness as a predictor of cause-specific mortality and stroke incidence in the rome longitudinal study	Article	NOT_FOUND	127	2019	10.1289/EHP2854	30775931	49	L
Mortality inequalities in rome: The role of individual education and neighbourhood real estate market	Article	31-37	44	2020	10.19191/EP20.5-6.S1.P031.071	33415944	1	F

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Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study	Article	NOT_FOUND	11	2012	10.1186/1476-069X-11-48	22808928	155	F
Sex differences in factors associated with heart failure and diastolic left ventricular dysfunction: a cross-sectional population-based study	Article	NOT_FOUND	21	2021	10.1186/s12889-021-10442-3	33639910	3	F
Long term exposure to ambient air pollution and incidence of acute coronary events: Prospective cohort study and meta-analysis in 11 european cohorts from the escape project	Article	NOT_FOUND	348	2014	10.1136/bmj.f7412	24452269	396	F
Educational Inequalities in COVID-19 Vaccination: A Cross-Sectional Study of the Adult Population in the Lazio Region, Italy	Article	NOT_FOUND	10	2022	10.3390/vaccines10030364	NOT_FOUND	0	F
Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome	Article	324-331	121	2013	10.1289/ehp.1205862	23308401	352	F
Residential exposure to air pollution and incidence of Parkinson¿s disease in a large metropolitan cohort	Article	e023	2	2018	10.1097/EE9.0000000000000023		0	L
Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study	Article	NOT_FOUND	18	2019	10.1186/s12940-019-0511-5	31399053	37	L
Development of land-use regression models for exposure assessment to ultrafine particles in Rome, Italy	Article	52-60	156	2017	10.1016/j.atmosenv.2017.02.028	NOT_FOUND	29	L
Incidence of SARS-CoV-2 Infection and Related Mortality by Education Level during Three Phases of the 2020 Pandemic: A Population-Based Cohort Study in Rome	Article	NOT_FOUND	11	2022	10.3390/jcm11030877	NOT_FOUND	1	L

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Selected peer-reviewed publications of the PI for the evaluation CV

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Exposure to residential greenness as a predictor of cause-specific mortality and stroke incidence in the rome longitudinal study	Article	NOT_FOUND	127	2019	10.1289/EHP2854	30775931	49
Air pollution and occurrence of type 2 diabetes in a large cohort study	Article	68-76	112	2018	10.1016/j.envint.2017.12.007	29253730	74
Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project	Article	NOT_FOUND	125	2017	10.1289/EHP1742	29033383	62
Particulate matter air pollution components and risk for lung cancer	Article	66-73	87	2016	10.1016/j.envint.2015.11.007	26641521	171
Long-term exposure to air pollution and cardiovascular mortality: An analysis of 22 European cohorts	Article	368-378	25	2014	10.1097/EDE.0000000000000076	24589872	188

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Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Long-term exposure to ambient air pollution and incidence of cerebrovascular events: Results from 11 European cohorts within the ESCAPE project	Article	919-925	122	2014	10.1289/ehp.1307301	24835336	219
Long term exposure to ambient air pollution and incidence of acute coronary events: Prospective cohort study and meta-analysis in 11 european cohorts from the escape project	Article	NOT_FOUND	348	2014	10.1136/bmj.f7412	24452269	396
Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project	Article	785-795	383	2014	10.1016/S0140-6736(13)62158-3	24332274	854
Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome	Article	324-331	121	2013	10.1289/ehp.1205862	23308401	352
Air pollution and lung cancer incidence in 17 European cohorts: Prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)	Article	813-822	14	2013	10.1016/S1470-2045(13)70279-1	23849838	922

** Autocertificated

Grant						
Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministry of Health	Dept. Epidemiology RHS	2014-2016	Long-term exposure to ambient air pollution and pregnancy outcomes in women of three large Italian longitudinal studies (RF-2011-02352442)	Coordinator	244.335,00	https://www.salute.gov.it/imgs/C_17_pagineAree_3878_listaFile_itemName_23_file.pdf
Ministry of Health	Department of Epidemiology RHS, ASL Rome 1	2019-2020	COVID19: epidemiological, clinical, genetic, and social determinants of infection and disease progression (COVID-2020-12371675)	Collaborator	570.830,00	https://www.salute.gov.it/imgs/C_17_bandi_216_3_file.pdf

Sent date: 07/07/2022 20.34

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.3 CO-PI Profile

Last Name: AGABITI	**Last name at birth:**
First Name: NERA	**Gender:** F

Title: CoPI

Nationality: Italiana

Date of birth: 07/11/1959

Country of residence: ITALY

Country of Birth: ITALY

Place of Birth: Cingoli

Official H index (Scopus or Web of Science): 36.0

Scopus Author Id: 13606076200   **ORCID ID:** 0000-0003-3385-1197   **RESEARCH ID:** K-1053-2016

Contact address

Current organisation name: Department of Epidemiology-Regional Health Service, ASL Roma 1

Current Department / Faculty / Institute / Laboratory name: Department of Epidemiology- Regional Health Service

Street: Via Cristoforo Colombo 112

Postcode / Cedex: 00147

Town: Roma

Phone: +393335083040

Phone 2: 3335083040

Education / training				
Educational institution and location	Degree	Field of study	From year	To year
University of Rome La Sapienza, Rome, Italy	Specialization / Specializzazione	Hygiene and Public Health	1997	2001
Catholic University , Rome, Italy	Specialization / Specializzazione	Respiratory Disease	1986	1989
Catholic University, Rome, Italy	Master's Degree / Laurea Magistrale	Medicine and Surgery	1978	1985

Personal Statement:

The project will investigate the association between SEP and multimorbidity, and will study the mediation effect of lifestyles, biomarkers and microbiome. The CoPI will support the coordination activities in all phases of the project. She is an epidemiologist with a background in medicine with large expertise in coordinating collaborative projects, promoting scientific research in the field of health care delivery and outcomes research, and implementing epidemiological studies on behalf of multidisciplinary teams.

The CoPI will contribute to the development of the study design, protocol definition, methodology and analysis plan, interpretation of results, reports and publications.

Positions and honors

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Positions

Institution	Division / Research group	Location	Position	From year	To year
Local Health Authority ASL Roma 1	Department of Epidemiology	Rome, Italy	Director Population Health Epidemiology Unit	2015	2022
Local Health Authority ASL Roma 1	Department of Epidemiology	Rome, Italy	Epidemiologist, senior researcher	2004	2015
Agency for Public Health Lazio Region	Hospital Care Service	Rome, Italy	Director Outcomes Research Unit	2001	2004
Local Health Authority ASL Roma E	Department of Epidemiology	Rome	Epidemiologist, senior researcher	1997	2001
Ente per le Nuove Tecnologie e l¿Ambiente (ENEA)	Environmental Epidemiology Unit	Rome, Italy	Epidemiologist	1996	1997

Other awards and honors

Coordinator of the Dialysis and Renal Transplantation Regional Register. Member of the following Lazio Region Committees: Piano Regionale Prevenzione 2021-2025; Obstructive Sleep Apnea Disordes; Metabolic Disorders; Alzheimer and other dementia. Member of the Scientific Committee of the Italian Arthroplasty Register. Reviewer for international scientific journals. Member of the Italian Epidemiology Association since 1995. Member of the Editorial Board of "Epidemiologia e Prevenzione".

Other CV informations

She started her career as a pneumologist and collaborated in clinical trials at Gemelli Hospital Catholic University, Rome. Since 1990 she has worked as an epidemiologist and completed her training in Hygiene and Public Health at University "La Sapienza" Rome. She participated in several collaborative international and national studies on respiratory and environmental epidemiology. Then she focussed on clinical epidemiology and contributed to developing the methodology of outcomes research, risk adjustment, and comparative effectiveness research using data from the health information systems. Main areas of interest: cardiovascular, respiratory, renal disease, socioeconomic health, health care inequity, health services research and outcomes research, and neurological degenerative diseases.

Selected peer-reviewed publications of the Co-PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Socioeconomic differences in one-year survival after ischemic stroke: The effect of acute and post-Acute care-pathways in a cohort study	Article	NOT_FOUND	16	2016	10.1186/s12889-016-3019-8	27184959	12	C
Polypharmacy in the elderly: A population based cross-sectional study in Lazio, Italy	Article	484-487	7	2016	10.1016/j.eurger.2016.05.008	NOT_FOUND	4	C
The tradeoff between travel time from home to hospital and door to balloon time in determining mortality among STEMI patients undergoing PCI	Article	NOT_FOUND	11	2016	10.1371/journal.pone.0158336	27336859	9	C
Thirty-day complications after laparoscopic or open cholecystectomy: A population-based cohort study in Italy	Article	NOT_FOUND	3	2013	10.1136/bmjopen-2012-001943	NOT_FOUND	17	F
Assessing the link between air pollution and heart failure	Note	1008-1010	382	2013	10.1016/S0140-6736(13)61167-8	23849323	24	L

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Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Idiopathic Pulmonary Fibrosis (IPF) incidence and prevalence in Italy	Article	191-197	31	2014	NOT_FOUND	25363218	32	F
Role of Tiotropium in Reducing Exacerbations of Chronic Obstructive Pulmonary Disease When Combined With Long-Acting ?<inf>2</inf>-Agonists and Inhaled Corticosteroids: The OUTPUL Study	Article	1423-1432	56	2016	10.1002/jcph.750	27095425	8	L
The impact of adherence to inhaled drugs on 5-year survival in COPD patients: a time dependent approach	Article	1295-1304	25	2016	10.1002/pds.4059	27396695	19	L
Inhaled Corticosteroid Use in Chronic Obstructive Pulmonary Disease and Risk of Pneumonia: A Nested Case-Control Population-based Study in Lazio (Italy)¿The OUTPUL Study	Article	311-317	14	2017	10.1080/15412555.2016.1254172	28406337	15	L
COPD and bronchodilators: should the heart pay the bill for the lung?	Review	NOT_FOUND	49	2017	10.1183/13993003.00370-2017	28536252	2	F
Age-related prevalence of non-cardiac surgery indications	Article	3-5	87	2017	10.4081/monaldi.2017.839	28967716	0	F
Determinants of venous catheter hemodialysis onset and subsequent switch to arteriovenous fistula: An epidemiological study in Lazio region	Article	749-758	22	2021	10.1177/1129729820959942	32993439	2	L
A&F to monitor and promote quality in healthcare during the covid-19 emergency: The easy-net work	Article	88-94	44	2020	10.19191/EP20.5-6.S2.106	33412798	0	F
Mortality inequalities in rome: The role of individual education and neighbourhood real estate market	Article	31-37	44	2020	10.19191/EP20.5-6.S1.P031.071	33415944	1	L

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Grant						
Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministry of Health and Regional Governments of Lazio, Friuli Venezia Giulia, Piemonte, Lombardia, Emilia Romagna, Calabria	ASL Roma 1	2019	Effectiveness of audit and feedback strategies to improve healthcare practice and equity in various clinical and organizational settings (NET-2016-02364191)	Coordinator	3.700.000,00	https://www.salute.gov.it/imgs/C_17_bandi_135_listaFile_itemName_6_file.pdf
Italian Medicines Agency ¿ Bando 2008	ASL Roma 1	2010	Esiti a lungo termine ed eventi avversi della terapia inalatoria cortisonici, long-acting beta2 agonisti ed anticolinergici in pazienti con BPCO studio di coorte basato su sistemi informativi sanitari in tre Regioni	Coordinator	175.332,00	https://www.aifa.gov.it/sites/default/files/bandi_2005-2009_al_28.01.2013.pdf

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	Finanziato dall'Unione europea NextGenerationEU
Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Italian Medicines Agency ¿ Lazio Region (Regione Lazio Pharmacovigilance Grant)	ASL Roma 1	2012	Trattamenti farmacologici per la Sclerosi Multipla: prevalenza d¿uso, analisi dei cambiamenti temporali, stima degli esiti ed eventi avversi in uno studio prospettico di popolazione nel Lazio	Coordinator	105.000,00	https://www.deplazio.net/images/stories/files/relazione_sclerosi-multipla.pdf
Ministry of Health	Presidio Nuovo Regina Margherita di Roma	2018	Implementazione del Presidio Nuovo Regina Margherita di Roma: sperimentazione del modello di Casa della Salute - ASL Roma 1	Coordinator	1.838.698,00	Bur Regione Lazio 24/05/2018 available at: https://sicer.regione.lazio.it/PublicBur/burl

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	**Finanziato dall'Unione europea** NextGenerationEU

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.3 Research Collaborators n. 2

Last Name: Badaloni		**Last name at birth:**	
First Name: Chiara		**Gender:** F	

Title: Research collaborator UO 1   **Country of residence:** ITALY

Nationality: Italiana   **Country of Birth:** ITALY

Date of birth: 25/05/1977   **Place of Birth:** Roma

Official H index (Scopus or Web of Science): 31.0

Scopus Author Id: 25122464100   **ORCID ID:** 0000-0003-3768-8841   **RESEARCH ID:** O-9750-2015

Contact address

Current organisation name: Department of Epidemiology-Regional Health Service, ASL Roma 1

Current Department / Faculty / Institute / Laboratory name: Department of Epidemiology- Regional Health Service

Street: Via Cristoforo Colombo 112

Postcode / Cedex: 00147   **Town:** Roma

Phone: +393475221388   **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Roma TRE University of Rome, Italy	Master's Degree / Laurea Magistrale	Geographic Information System for land use planning	2007	2008
La Sapienza University of Rome, Italy	Master's Degree / Laurea Magistrale	Sources, Tools and Methods for Social Research	2003	2005
La Sapienza University of Rome, Faculty of Statistical Science, Italy	Bachelor Degree / Laurea Triennale	Statistics, demography and environment	1996	2002

Personal Statement:

The project aims at investigating socioeconomic inequalities in multimorbidity. She will contribute to the analyses of the Lazio Region Longitudinal Study to fulfil the AIM 1 of the project. She have experience in the analysis of large administrative cohorts with a focus on both social and environmental exposures. She will support the PI and CoPI in conducting the project, in writing reports and papers, and in disseminating the results.

Positions and honors

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Positions

Institution	Division / Research group	Location	Position	From year	To year
ASL Roma 1	Department of Epidemiology - Lazio Region Health Service, Etiological and Occupational Epidemiology	Rome, Italy	Senior Statistician	2018	2022
ASL Roma 1	Department of Epidemiology - Lazio Region Health Service, Etiological and Occupational Epidemiology Unit	Rome, Italy	Statistician	2006	2018
Institute for Studies and Research on Civil Protection and Civil Defense. (ISPRO)	Statistical analysis	Rome, Italy	statistician	2006	2006
World Food Programme (W.F.P.)	Fund raising and communication Department, Donor relation	Rome, Italy	Regular Junior Consultant	2006	2006
World Food Programme (W.F.P.)	Administration Department, Human Resource Division	Rome, Italy	Regular Junior Consultant	2006	2006
World Food Programme (W.F.P.)	Fund raising and communication Department, Donor relation	Rome, Italy	Internship	2004	2005

Other awards and honors

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministero dell¿Ambiente e della Tutela del Territorio e del Mare	Dipartimento di Epidemiologia del SSR	20-22	Programma di valutazione epidemiologica della popolazione residente nel Sito di Interesse Nazionale (SIN) Valle del Sacco	Collaborator	960.000,00	https://www.deplazio.net/it/vai-alla-pagina-delle-news/468-valle-del-sacco-al-via-nuove-indagini-epidemiologiche

Sent date: 07/07/2022 20.34

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	**Finanziato dall'Unione europea** NextGenerationEU

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.4 Research Collaborators n. 3

Last Name: Uzzau	**Last name at birth:** uzzau
First Name: Sergio	**Gender:** M

Title: UO 3 coordinator   **Country of residence:** ITALY

Nationality: Italiana   **Country of Birth:** ITALY

Date of birth: 27/05/1967   **Place of Birth:** Sassari

Official H index (Scopus or Web of Science): 44.0

Scopus Author Id: 57195271769   **ORCID ID:** 0000-0001-6246-2794   **RESEARCH ID:** F-3233-2015

Contact address

Current organisation name: Azienda Ospedaliera di Sassari

Current Department / Faculty / Institute / Laboratory name: Struttura Complessa Microbiologia e Virologia

Street: sv rizzeddu-gioscari n.48, sv rizzeddu-gioscari n.48

Postcode / Cedex: 07100   **Town:** Sassari

Phone: +393337252753   **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Sassari, Italy	Specialization / Specializzazione	Clinical Microbiology	2002	2006
University of Pisa, Italy	PhD	Experimental and Medical Microbiology	1995	1998
Univesity of Sassari, Italy	Master's Degree / Laurea Magistrale	Medicine	1987	1992

Personal Statement:

The overall goals of this proposal are to identify the association between Socioeconomic Position (SEP) and multimorbidity, integrating life-style data and epigenetic and metabolic biomarkers. His responsibilities in this project will include the investigation of the gut microbiota structure and the relationships of its community members with the biological processes underneath the association between SEP and multimorbidity.

Positions and honors

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Positions

Institution	Division / Research group	Location	Position	From year	To year
Azienda Ospedaliera di Sassari	Microbiology and Virology	Sassari, Italy	Dirigente Medico - Clinical Microbiology	2020	2022
Università degli Studi di Sassari	Department of Biomedical Sciences	Sassari, Italy	Full Professor of Microbiology and Clinical Microbiology	2018	2022
Università degli Studi di Sassari	Department of Biomedical Sciences	Sassari, Italy	Associate Professor of Microbiology and Clinical Microbiology	2005	2018
Università degli Studi di Sassari	Department of Biomedical Sciences	Sassari, Italy	Assistant Professor of Microbiology and Clinical Microbiology	2002	2005
Azienda Ospedaliera Universitaria di Sassari	Microbiology and Virology	Sassari, Italy	Dirigente Medico - Clinical Microbiology	2002	2005
Centre National de la Recherche Scientific (CNRS)	Centre de Genetique Moleculaire	Gif-sur-Yvette, France	Chercheur Associè - Molecular Microbiologist	2000	2001
University of Sassari	Dipartimento di Scienze Biomediche	Sassari, Italy	Research Fellow - Molecular Microbiologist	1997	1999
University of Maryland	Division of Pediatrics Gastroenterology and Nutrition - Alessio Fasano Lab	Baltimore, MD, USA	Assistant Professor	1995	1997
University of Maryland	Center for Vaccine development	Baltimore, MD, USA	Research Fellow	1994	1995
Stanford University	Department of Microbiology and Immunology - Bruce A.D. Stocker Lab	Stanford, CA, USA	Post Doctoral Fellow	1993	1994

Other awards and honors

1990. Nato/Embo fellowship (Spetses Summer School)

1995. Mead and Johnson Award (A.G.A. Conference Award)

2001. FEMS fellowship - Visiting Scientist

2010. Sardinian Region award for research 2010

2013. Ministry for Education, University and Research - Habilitation as Full Professor 07/H3, Animal Infectious Diseases

2014. Sardinian Region award for research 2014

2014. Ministry for Education, University and Research - Habilitation as Full Professor 06/A3, Microbiology and Clinical Microbiology

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Fondazione di Sardegna	University of Sassari	2021	Controllo della diffusione di nuovi ceppi virali di SARS-CoV-2 in Sardegna mediante sequenziamento e genotipizzazione rapida	Coordinator	70.000,00	https://scienzebiomediche.uniss.it/it/ricerca/principali-progetti-di-ricerca/altri-progetti

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Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MIUR	University of Sassari	2016	Pathology in automated traceable healthcare - MIUR PON04a2_00557	Collaborator	2.070.000,00	https://www.crs4.it/it/projectdetails/c53c36ee-e349-1033-8a7a-0030485a3848/
Fondazione di Sardegna	University of Sassari	2021	Identificazione di profili tassonomici e funzionali del microbiota intestinale in soggetti affetti da tiroidite cronica autoimmune e ipotiroidismo	Coordinator	20.000,00	https://www.aousassari.it/documenti/11_591_20220126155711

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	**Finanziato dall'Unione europea** NextGenerationEU

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.5 Research Collaborators n. 4

Last Name: Ricceri

First Name: Fulvio

Last name at birth:

Gender: M

Title: UO 2 coordinator

Nationality: Italiana

Date of birth: 26/11/1980

Country of residence: ITALY

Country of Birth: ITALY

Place of Birth: Torino

Official H index (Scopus or Web of Science): 50.0

Scopus Author Id: 24482495400   **ORCID ID:** 0000-0001-8749-9737   **RESEARCH ID:** I-9910-2018

Contact address

Current organisation name: University of Turin

Current Department / Faculty / Institute / Laboratory name: Dept. of Clinical and Biological Sciences, centre for biostatistics, epidemiology, and public health

Street: Regione Gonzole 10

Postcode / Cedex: 10045   **Town:** Orbassano

Phone: +393298963487   **Phone 2:** +393298963487

Education / training				
Educational institution and location	Degree	Field of study	From year	To year
University of Turin	PhD	Biomedical Sciences, Human Oncology,Human Genetics	2009	2012
ISI Foundation and University of Turin	Master's Degree / Laurea Magistrale	Epidemiology and Statistics (thesis in molecular epidemiology)	2007	2008
University of Turin	Master's Degree / Laurea Magistrale	Mathematics (Algebra, Geometry, Calculus with a thesis in algebraic statistics)	1999	2005

Personal Statement:

The overall goal of the project is to evaluate the association between SEP and multimorbidity, evaluating the mediation role of several biomarkers. Fulvio Ricceri, thanks to his mathematical and biomedical background will contribute to the progress of the project coordinating the molecular epidemiological analysis. Moreover, he is the co-PI of the EPIC-Turin study and will be responsible for the recall of subjects. He will be also involved in the interpretation of results and dissemination.

Positions and honors

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità	Finanziato dall'Unione europea NextGenerationEU

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Turin	Department of Clinical and Biological Sciences	Orbassano (TO), Italy	Associate professor	2021	2022
University of Turin	Department of Clinical and Biological Sciences	Orbassano (TO), Italy	Assistant professor (RTD-B)	2018	2021
University of Turin	Department of Clinical and Biological Sciences	Orbassano (TO), Italy	Post Doc (Social and Molecular Epidemiology)	2016	2018
University of Turin	Department of Economics and Statistics ¿Cognetti de Martiis¿	Turin (Italy)	Post Doc (Social epidemiology)	2015	2016
Città della Salute e della Scienza Hospital	Unit of cancer epidemiology	Turin (Italy)	Research fellow (molecular epidemiology)	2014	2015
Ordine Mauriziano Hospital	Health management unit	Turin (Italy)	Research fellow (clinical epidemiology)	2012	2013
Human Genetic Foundation	Unit of molecular and genetics epidemiology	Turin (Italy)	Research fellow	2011	2012

Other awards and honors

Member of the Research Commission, department of Clinical and Biological Sciences, 2018-ongoing

Chair of the Socioeconomical Factors and Health working group, steering committee of the European Prospective Investigation into Cancer and Nutrition EPIC study 2019-ongoing

Chair of the group Health of immigrant and migrant health, Epidemiology Italian Association (AIE), 2021-ongoing

Board Member of the Epidemiology Italian Association (AIE), 2018-2021

Winner of the Anglesio-Moroni prize (2006)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Compagnia di San Paolo (TRAPEZIO) / Italy	University of Turin	2022	ULYSSES ¿ sUpport through an artificiaL intelligence sYstem for helping cancer-SurvivorS to succEsSfully return to work	Coordinator	100.000,00	ttps://www.compagniadisanpaolo.it/it/contributi/trapezio-paving-the-way-to-research-excellence-and-talent-attraction/#1623315232073-4a03ba2e-a3bc
Compagnia di San Paolo and University of Turin (ex-post) /Italy	University of Turin	2020	Work after cancer for young adults	Coordinator	51.896,00	https://www.unito.it/ricerca/finanziamenti-la-ricerca/ricerca-nazionale-e-regionale/progetti-finanziati-da-compagnia-san

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministry of University (PRIN) / Italy	University of Turin	2020	SOcial and health Frailty as determinants of Inequality in Aging. (SOFIA)	Collaborator	692.409,00	https://www.mur.gov.it/it/atti-e-normativa/decreto-direttoriale-n-222-del-18-02-2022

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Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.6 Research Collaborators n. 5

Last Name: GIACHINO	**Last name at birth:** Giachino
First Name: CLAUDIA	**Gender:** F

Title: Research collaborator UO 2 **Country of residence:** ITALY

Nationality: Italiana **Country of Birth:** SWITZERLAND

Date of birth: 04/11/1964 **Place of Birth:** Zurigo

Official H index (Scopus or Web of Science): 27.0

Scopus Author Id:35593442300 **ORCID ID:**0000-0001-7957-3925 **RESEARCH ID:**M-1894-2019

Contact address

Current organisation name: University of Turin

Current Department / Faculty / Institute / Laboratory name: Dept. of Clinical and Biological Sciences, centre for biostatistics, epidemiology, and public health

Street: Regione Gonzole No 10

Postcode / Cedex: IT-10043 **Town:** Orbassano

Phone:+393337811229 **Phone 2:**

Education / training				
Educational institution and location	Degree	Field of study	From year	To year
University of Turin, Turin, Italy	PhD	Biomedical Sciences, Human Oncology,Human Genetics	1992	1995
University of Turin, Turin, Italy	Master's Degree / Laurea Magistrale	Biomedical Sciences, Molecular Biology, Cellular Biology	1984	1989

Personal Statement:

The overall goal of the project is to evaluate the association between SEP and multimorbidity, evaluating the mediation role of several biomarkers. Claudia Giachino, thanks to her molecular biology and human genetics background, will contribute to the progress of the project and will lead the bio-molecular analyses on blood biomarkers. She will be also involved in the interpretation of results and dissemination.

Positions and honors

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Turin	Department of Clinical and Biological Sciences/	Turin, Italy	Full Professor, Head	2021	2022
University of Turin	Department of Clinical and Biological Sciences/Translational Research Center for Innovative Medicine	Turin, Italy	Coordinator	2020	2022
University of Turin	Department of Clinical and Biological Sciences/Human Genetics research group	Turin, Italy	Associate Professor, Head	2006	2020
University of Turin	Department of Clinical and Biological Sciences/Molecular Biology research group	Turin, Italy	Assistant Professor, Head	1999	2005
IRCCS Maugeri Foundation	Experimental Immunology research group	Pavia, Italy	Head	1998	2003

Other awards and honors

Roche Prize for Immunological Research, 1996

Joseph Wang Award for publications in the Nanoscience field, 2016

1st Discoveries Entrepreneurship Prize in Regenerative Medicine, Porto, Portugal, 2019

PUBLICATION AWARDS:

-"Inside" LAB INVEST. For the novelty and perspectives of the described features, 2003

-"In this issue" Journal of Investigative Dermatology, 2003

MEMBER of: SCIENTIFIC COMMITTEE of SCIENZA NUOVA Institute, since 2021; TURIN UNIVERSITY PATENT COMMITTEE, since 2019

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MISE-ICE-CRUI/Italy	University of Turin	2010	Bio-nano-technologies for regenerative medicine	Coordinator	125.000,00	https://www.clubimpreseinnovative.it/internazionalizzazione-bando-2010-mise-ice-crui/
Veronesi Foundation/Italy	University of Turin	2013	DNA repair capacity, telomere length and epigenetic changes as aging biomarkers in bladder cancer.	Collaborator	19.166,67	https://www.fondazioneveronesi.it/la-fondazione/news-dalla-fondazione/online-i-vincitori-delle-borse-di-ricerca-e-dei-progetti-2013

Ministero della Salute	Finanziato dall'Unione europea
Direzione generale della ricerca e dell'innovazione in sanità	NextGenerationEU

PNRR: M6/C2_CALL 2022 Full Proposal

Project Code:	PNRR-MAD-2022-12376416	**Call section:**	Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution:	Lazio	**Applicant/PI Coordinator:**	Cesaroni Giulia

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
POR-FESR 2014-2020 BIOPMED INNOVATION CLUSTER, PIEDMONT REGION/UE-Italy	University of Turin	2013	MAIN-CARD: Sviluppo di materiali polimerici iniettabili per la rigenerazione cardiaca	Collaborator	20.000,00	https://www.regione.piemonte.it/web/temi/fondi-progetti-europei/fondo-europeo-sviluppo-regionale-fesr/ricerca-sviluppo-tecnologico-innovazione/pass-programmi-accesso-servizi-qualificati-studi-fattibilita
POR-FESR 2014-2020 BIOPMED INNOVATION CLUSTER, PIEDMONT REGION/UE-Italy	University of Turin	2015	ADI-STEM: Un innovativo sistema integrato di concentrazione cellulare da tessuto adiposo e chip per controllo di qualità	Collaborator	17.000,00	https://www.regione.piemonte.it/web/temi/fondi-progetti-europei/fondo-europeo-sviluppo-regionale-fesr/ricerca-sviluppo-tecnologico-innovazione/pass-programmi-accesso-servizi-qualificati-studi-fattibilita
CRT foundation/Italy	University of Turin	2015	Micro-nanovettori a rilascio di farmaco capaci di superare la barriera mucosa per un efficace trattamento della Fibrosi Cistica	Coordinator	38.000,00	https://www.fondazionecrt.it/progetti-e-bandi/?_categories=ricerca-e-istruzione
European Union M-ERAnet/EU	University of Turin	2018	INCIPIT: INtegrated Conductive and biomimetic polymeric Interfaces able to serve as micro-nanostructured Patches for myocardIal regeneration	Collaborator	79.727,73	https://m-era.net/joint-calls/joint-call-2016/results-of-m-
Compagnia di San Paolo and University of Turin (ex-post) /Italy	University of Turin	2019	EMPIR	Coordinator	50.000,00	https://www.unito.it/sites/default/files/esito_bando_sanpaolo2018_ex_post.pdf
Fondazione PRIMASPES/Italy	University of Turin	2019	Interfacce polimeriche biomimetiche e conduttive integrate in gradi di svolgere la funzione di `patch¿ micro-nanostrutturati per la rigenerazione del miocardio	Coordinator	18.000,00	http://www.fondazioneprimaspes.org/it/4/progetti-finanziati.html
Italian Ministry of Health-Progetti ordinari di Ricerca Finalizzata/Italy	University of Turin	2020	Association of paid work	Collaborator	82.600,00	https://www.salute.gov.it/imgs/C_17_bandi_208_8_file.pdf

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Compagnia di San Paolo-LIFTT PoC INSTRUMENT/Italy	University of Turin	2021	IMPAVID: A polymeric scaffold for cardiac regeneration and protection from reperfusion injury	Coordinator	48.900,00	https://linksfoundation.com/wp-content/uploads/2020/09/Cut-off-II-Graduatoria-pubblica_agg.pdf

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.7 Research Collaborators n. 6 - Under 40

Last Name: Civra		**Last name at birth:**	
First Name: Andrea		**Gender:** M	

Title: Research collaborator UO 2

Nationality: Italiana

Date of birth: 09/10/1984

Country of residence: ITALY

Country of Birth: ITALY

Place of Birth: Torino

Official H index (Scopus or Web of Science): 19.0

Scopus Author Id: 26538625200   **ORCID ID:** 0000-0003-1837-3342   **RESEARCH ID:** NA

Contact address

Current organisation name: University of Turin

Current Department / Faculty / Institute / Laboratory name: Dept. of Clinical and Biological Sciences, centre for biostatistics, epidemiology, and public health

Street: Regione Gonzole 10

Postcode / Cedex: 10043

Phone: +393493669279

Town: Orbassano

Phone 2: 3493669279

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Turin	PhD	Experimental Medicine and Therapy	2011	2014
University of Turin	Master's Degree / Laurea Magistrale	Biotechnology	2006	2008
University of Turin	Bachelor Degree / Laurea Triennale	Biotechnology (Laboratory of Molecular Virology and Antivirals Research, Department of Clinical and Biological Sciences of the University of Turin)	2004	2006

Personal Statement:

The project aims at investigating the association between socioeconomic position and multimorbidity.
Dr Civra will support UO 2 in dealing with microbioma data due to his expertise in microbiology.

Positions and honors

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Turin	Laboratory of Molecular Virology and Antivirals Research, Department of Clinical and Biological Sciences	Orbassano (Turin), ITALY	Lecturer (i.e. fixed-term researcher of type B) in Microbiology and Clinical Microbiology (SSD MED / 07).	2021	2022
Regional Agency for Environmental Protection (ARPA) of Piedmont	Environmental Protection	Turin, Italy	Consultant	2021	2022
University of Turin	Laboratory of Molecular Virology and Antivirals Research, Department of Clinical and Biological Sciences	Orbassano (Turin), ITALY	Lecturer (i.e. fixed-term researcher of type A) in Microbiology and Clinical Microbiology (SSD MED / 07).	2019	2021
Panoxyvir Ltd.	Academic spin-off of the University of Turin. This start-up company aims to develop wide-spectrum antivirals.	Turin, ITALY	Co-founder and CTO	2016	2022
University of Turin	Laboratory of Molecular Virology and Antivirals Research, Department of Clinical and Biological Sciences of the University of Turin	Orbassano (Turin), ITALY	Post-doctoral research associate	2015	2019

Other awards and honors

1.   Shortlist of the best PhD Alumni of the University of Turin

2.   As founder of Panoxyvir Ltd: Leonardo Startup Award (2018), Prize of Prizes (2017), National Award for Innovation (2016), StartCup Piedmont and Val D'Aosta Award (2016), Winner of Bioupper, the Italian platform for entrepreneurial acceleration for innovative ideas in the medical field (2016).

3.   Desenzano Young Scientist Award at the first Congress Italian experience in biomedical research: young minds at work (2013).

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Fondazione CRT	University of Turin	2020	New antiviral strategies for coronavirus epidemics: validation of the protective activity of oxysterols and preclinical development	Coordinator	35.000,00	https://www.fondazionecrt.it/

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	**Finanziato dall'Unione europea** NextGenerationEU

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.8 Research Collaborators n. 7 - Under 40

Last Name: RONCHI	**Last name at birth:**
First Name: GIULIA	**Gender:** F

Title: Research collaborator UO 2

Nationality: Italiana

Date of birth: 27/11/1982

Country of residence: ITALY

Country of Birth: ITALY

Place of Birth: Vimercate

Official H index (Scopus or Web of Science): 21.0

Scopus Author Id: 24074868100   **ORCID ID:** 0000-0002-4795-7024   **RESEARCH ID:** J-4785-2018

Contact address

Current organisation name: University of Turin

Current Department / Faculty / Institute / Laboratory name: Dept. of Clinical and Biological Sciences, centre for biostatistics, epidemiology, and public health

Street: Regione Gonzole 10

Postcode / Cedex: 10043   **Town:** Orbassano

Phone: +393460254251   **Phone 2:**

Education / training				
Educational institution and location	Degree	Field of study	From year	To year
University of Turin, Turin, Italy	PhD	Neuroscience	2009	2012
University of Turin, Turin, Italy	Master's Degree / Laurea Magistrale	Neurobiology	2005	2007
University of Milano-Bicocca, Milano, Italy	Bachelor Degree / Laurea Triennale	Biology (Neuroscience)	2001	2005

Personal Statement:

The objective of the project is to investigate the association between socioeconomic position and multimorbidity, and the mediation role of lifestyles, biomarkers, and microbiome. Thanks to her biological background she will contribute to the analysis and interpretation of the items related to biomarkers.

Positions and honors

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Applicant Institution: Lazio		**Applicant/PI Coordinator:** Cesaroni Giulia	

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Turin	Department of Clinical and Biological Sciences	Orbassano (Turin), ITALY	Associate Professor BIO/16 (Human Anatomy)	2021	2022
University of Turin	Department of Clinical and Biological Sciences	Orbassano (Turin), ITALY	Assistant Professor (RTD-B)	2018	2021
University of Turin	University of Turin Department of Clinical and Biological Sciences	Orbassano (Turin), ITALY	Senior Research Fellow (RTD-A)	2017	2018
University of Turin	Department of Clinical and Biological Sciences	Orbassano (Turin), ITALY	Post-doctoral fellowship recipient	2013	2017
University of Turin	Department of Clinical and Biological Sciences	Orbassano (Turin), ITALY	Fellowship recipient	2006	2008

Other awards and honors

- Individual grants for young researchers to attend the following congresses:
1. PNS Meeting, Quebec City, Canada, Jun 2015
2. 15th ISNR, Pacific Grove, California USA, Dec 2013
3. XXII GISN, Bologna, Nov 2012
4. 8th FENS, Barcelona, Spain Jul 2012
5. 8th IBRO, Florence, Jul 2011
6. 7th FENS, Amsterdam, Jul 2010
7. XIV SINS, Milan, Oct 2009
- 2021-present: Editorial Board Member of Micro
- 2017-present: Youth Editorial Board Member of Neural Regeneration Research

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
			No grants available	Collaborator	0,00	

Sent date: 07/07/2022 20.34

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Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.9 Additional Research Collaborators n. 2 - Under 40 to hire

Last Name: Abbondio	**Last name at birth:**
First Name: Marcello	**Gender:** M

Title: To sequence and analyze the microbiota samples   **Country of residence:** ITALY

Nationality: Italiana   **Country of Birth:** ITALY

Date of birth: 17/11/1985   **Place of Birth:** Sassari

Official H index (Scopus or Web of Science): 9.0

Scopus Author Id: 56690543700   **ORCID ID:** 0000-0003-2126-4817   **RESEARCH ID:** NA

Contact address

Current organisation name: Azienda Ospedaliera di Sassari

Current Department / Faculty / Institute / Laboratory name: Struttura Complessa Microbiologia e Virologia

Street: Viale San Pietro 43

Postcode / Cedex: 07100   **Town:** Sassari

Phone: +393405812273   **Phone 2:**

Education / training				
Educational institution and location	Degree	Field of study	From year	To year
University of Sassari, Sassari, Italy	PhD	Life Sciences and Biotechnologies (Microbiology, Metagenomics, Metaproteomics)	2014	2018
University of Sassari, Sassari, Italy	Master's Degree / Laurea Magistrale	Biotechnology (thesis in chemistry and neurosciences)	2008	2011
University of Sassari, Sassari, Italy	Bachelor Degree / Laurea Triennale	Biotechnology (thesis in biochemistry and molecular biology)	2004	2008

Personal Statement:

The overall goal of the project is to study the association between socioeconomic position and multimorbidity, investigating the mediation of several biomarkers, including the microbiota. Dr. Marcello Abbondio, thanks to his experience in metagenomic sequencing and analysis, will contribute to the progress of the project by sequencing and analyzing the microbiota samples.

His scientific activity has resulted in 20 scientific publications in peer-reviewed international journals.

Positions and honors

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Sassari	Department of Biomedical Sciences of the University of Sassari	Sassari, Italy	Post Doc (Microbiology)	2018	2022
Istituto Zooprofilattico Sperimentale della Sardegna	C.Re.N.M.O.C. National Reference Center for Sheep and Goat Mastitis	Sassari, ITALY	Research fellow	2017	2018
Porto Conte Ricerche	Proteomics Laboratory	Alghero (SS), ITALY	Research fellow	2014	2015
Porto Conte Ricerche	Proteomics Laboratory	Alghero (SS), ITALY	Research fellow	2013	2014
Sardegna Ricerche	Biosistema S.c.r.l. ¿ Consorzio per le Biologie Avanzate	Alghero (SS), ITALY	Research training	2012	2013

Other awards and honors

Selected for EuPA Young Investigator Poster Prize session at the 9th Annual Congress European Proteomics Association (2015).

Dr. Marcello Abbondio is also Review Editor in Infectious Agents and Disease for Frontiers journals.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
			No grants available	Collaborator	0,00	

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.10 Additional Research Collaborators n. 3 - Under 40 to hire

Last Name: FIORITO

First Name: GIOVANNI

Last name at birth:

Gender: M

Title: Statistical analyses of epigenetic data, pre-processing and normalisation, differential analyses and dissemination of the results.

Nationality: Italiana

Date of birth: 25/01/1985

Country of residence: ITALY

Country of Birth: ITALY

Place of Birth: Torino

Official H index (Scopus or Web of Science): 27.0

Scopus Author Id: 55359650800   **ORCID ID:** 0000-0002-7651-5452   **RESEARCH ID:** NA

Contact address

Current organisation name: Azienda Ospedaliera di Sassari

Current Department / Faculty / Institute / Laboratory name: Struttura Complessa Microbiologia e Virologia

Street: Via Padre Manzella

Postcode / Cedex: 10137   **Town:** Sassari

Phone: +393405255785   **Phone 2:**

Education / training				
Educational institution and location	Degree	Field of study	From year	To year
University of Torino, Torino, Italy	PhD	Complex Systems for Life Sciences (Biostatistics, System Biology)	2012	2016
University of Torino, Torino, Italy	Master's Degree / Laurea Magistrale	Mathematics	2009	2011
University of Torino, Torino, Italy	Bachelor Degree / Laurea Triennale	Mathematics	2005	2008

Personal Statement:

The project aims to investigate the association between Socioeconomic Position (SEP) and multimorbidity and evaluate the mediating role of several biomarkers, including blood DNA methylation.

Giovanni Fiorito has substantial experience in analysing multi-omic datasets and epigenetic biomarkers of biological ageing (epigenetic clocks). He will be in charge of the statistical analyses of epigenetic data, including pre-processing and normalisation, differential analyses and results interpretation. He will also be involved in the dissemination of the project results.

Positions and honors

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| **Applicant Institution:** Lazio | **Applicant/PI Coordinator:** Cesaroni Giulia |

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Sassari	Department of Biomedical Sciences	Sassari, Italy	Fixed-term researcher (RTDa)	2019	2022
Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Toscana	`Cancer Risk Factors and life-style epidemiology¿ research group	Firenze, Italy	Research fellow	2019	2019
Italian Institute for Genomic Medicine (IIGM)	`Molecular epidemiology and exposomics¿ unit	Torino, Italy	Post Doc (Biostatistics and molecular epidemiology)	2017	2019
University of Turin	Department of Medical Sciences	Torino, Italy	Post Doc (Biostatistics and molecular epidemiology)	2016	2017

Other awards and honors

2022 National Scientific Habilitation for the s.s.d 06/M1: `General and applied hygiene, nursing sciences and medical statistics.¿

2020 Honorary position at the School of Public Health, Imperial College, London.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
EU	Imperial College London	2015-2019	Lifepath: Healthy Ageing for all	Collaborator	0,00	https://www.lifepathproject.eu/

Ministero della Salute		Finanziato dall'Unione europea NextGenerationEU
Direzione generale della ricerca e dell'innovazione in sanità		
PNRR: M6/C2_CALL 2022 Full Proposal		

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

2.17 Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators									
Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Uzzau Sergio	Evaluating the impact of different sequence databases on metaproteome analysis: Insights from a lab-assembled microbial mixture	Article	NOT_FOUND	8	2013	10.1371/journal.pone.0082981	24349410	71	L
Uzzau Sergio	Genetic variants regulating immune cell levels in health and disease	Article	242	155	2013	10.1016/j.cell.2013.08.041	24074872	200	O
Uzzau Sergio	A straightforward and efficient analytical pipeline for metaproteome characterization	Article	49	2	2014	10.1186/s40168-014-0049-2	25516796	58	L
Uzzau Sergio	Enrichment or depletion? The impact of stool pretreatment on metaproteomic characterization of the human gut microbiota	Article	3474-3485	15	2015	10.1002/pmic.201400573	25677681	49	L
Uzzau Sergio	The impact of sequence database choice on metaproteomic results in gut microbiota studies	Article	NOT_FOUND	4	2016	10.1186/s40168-016-0196-8	27671352	61	L
FIORITO GIOVANNI	Social adversity and epigenetic aging: A multi-cohort study on socioeconomic differences in peripheral blood DNA methylation	Article	NOT_FOUND	7	2017	10.1038/s41598-017-16391-5	29176660	75	F
FIORITO GIOVANNI	Socioeconomic position, lifestyle habits and biomarkers of epigenetic aging: A multi-cohort analysis	Article	2045-2070	11	2019	10.18632/aging.101900	31009935	56	F
FIORITO GIOVANNI	Determinants of accelerated metabolomic and epigenetic aging in a UK cohort	Article	NOT_FOUND	19	2020	10.1111/acel.13149	32363781	26	O
FIORITO GIOVANNI	GrimAge Outperforms Other Epigenetic Clocks in the Prediction of Age-Related Clinical Phenotypes and All-Cause Mortality	Article	741-749	76	2021	10.1093/gerona/glaa286	33211845	36	O
FIORITO GIOVANNI	DNA methylation-based biomarkers of aging were slowed down in a two-year diet and physical activity intervention trial: the DAMA study	Article	NOT_FOUND	20	2021	10.1111/acel.13439	34535961	0	F

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
RONCHI GIULIA	Acylated and unacylated ghrelin impair skeletal muscle atrophy in mice	Article	611-622	123	2013	10.1172/JCI39920	23281394	131	O
RONCHI GIULIA	Chitosan-film enhanced chitosan nerve guides for long-distance regeneration of peripheral nerves	Article	33-51	76	2016	10.1016/j.biomaterials.2015.10.040	26517563	111	O
RONCHI GIULIA	The Neuregulin1/ErbB system is selectively regulated during peripheral nerve degeneration and regeneration	Article	351-364	43	2016	10.1111/ejn.12974	26061116	32	F
RONCHI GIULIA	Irreversible changes occurring in long-term denervated Schwann cells affect delayed nerve repair	Article	843-856	127	2017	10.3171/2016.9.JNS16140	28059646	28	F
RONCHI GIULIA	The role of dietary nutrients in peripheral nerve regeneration	Article	NOT_FOUND	22	2021	10.3390/ijms22147417	34299037	5	L
Civra Andrea	Additives for vaccine storage to improve thermal stability of adenoviruses from hours to months	Article	NOT_FOUND	7	2016	10.1038/ncomms13520	27901019	51	O
Civra Andrea	Antiviral oxysterols are present in human milk at diverse stages of lactation	Article	NOT_FOUND	193	2019	10.1016/j.jsbmb.2019.105424	31302219	13	F
Civra Andrea	25-Hydroxycholesterol and 27-hydroxycholesterol inhibit human rotavirus infection by sequestering viral particles into late endosomes	Article	318-330	19	2018	10.1016/j.redox.2018.09.003	30212801	34	F
Civra Andrea	The cholesterol metabolite 27-hydroxycholesterol inhibits SARS-CoV-2 and is markedly decreased in COVID-19 patients	Article	NOT_FOUND	36	2020	10.1016/j.redox.2020.101682	32810737	29	O
Civra Andrea	SARS-CoV-2 and indoor/outdoor air samples: a methodological approach to have consistent and comparable results	Article	NOT_FOUND	195	2021	10.1016/j.envres.2021.110847	33556355	19	L
Badaloni Chiara	Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome	Article	324-331	121	2013	10.1289/ehp.1205862	23308401	352	O
Badaloni Chiara	Long term exposure to ambient air pollution and incidence of acute coronary events: Prospective cohort study and meta-analysis in 11 european cohorts from the escape project	Article	NOT_FOUND	348	2014	10.1136/bmj.f7412	24452269	396	O

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Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Badaloni Chiara	Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project	Article	785-795	383	2014	10.1016/S0140-6736(13)62158-3	24332274	854	O
Badaloni Chiara	Morbidity and mortality of people who live close to municipal waste landfills: A multisite cohort study	Article	806-815	45	2016	10.1093/ije/dyw052	27222499	33	O
Badaloni Chiara	Effects of long-term exposure to particulate matter and metal components on mortality in the Rome longitudinal study	Article	146-154	109	2017	10.1016/j.envint.2017.09.005	28974306	50	F
AGABITI NERA	Occurrence of inflammatory bowel disease in central Italy: A study based on health information systems	Article	777-782	46	2014	10.1016/j.dld.2014.04.014	24890621	39	O
AGABITI NERA	Prevalence of multiple sclerosis in the Lazio region, Italy: use of an algorithm based on health information systems	Article	751-759	263	2016	10.1007/s00415-016-8049-8	26886201	33	O
AGABITI NERA	Anticholinergic Medication Burden and 5-Year Risk of Hospitalization and Death in Nursing Home Elderly Residents With Coronary Artery Disease	Article	1056-1059	17	2016	10.1016/j.jamda.2016.07.012	27590402	33	O
AGABITI NERA	Air pollution and occurrence of type 2 diabetes in a large cohort study	Article	68-76	112	2018	10.1016/j.envint.2017.12.007	29253730	74	O
AGABITI NERA	Immigrants¿ health and socioeconomic inequalities of overall population residing in Italy: Evaluated through the Italian network of longitudinal metropolitan studies	Article	1-80	43	2019	10.19191/EP19.5-6.S1.112	31744272	19	F
Ricceri Fulvio	454 Pyrosequencing Analysis on Faecal Samples from a Randomized DBPC Trial of Colicky Infants Treated with Lactobacillus reuteri DSM 17938	Article	NOT_FOUND	8	2013	10.1371/journal.pone.0056710	23468874	74	O
Ricceri Fulvio	Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data	Article	NOT_FOUND	349	2014	10.1136/bmj.g4164	25011450	420	O

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Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Ricceri Fulvio	Socioeconomic status and the 25?×?25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women	Article	1229-1237	389	2017	10.1016/S0140-6736(16)32380-7	28159391	484	O
Ricceri Fulvio	Risk of second primary malignancies in women with breast cancer: Results from the European prospective investigation into cancer and nutrition (EPIC)	Article	940-948	137	2015	10.1002/ijc.29462	25650288	44	F
Ricceri Fulvio	Lifestyle factors and risk of multimorbidity of cancer and cardiometabolic diseases: A multinational cohort study	Article	31918762	18	2020	10.1186/s12916-019-1474-7	31918762	39	O
GIACHINO CLAUDIA	High basal gamma H2AX levels sustain self-renewal of mouse embryonic and induced pluripotent stem cells	Article	1414-1423	30	2012	10.1002/stem.1133	22628289	55	L
GIACHINO CLAUDIA	Persistent DNA damage-induced premature senescence alters the functional features of human bone marrow mesenchymal stem cells	Article	734-743	19	2015	10.1111/jcmm.12387	25619736	40	L
GIACHINO CLAUDIA	Survey and summary multiple facets of histone variant H2AX: A DNA double-strand-break marker with several biological functions	Article	2489-2498	43	2015	10.1093/nar/gkv061	25712102	207	L
GIACHINO CLAUDIA	Senescence in human mesenchymal stem cells: Functional changes and implications in stem cell-based therapy	Article	1164	17	2016	10.3390/ijms17071164	27447618	243	L
GIACHINO CLAUDIA	Dual Role of Autophagy in Regulation of Mesenchymal Stem Cell Senescence	Article	276	8	2020	10.3389/fcell.2020.00276	32391362	15	L
Abbondio Marcello	Metaproteogenomics reveals taxonomic and functional changes between cecal and fecal microbiota in mouse	Article	391	8	2017	10.3389/fmicb.2017.00391	28352255	38	O
Abbondio Marcello	Potential and active functions in the gut microbiota of a healthy human cohort	Article	NOT_FOUND	5	2017	10.1186/s40168-017-0293-3	28709472	65	O
Abbondio Marcello	Caloric restriction promotes rapid expansion and long-lasting increase of Lactobacillus in the rat fecal microbiota	Article	104-114	9	2018	10.1080/19490976.2017.1371894	28891744	35	O

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Abbondio Marcello	Caloric restriction promotes functional changes involving short-chain fatty acid biosynthesis in the rat gut microbiota	Article	NOT_FOUND	8	2018	10.1038/s41598-018-33100-y	30283130	34	O
Abbondio Marcello	Fecal metaproteomic analysis reveals unique changes of the gut microbiome functions after consumption of sourdough Carasau bread	Article	-	10	2019	10.3389/fmicb.2019.01733	31417524	12	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

3 - Ethics

1. HUMAN EMBRYOS/FOETUSES	
Does your research involve Human Embryonic Stem Cells (hESCs)?	No
Does your research involve the use of human embryos?	No
Does your research involve the use of human foetal tissues / cells?	No
2. HUMANS	
Does your research involve human participants?	Yes
Does your research involve physical interventions on the study participants?	Yes
3. HUMAN CELLS / TISSUES	
Does your research involve human cells or tissues (other than from Human Embryos/ Foetuses?	Yes
4. PERSONAL DATA	
Does your research involve personal data collection and/or processing?	Yes
Does your research involve further processing of previously collected personal data (secondary use)?	Yes
5. ANIMALS	
Does your research involve animals?	No
6. ENVIRONMENT & HEALTH and SAFETY	
Does your research involve the use of elements that may cause harm to the environment, to animals or plants?	No
Does your research deal with endangered fauna and/or flora and/or protected areas?	No
Does your research involve the use of elements that may cause harm to humans, including research staff?	No

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7. DUAL USE	
Does your research involve dual-use items in the sense of Regulation 428/2009, or other items for which an	No
8. EXCLUSIVE FOCUS ON CIVIL APPLICATIONS	
Could your research raise concerns regarding the exclusive focus on civil applications?	No
9. MISUSE	
Does your research have the potential for misuse of research results?	No
10. OTHER ETHICS ISSUES	
Are there any other ethics issues that should be taken into consideration? Please specify	No
I confirm that I have taken into account all ethics issues described above and that, if any ethics issues apply, I will complete the ethics self-assessment and attach the required documents.	X

4 - Call-specific questions

Eligibility	
I acknowledge that I am aware of the eligibility requirements for applying as specified in the Call-PNRRXXXX_M6/C2, and certify that, to the best of my knowledge my application is in compliance with all these requirements. I understand that my proposal may be declared ineligible at any point during the evaluation or granting process if it is found not to be compliant with these eligibility criteria.	X
I confirm that the proposal that I am about to submit draws substantially don't repeat on an existing or recently finished GRANT funded.	X
Data-Related Questions and Data Protection (Consent to any question below is entirely voluntary. A positive or negative answer will not affect the evaluation of your project proposal in any form and will not be communicated to the evaluators of your project.)	
For communication purposes only, the MoH asks for your permission to publish,in whatever form and medium, your name, the proposal title, the proposal acronym, the panel, and host institution, should your proposal be retained for funding.	X
Some national and regional public research funding authorities run schemes to fund MoH applicants that score highly in the MoH's evaluation but which can not be funded by the MoH due to its limited budget. In case your proposal could not be selected for funding by the MoH do you consent to allow the MoH to disclose the results of your evaluation (score and ranking range) together with your name, non- confidential proposal title and abstract, proposal acronym, host institution and your contact details to such authorities?	X

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The MoH is sometimes contacted for lists of MoH funded researchers by institutions that are awarding prizes to excellent researchers. Do you consent to allow the MoH to disclose your name, non-confidential proposal title and abstract, proposal acronym, host institution and your contact details to such institutions?	X
The Ministry of Health occasionally could contacts Principal Investigators of funded proposals for various purposes such as communication campaigns, pitching events, presentation of their project's evolution or outcomes to the public, invitations to represent the Ministry of Health in national and international forums, studies etc. Should your proposal be funded, do you consent to the Ministry of Health staff contacting you for such purposes?	X

For purposes related to monitoring, study and evaluating implementation of MoH actions, the MoH may need that submitted proposals and their respective evaluation data be processed by external parties. Any processing will be conducted in compliance with the requirements of Regulation 45/2001.

5 – Description Project

Summary description

Multimorbidity, defined as the coexistence of two or more chronic diseases, is a growing phenomenon, representing a global public health challenge as populations age rises and access to therapies enables the survival of critical patients. Susceptibility to more than one disease might be due to several factors, including genetic background, lifestyle, and environment. Socioeconomic position (SEP) might significantly affect the homeostatic interaction between human metabolism, gut microbiota, immunity and inflammation, and epigenetic control.
This study will investigate the association between SEP and the acquisition of multimorbidity. We will explore the biological basis underneath this relationship by integrating lifestyle data and a wide array of functional data originating from the individual metabolism and immunity (blood biomarkers), genome-wide DNA methylation, and the gut microbiota.

Background / State of the art

Multimorbidity is a challenge for healthcare systems worldwide. With the increase in life expectancy, the prevalence of chronic conditions and multimorbidity is dramatically rising, affecting the quality of life, increasing premature death, loss of physical functioning, and hospitalisation.
While the association between SEP and chronic disease is established, only a few studies examined its association with multimorbidity. The results suggested that SEP and lifestyles could be the main determinants of the increase of multimorbidity in the population. However, most of those studies focused on one measure of SEP only, did not stratify by age and gender, and did not consider the mediation effect of lifestyle and biomarkers.
Recent evidence showed an influence of SEP in -omic biomarkers, including methylation and gut microbiota (hereafter GM). In particular, alpha-diversity, which measures the variety of microbial species (richness) and their relative abundance within the community (evenness), has increased as SEP increases, both at the individual and neighbourhood levels. Moreover, intestinal bacteria composition, generally measured through beta-diversity, has been found to differ among subjects with different SEP, with a greater abundance of some genera (e.g., Bacteroides) and a lower abundance of others (e.g., Prevotella) in individuals with higher SEP. This observation supports the hypothesis that GM could be a mediator in the association between SEP and multimorbidity.

Description and distribution of activities of each operating unit

Three units with complementary expertise (social and molecular epidemiology, medicine, biology, microbiology, statistics, and methodology) will conduct the project.

The Unit leading the project is the Department of Epidemiology of Regional Health Service (DEP, UO 1), ASL Roma 1. DEP

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has the role, among the structure of Regional Health Services, of evaluating health services and conducting research in etiological, environmental, occupational, and clinical epidemiology. Several projects have been conducted at DEP regarding health inequality, in particular considering how and why disadvantaged people are more at risk of chronic diseases. In addition, at DEP, the Lazio Region Longitudinal Study is available, and the researchers involved in the project have worked intensively with these data, as demonstrated by their publication.

The Department of Clinical and Biological Sciences (DCSB, UO 2) is one of the medical and biological departments of the University of Turin. At DSCB researchers worked on studies on the cellular and genetic-molecular mechanisms that regulate the physiology of the human organism, and on their interactions with environmental and cultural factors, as determinants of the state of health and disease. The Group of Biostatistics, Epidemiology, and Public Health is one of the groups of DCSB where several studies on social and molecular epidemiology have already been conducted. The Unit responsible is the co-PI of the EPIC-Turin study.

The unit of Microbiology and Virology of the AOU Sassari Hospital (AOUSS, UO 3) has a strong expertise in the analysis of the gut microbiota structure and functional features, having several funded projects on that topic. At AOUSS there are all the facilities needed for the `omic analyses of complex microbial communities. Moreover, the researchers that will be recruited for the project can contribute both at laboratory and at statistical level; in fact they already possess multi-year experience in these fields.

In particular, UO 1 will be responsible for the coordination of the project and will lead the analyses on the longitudinal studies. Together with UO 2, they will provide algorithms to define multimorbidity and will study and eventually develop the methodology for the analyses. U2 will be responsible for the recall of the EPIC-Turin cohort and will lead the epigenomic analyses. UO 3 will be responsible for the microbiota analyses, carrying out the laboratory assessment and their interpretation.

The three units together will include all the required experiences (social and molecular epidemiology, medicine, biology, statistics, and mathematics) to carry out the project under the coordination role of DEP. During the entire length of the project, results will be shared within the 3 units that are already profitably collaborating in other projects.

5.4 Specific Aims and Experimental Design

Specific aim 1

The first aim of the project is to evaluate the association between socioeconomic position and multimorbidity, specifically:

1.1 To evaluate the role of different individual and area-based indicators of socioeconomic position in the development of multimorbidity.
1.2 To evaluate the role of baseline socioeconomic position vs. time-varying indicators of socioeconomic disadvantage during the follow-up.
1.3 To investigate occupational sectors associated with multimorbidity.
1.4 To investigate the mediation role of occupation in the relationship between socioeconomic position and multimorbidity.
1.5 To study the socioeconomic factors associated with multimorbidity's severity and outcomes (mortality and hospitalisations).
The data are from the Lazio Region Longitudinal Study, which includes all 5.5 million residents followed from the 2011 census of the population to 2022. The follow-up is conducted through record-linkage procedures with administrative databases (Health Information System with mortality, hospital discharges, pharmaceutical prescriptions, chronic conditions co-payment exemptions registries).

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Several indices of baseline socioeconomic position are available: from the census (individual education, occupational status, housing conditions), a deprivation index at the census block level, and an indicator of the wealth of the residential neighbourhood. Moreover, income-related co-payment exemption during the follow-up will allow for identifying periods of severe economic disadvantage. The record linkage with the National Social Insurance Agency (INPS) database will allow for investigating the role of occupational sectors, related occupational exposures, and intervals of unemployment.

First, we will define multimorbidity as the occurrence of two conditions among cancer, cardiovascular diseases, and diabetes, which are the leading causes of death in high-income countries. Then we will add neurological, respiratory, and kidney diseases. Finally, we will use the record linkage with ESRD (End Stage Renal Disease) Registry and Regional Cancer Registry to better characterize the multimorbid population.

Specific aim 2

Integrated analyses of gut microbiota and DNAm to generate functional data for the SEP-multimorbidity association studies

We hypothesise that integrated analyses of gut microbiota (GM) and host methylome might help elucidate biological mechanisms behind social gradient on multimorbidity. In fact, the GM synthesises a variety of metabolites serving as epigenetic substrates, co-factors or regulators of epigenetic enzyme activity, including DNA or histone modifications. The assortment of these metabolites is expected to be partly specific for each individual, according to the structure of the microbial communities and their metabolic response to external stimuli (food, inflammation, host metabolism). In addition, intrinsic molecules associated with bacterial taxa have a proinflammatory role, and DNAm changes also accompany the host immune response.

We will produce new data on GM structures matched with already existent DNA methylation profiles in the EPIC Turin cohort. This cohort includes 10,604 participants aged 35-65 and cancer-free at data collection (between 1993 and 1998). Eligible participants gave written informed consent and completed questionnaires on diet, lifestyle, anthropometric measurements, and medical history at baseline. Blood samples were collected for all the participants and stored in liquid nitrogen. EPIC Turin has more than 20 years of follow up for cancer, diabetes, cardio e cerebrovascular diseases and mortality. Further, the EPIC dataset is very rich in the measurement of biomarkers. A large number of inflammatory, metabolic syndrome, and insulin resistance markers in different case-control studies nested in the cohort (on breast, lung, colon cancers, and cardiovascular diseases) and sub-cohort of about 500 healthy subjects have been previously measured. Finally, in more than 900 individuals from case-control studies, a blood DNA methylation wide scan has been already performed (Illumina 450k array), and epigenetic biomarkers of ageing (epigenetic clocks) have been computed. All EPIC-Turin patients with two or more chronic conditions after recruitment and a subsample of healthy subjects will be invited to participate in a new wave of the study with a case-cohort design. In particular, about 1,200 EPIC Turin participants will be invited to fix a hospital appointment with the goal of 50% participation (about 500-600 subjects). Participants will complete a self-administered questionnaire, have new anthropometric measurements, and blood and stool samples will be retrieved. Stool samples will be used to obtain the GM profiles via 16S rRNA gene sequencing analysis. DNA will be extracted, and the V4 region of the 16S rRNA gene will be amplified. After library preparation and sequencing, 16S rRNA gene reads will be subjected to taxonomic annotation through bioinformatic tools, and amplicon sequence variants will be inferred. Further, faecal samples will be subjected to functional profiling through shotgun metaproteomic analysis. Proteins will be extracted from the stool and undergo on-filter reduction, alkylation, and trypsin digestion. Finally, peptides will be separated by long-gradient liquid chromatography and analysed by high-resolution mass spectrometry. Mass spectrometry data will undergo bioinformatic processing, enabling the identification of peptide sequences and their taxonomic and functional annotation. Blood samples will be used to perform genome-wide DNA methylation measurements with the Illumina EPIC array. Part of the already characterised sample (Illumina 450k array) will be re-analysed using the Illumina EPIC array for calibration to make new measurements comparable to those already existent. The Illumina EPIC array is an improved version of the Illumina 450k offering comprehensive coverage of genes, 95% CpG islands, and enhancer regions. The epigenetic next generation measurements of biological age (epigenetic clocks and epigenetic drift) will be computed using up-to-date algorithms.

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Specific aim 3

In this third step, we aim to disentangle the effect of Socioeconomic Position (SEP) on multimorbidity by possible mediators (lifestyle and blood biomarkers) using the EPIC cohort.

The specific objectives are:
3.1 To investigate the association between SEP and multimorbidity taking into account the mediation role of lifestyle and already measured blood biomarkers.
3.2 To investigate the association between SEP and the microbiome.
3.3 To investigate the association between SEP and multimorbidity taking into account the mediation role of the microbiome.
3.4 To investigate the association between SEP and multimorbidity taking into account the mediation role of the epigenetic clocks.

The socioeconomic position has been extensively reported to have a fundamental role in developing chronic conditions, however, its role in developing multimorbidity is still under-investigated. Understanding which factors play a role in the increasing prevalence of multimorbidity is fundamental to effectively addressing this challenging condition. To understand the complex relationship between SEP and multimorbidity, mediation analysis is an essential tool due to its capability in separating the total effect of SEP into an effect that directly acts from SEP to multimorbidity and an indirect effect that goes through intermediate factors. Those intermediate factors are modified by SEP and could influence multimorbidity. Understanding such mechanisms is important because it could highlight possible solutions to inequality in health.

The EPIC-Turin Cohort will be used to achieve the four specific objectives. This cohort includes information about SEP and lifestyle for more than 10.000 subjects and in subsamples, blood biomarkers have been already measured. Furthermore, information collected in Aim 2 about the microbiota and epigenetic clocks will be used.

Methylation and metabolomic biomarkers (already measured for other funded projects), and lifestyle factors (such as smoking, alcohol, diet, and obesity) will be included to achieve the first objective. The lifestyle factors are available for the Turin cohort and there is the opportunity to extend the analysis to all the European EPIC cohorts, with information about multimorbidity for approximately 280 000 subjects.

To achieve the second objective, we will use information from the gut microbiota (GM) analysis carried out in aim 2. Approximately 500 subjects from the EPIC-Turin cohort will be included. Different measures will be used to describe the GM (such as cumulative measurements: alpha and beta diversity, and other specific features: relative abundance of microbial taxa, protein families, metabolic pathways, etc.), allowing us to identify any differences and similarities both in the variety of microbial species and in their functions among subjects from different socioeconomic positions, evaluating how SEP impacts the human GM. The use of different SEP measurements (father¿s occupation, and subject¿s education and occupation) will help in distinguishing between the GM components that depend on early and recent SEP exposure.

To achieve the third and fourth objectives, mediation analysis will be performed. Firstly, the GM will be considered a possible mediator of the association between SEP and multimorbidity, using the results from aim 2 and the previous objective. This analysis will be conducted on the 500 subjects included in aim 2. Secondly, the mediation role of epigenetic clocks will be investigated. Data already available from previously analysed epigenetic clocks will be used together with data from aim 2 (in which epigenetic clocks will be conducted on approximately 300 subjects).

Experimental design aim 1

The study population will include the entire population of the Lazio Region at the last population census (2011), followed through administrative databases until 2022 using a cohort design. All data is anonymised and linkable through an identifier on regional servers, under strict procedures to protect individual privacy. Baseline health status and conditions during the follow-up will be assessed through validated or commonly used algorithms (Marino et al 2020; Di Domenicantonio et al. 2018; Bargagli et al 2016; www.dep.lazio.it/prevale2021/) using all available health databases and registries. Multimorbidity will be defined using the definition by Freisling et al (2020): "Incident multimorbidity of cancer and

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cardiometabolic diseases was defined as developing subsequently two diseases including first cancer at any site, CVD, and T2D in an individual". Moreover, a broader definition including neuro-degenerative, mental, pulmonary diseases, and others will be used.

First (Aim 1.1), we will evaluate the association between several individual and area-based indices of SEP and the development of multimorbidity. Individual indicators will include education, occupational status, type of occupation (blue/white collar), family composition (available from the census), and severe economic disadvantage (available from the co-payment exemptions registry). The geocoding of all Lazio Region addresses (Mataloni et al. 2022) will allow to attribute to each subject several area-based indicators: the national deprivation index at the census block level (Rosano et al. 2020); the average real estate price at the neighbourhood level (Cesaroni et al. 2020), or aggregate measures of socioeconomic characteristics of the area (unemployment rate, % migrants, % of low educated, etc.). Since each indicator represents different aspects of socioeconomic position (Galobardes et al. 2007), disentangling the role of each socioeconomic indicator will allow us to better understand the process and underlying mechanisms of multimorbidity development, and to identify possible actions to reduce inequalities.

For Aim 1.2, we will evaluate the impact of adverse events during the follow-up on multimorbidity. The possible individual indicators of disadvantage during the follow-up are: the acquisition of a copayment exemption for severe economic disadvantage, the loss of job for private sector workers, available from data retrieved in an ongoing project (www.bigepi.it); the change of residence from a high SEP area to a deprived area; and finally, for the subpopulation of residents in Rome (2.5 million subjects), the changes in family structure (separation or widowhood). We will study the association between downward trajectories in SEP and multimorbidity.

The record-linkage with data from the National Social Insurance Agency will allow us to characterise each private-sector worker with occupational sector, and relative exposures, since the 70s and during the follow-up. The private sector workers are 43% of the adult population of Rome, presumably the percentage is higher than 43% for the entire region. The occupational sectors will be classified in 23 categories, with homogeneous exposures. Both baseline occupational sector, which is also available from the census for a small sample of the population only, and occupational sector during the follow-up will be analysed in relation to multimorbidity. Clusters of chronic conditions related to each sector will be evaluated, such as the association between sector of employment and incidence of multimorbidity (Aim 1.3). We will evaluate the role of occupational exposure in the association between SEP and multimorbidity (Aim 1.4) and the role of both SEP and occupational sector in the severity and outcomes of multimorbidity (Aim 1.5). We will assess the severity of a disease using individual drug prescriptions, hospitalizations, emergency room visits, and mortality data.

Experimental design aim 2

To generate functional data for the SEP-multimorbidity association studies, we propose to integrate analyses of gut microbiota (GM) and host methylome. We will to investigate GM taxonomy and functional features by means of metaproteogenomic analytical pipelines, previously applied by our group in pre-clinical and clinical studies related to autoimmune, cancer, and other chronic diseases (Tanca et al 2018; Bibbò et al 2020; Tanca et al 2022). Strong relationships occur between microbial moieties and regulators of epigenetic enzyme activities, due to continuous activities of individual GM functions. Besides, a variety of microbial associated molecular patterns (MAMPs) have a proinflammatory role and, in turn, host response is associated to DNAm changes (Bierne et al. 2012). Hence, GM analyses will be integrated with the investigation of host methylome variations.

Functional analyses will be performed by Unit 3 on samples collected from EPIC-Turin patients with two or more chronic conditions and a subsample of healthy subjects recruited in a new study wave with a case-cohort design. EPIC recruitment will be performed by Unit 2 using the same protocol used for the first wave. Details will be provided in section 5.5.1. Collected stool samples and previously stored (at the time of recruitment in the EPIC study) blood samples will be sent in dry ice to Unit 3 for microbiota and epigenetic analyses. New measurements of DNA methylation will include a re-analysis of 50 samples previously characterised for calibration.

DNA and protein extraction will be performed randomly to control possible biases related to reagents, extraction, and analysis batches. DNA will be extracted with QIAamp Fast DNA Stool Mini Kit (Qiagen), and the variable region 4 of the

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small subunit ribosomal rRNA will be amplified. Illumina amplicon libraries will be prepared following the "16S Metagenomic Sequencing Library Preparation protocol" and sequenced with an Illumina MiSeq sequencer in paired-end modality. 16S rRNA gene sequencing reads will undergo bioinformatic analysis to filter low-quality reads, assemble read pairs, remove chimaeras, and infer the amplicon sequence variants (ASV)s present. ASVs will be taxonomically annotated with the reference sequence database SILVA to obtain the microbiota composition profile. Stools will also be subjected to functional profiling through shotgun metaproteomic analysis to compare functional features of GM in patients according to their SEP. Proteins will be extracted from stool (Tanca et al. 2014) and undergo on-filter reduction, alkylation, and trypsin digestion (Wi¿niewski et al. 2009). Peptides will be separated by long gradient liquid chromatography and analysed by high-resolution mass spectrometry. Mass spectrometry data will undergo specific bioinformatic processing (Tanca et al. 2016; Singh et al. 2019; Cantalapiedra et al. 2021), enabling the identification of peptide sequences taxonomic and functional annotation.

Blood samples will be subjected to genomic DNA extraction with DNeasy Blood and Tissue Kit (Qiagen). DNA extracts will be subjected to bisulfite conversion using the EZ-96 DNA Methylation-Gold¿ Kit (Zymo Research) on 500 ng of each sample. Then, bisulfite-converted DNA will be subjected to DNAm profiling using the Illumina Infinium Methylation EPIC Beadchip array, consisting of around 850,000 CpG sites over all the genome. The arrays will be washed and scanned using the Illumina iScan System. Data pre-processing, quality control and batch effect removal will be performed according to standardised epigenome-wide association studies (EWAS) procedures. DNAm analyses on bisulfite-converted DNA samples will be performed as an external service.

Experimental design aim 3

The general goal of this aim is to provide evidence supporting the causal mechanisms that link together SEP and multimorbidity risk. This evidence will benefit from the use of the full EPIC-Turin cohort (described in the previous aims) where several information about intermediate variables is available. In fact, for more than 10,000 subjects, information about lifestyles, dietary habits, environmental exposures, and clinical factors are available and their role as mediators of the association between SEP and multimorbidity could be investigated. Moreover, for this purpose, a request to use the EPIC-Europe full data (more than 280,000 subjects with data on multimorbidity available) has already been submitted by Unit 2 and has been recently approved by the EPIC-Europe Steering committee. Definition of multimorbidity is the same provided in aim 1, based on follow-up assessment.

Moreover, in the subset of subjects for which biomarkers of ageing (epigenetic clock) and/or data on gut microbiota are available, the study of the causal mechanisms will be enriched by this biological information.

Since SEP does not act directly on the genesis of morbidities, we will investigate through proper mediation analyses if some portion of the associations observed in the previous objectives between SEP and multimorbidity may be explained by differences in intermediate variables, including lifestyles, dietary habits, environmental exposures, and clinical factors (cohort approach) as well as gut microbiome and epigenetic clock (case-cohort approach). Indeed, in the context of social epidemiology, increasing interest has been focused on the mechanisms through which social adversity may get biologically embedded.

Firstly, individual and environmental exposures will be considered as possible mediators of the association between SEP and multimorbidity; secondly, using the results from aim 2 the mediation role of gut microbiome and epigenetic clocks will be investigated. Available confounders of the following associations: exposure-mediator, mediator-outcome, exposure-outcome, identified in previous aims and objectives will be included in the analyses.

Mediation analyses will be performed through the counterfactual approach (VanderWeele 2014) that allows the presence of nonlinearities and interactions between exposure and mediator. In the counterfactual framework, the total effect of the exposure on the outcome can be disentangled in pure direct (PDE) and total indirect (TIE) effects. PDE is the effect of the exposure on the outcome, not mediated by the mediator, and TIE is the effect of the exposure on the outcome mediated by the mediator. Different counterfactual methods have been already developed for the most common types of outcomes in epidemiology, such as continuous, binary, and survival variables (VanderWeele 2015): Fasanelli et al. (Fasanelli 2019) adapted to non-rare time-to-event outcomes the approaches proposed by VanderWeele involving specific weights. To make

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results more comprehensible, PDE and TIE will be combined into a measure called ¿proportion mediated¿ which expresses the extent to which the total effect of the exposure on the outcome operates through the mediator (VanderWeele 2015). To be able to give a causal interpretation to direct and indirect effects, the aforementioned approach requires all the confounders of the following associations: exposure-outcome, exposure-mediator, and mediator-outcome, to be included in the analysis. In presence of unmeasured potential confounders, sensitivity analyses (VanderWeele 2015) will be performed to assess the extent to which the missing variables would have influenced the obtained results.

Picture to support preliminary data

Figura.pdf

Hypothesis and significance

The sixth mission (Health) of the National Recovery and Resilience Plan (NRRP) is devoted to the promotion of research for the national health system. Moreover, the recently published National Plan for Research and the National Plan for Health Research included the research on ageing among the urgent relevant topics, due to the impact on a part of the population that is steadily increasing. The SEMM project will tackle one of the main problems of unhealthy ageing, namely multimorbidity, which is the major contributor to years of potential life lost and to years lived with disability.
While the association between SEP and the prevalence of individual chronic diseases is well established, only few studies have examined its association with multimorbidity. However, those few studies identified a clear involvement of SEP in the development of multiple chronic conditions in the same subject. For this reason, it is increasingly recognized that health inequalities exist between several comorbidities and are amplified in populations that face structural, political and social vulnerabilities. This association is particularly relevant for public health because socioeconomic circumstances and their consequences are modifiable through policies at several levels (local, national, and international).
To propose new policies, however, it is important to identify the mechanisms through which SEP influences multimorbidity, in order to promote targeted interventions for prevention in subjects at higher risk of unhealthy ageing. This is in line with the fifth mission of the NRRP (inclusion and cohesion) where it is pointed out a need for specific interventions in vulnerable populations. The SEMM project will take advantage of the longitudinal studies¿ data and of the lifestyle and biomarkers information of the EPIC-Turin cohort. The project will provide substantial evidence to explain the pathways involved in the mechanisms of unhealthy and unfair ageing in disadvantaged populations. Several mechanisms will be tested, including the role of modifiable risk factors (smoking, diet, obesity, physical activity,...) and those of blood biomarkers. The latter are particularly important to identify earlier markers of multimorbidity risk. Moreover, the new and challenging hypothesis that the gut microbiota could have a role in those pathways will be tested in the SEMM project. At the moment, only few studies investigated the relationship between SEP and individual microbiota, but the results are promising and it is reasonably conceivable that microbiota is a mediator of the SEP/multimorbidity relationship.
In conclusion, the SEMM project is based on challenging but robust hypotheses and, in accordance to the NRRP missions, it will contribute to identify lifestyle habits, blood biomarkers, and gut microbiota features that should be monitored in order to build fairer ageing strategies and tailored interventions.

5.5 Methodologies and statistical analyses

Methods of data collection

The Lazio Region Longitudinal Study is the administrative cohort of the residents in the Lazio Region at the last population census (9/10/2011) followed through administrative databases. The Regional Health Information System includes Hospital Discharge Register, Mortality Register, Pharmaceutical Prescriptions, and Co-payment Exemption Register (for chronic conditions). Are all accessible using SAS on regional servers. Using validate algorithms, it is possible to identify specific comorbid conditions at the baseline and during the follow-up. The data are stored in the Lazio Region servers and anonymized. The record linkage between archives is possible through an identifier in all databases.
The EPIC-Turin study has already recruited 10,604 healthy subjects in the 1990s with a standardised protocol that is described in (Palli 2003). Briefly, all recruited subjects filled a detailed questionnaire about diet and life-style habits, and

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anthropometric measurements and a blood sample was collected and stored in liquid nitrogen, after signing an informed consent form. After the recruitment, subjects have been followed-up for life status and cancer incidence through record linkage with cancer registry, hospital discharges, drugs register, and mortality register. Moreover, specific projects for identifying the incidence of several diseases (diabetes, cardio and cerebrovascular diseases, neurological diseases, inflammatory bowel diseases, ¿) have been further conducted.

For the recruitment of the new wave, subjects will be invited to join the study and a hospital appointment will be fixed for those who will accept to participate. On the day of the visit, subjects will answer a new version of the dietary and lifestyle questionnaire and will be invited to provide a new blood sample and to bring a stool sample that will be stored in liquid nitrogen and in a -80° freezer, respectively. Batches of at least 50 stool samples will be shipped to Unit 3 in dry ice.

Statistic plan

The Rome Longitudinal Study, the census cohort of the residents in Rome with its 2.5 million subjects, constitutes half of the Lazio Region Longitudinal study. Preliminary studies on the subset of residents in Rome aged 25 years or more have identified as greater than 8% the prevalence of two or more chronic conditions, a prevalence which is greater than 20% in elderly. Therefore, considering the assumptions of a type I error of 5% and power of 80%, the study on 5 million subjects will be able to detect very tiny differences (i.e., HR < 1.05) relating to the objectives proposed in Aim 1.

Regarding the EPIC cohort study, the Turin and Europe cohorts consist of 10,604 and approximately 280,000 subjects, respectively. Therefore, assuming a type I error of 5% and power of 80%, our study will be able to detect also tiny differences (i.e., HR < 1.10) for the objective 1 of the Aim 3. In addition, to achieve objectives 2, 3, and 4 of Aim 3, 500 subjects will be recalled from the Turin EPIC cohort including both healthy individuals and patients with two or more pre-existing chronic conditions. In fact, in a previous postal follow-up more than 1,500 people from the initially recruited cohort have given their willingness to be recalled in attendance. Therefore, we believe we can guarantee the recall of about 500 subjects, which is the number of subjects that can be recalled in one year. From previous studies that investigated the relationship between SEP and the gut microbiome (Lapidot et al. 2021; Miller et al. 2016), we observed that their sample size was smaller than the number of subjects we would recall. For this reason, our sample size will be able to detect any relevant clinical differences. This will allow both alpha and beta differences to be measured with any index generally used on this topic.

Statistical analysis

The Lazio Region Longitudinal Study will be analysed using a longitudinal approach with survival analyses and multi-state modelling based on Cox regression. Stratified analyses by sex will be considered. To investigate the multimorbidity patterns, and their dependence from SEP, we will also use Conditional Inference Trees (Hothorn et al. 2006). This class of non-parametric trees, unlike most recursive partitioning algorithms, takes into account the distributional properties of the measures. In fact, the simple recursive partitioning algorithms may suffer overfitting and selection bias of the covariates, when those allow for many splits to choose from. Moreover, multiple test procedures are applied to determine whether no significant association between any of the covariates and the response can be stated and the recursion needs to stop. As output, they will provide a cluster distribution of multimorbidity and the list of variables that discriminate among clusters. Alpha diversity will be calculated according to various indexes: Richness, Evenness, Chao1, Shannon, Simpson, Inverse Simpson, and Phylogenetic Diversity (Owen et al. 2019), each capturing a different aspect of microbial diversity. Differences among SEP groups and the role of microbial diversity in multimorbidity will be investigated using standard epidemiological approaches for mediation analyses. Beta diversity among the groups will be evaluated by performing the principal coordinates analysis (PCoA) on read count data and peptide intensity data, which has been shown to outperform classical principal component analysis (PCA) for microbial datasets. To calculate the proportion of variability in both whole metagenomic and metaproteomic datasets explained by each clinical variable, we will use an ad-hoc modified version of the principal component partial R-square (PCPR2) method [Fages et al. 2014]. Briefly, this method is composed of two main steps: (1) for each clinical variable and each eigenvector of the PCoA, the mutual R^2 parameter (proportion of variance explained) is computed from a one-way ANOVA test; (2) for each clinical variable, the proportion of variability explained on the whole dataset is calculated as the sum of the R^2 parameters weighted by the PCA eigenvalues.

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Differential analyses (DAs) will be performed on log-transformed read counts and peptide intensities using the approach implemented in the DeSeq2 R package, originally applied for the analysis of RNA sequence data [Love et al. 2014]. Briefly, the method model peptide intensities with a Negative Binomial Distribution and a shrinkage estimation for dispersions and fold changes to improve the stability and interpretability of estimates and to deal with the high number of outliers in gut microbiome data.

Further, the relationships between gut microbiome and whole genome DNAm profiles will be investigated to identify commonalities between epigenetic and microbial profiles and associated biological pathways mediating the social gradient in health. Partial Least Squares Regression implemented in the mixOmics R package will be used for these analyses. Extensive sensitivity analyses will be performed to identify the most robust results among the identified significant peptides. Mediation analysis has already been explained in the Experimental Aim 3 Section.

Timing of analysis data

Data from the Lazio Region Longitudinal Study are available with a follow-up from the baseline (2011) to 2021. Presumably, during the project the follow-up will be possible till 2022. However, data on cause-specific mortality are available until 2018, hence, during the project we will be able to investigate cause specific mortality in the period 2011-19. Data on health information systems are generally available with one year of delay, hence the follow-up will be possible from 2011 to one year before the end of the project. The record-linkage between census, regional population registry and administrative databases is already performed for hospitalizations, emergency room visits, mortality, and drug prescriptions. The record-linkage with mortality registry (available from 2013 to 2020), and end stage renal disease registry (available from 2008 to 2021) will be performed within the project. The subjects included in the study will be followed from 2011 to the first among: the date of death, the date of migration from the Lazio Region, the date of the outcome in study, or the end of the study (presumably 31/12/2022, depending on the availability of the data).

Regarding the EPIC Turin cohort study, 500 healthy subjects and patients with two or more comorbid conditions will be recalled for up to 12 months, in order to leave some time to analyse the gut microbiome and conduct statistical analyses. In addition to the new information that will be collected at the time of the recall, from the EPIC-Turin study we will use the available data obtained at the baseline (recruitment period 1993-1998) and the clinical information updated until 2018, since linked to hospital discharge information and to the local cancer registry.

5.6 Expected outcomes

We expect to disentangle the role of the different dimensions of disadvantage on the acquisition of multimorbidity and its severity.

We expect to elucidate the biological mechanisms behind social gradient in multimorbidity investigating gut microbiota taxonomy and functional features.

We expect to understand the pathways linking socioeconomic position to multimorbidity, investigating the role as mediators of lifestyles, dietary habits, environmental and occupational exposures, clinical factors, gut microbiome, and epigenetic clock.

Finally, we expect that the results of our study will provide the basis for personalised prevention in frail subjects.

5.7 Risk analysis, possible problems and solutions

Concerning the Lazio Region Longitudinal Study, the large amount of data could constitute a computational problem in multi-state modelling or conditional inference trees. If so, traditional Cox regression models will be used to provide the results, and multi-state modes will be used on subsets of the population, for example, the elderly.

Concerning 16S rRNA gene sequencing and shotgun metaproteomics analyses, potential biases that will be taken under control are related to the batch effect. To minimise this type of biases, we will perform randomization of samples for each processing step, including DNA and protein extraction, amplicon libraries and sequencing, on-filter protein trypsinization and peptide analysis via liquid chromatography-mass spectrometry. Moreover, as amplicon libraries will be sequenced in

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separate flow cells due to the high number of samples analysed, a few randomly chosen samples will be reanalysed in all flow cells of the study as internal standards of sequencing batches. Potential residual batch effects will be subtracted during statistical analyses. First, the PC-PR2 method (Fages et al. 2014) will be implemented to identify wet lab-related variables explaining a substantial proportion of data variability, if any. Subsequently, batch effects will be removed using empirical Bayes methods (Johnson et al. 2007) implemented in the ComBat R function (sva R package) if needed. Finally, quantile normalisation will be applied to microbial features (bacterial families and taxa) to improve the reliability and reproducibility of differential analysis results as suggested by Gibbons et al. (2018).

Another risk could be related to incomplete recruitment of the cohort, due to the non-responsiveness of the recalled EPIC subjects. However, in a previous recall done by mail in 2006-2008, about 65% of the subjects answered the new questionnaires and about half of them agreed to be recalled for a new in-person wave of the study. For this reason, about 3,000 subjects would be potentially available for the study. This amount will allow us to recruit the needed number, and account for an overestimated 50% of refusals.

5.8 Significance and Innovation

The relationship between SEP and multimorbidity is still under investigated. Little evidence is available on which mediators could affect it. The microbiome and biomarkers are known to influence the development of some chronic diseases, and some initial evidence has shown their association with SEP. Investigating their role as possible mediators for the association between SEP and multimorbidity will help in understanding how SEP and multimorbidity could be related. This will allow us to identify possible microbiome features, biomarkers, and lifestyle factors to inform prevention and intervention strategies. With the increase in life expectancy, multimorbidity is already a global health challenge, and it will increase globally in the next decades. To properly address this issue, multidisciplinary and integrated approaches are needed, together with more targeted research to fully understand the complex biological, social, and economical mechanisms underlying this condition.

5.9 Bibliography

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5.10 Timeline / Deliverables / Payable Milestones

As indicated in the gantt chart, in the first month we will meet, we will work on the protocols, and we will submit the request of approval to the Ethical Committee. Soon UO1 will start working on the Lazio Region Longitudinal Study and UO2 to recruit the patients. Laboratory analyses will start at month 4 (UO3). A monthly web meeting will permit all participants to be updated on the development of the project, and at least three meetings in presence will be held.

The payable milestones will be the milestones defined below.
Deliverable 1. Aim 1 Intermediate report (UO 1, Month 14)
Deliverable2. Aim 2 Intermediate report (UO 3, Month 14)
Deliverable 3. Aim 3 Intermediate report (UO 2, Month 14)
Deliverable 4. Final Report (UO1, UO2, UO3, Month 24)

Milestones 12 month

M1 Ethical approval
M2 Draft of a scientific paper on the association between socioeconomic position and acquisition of multimorbidity in the Lazio Longitudinal Study (Aim 1.1)
M3 Draft of the manuscript for Aim 3.1

Milestones 24 month

M4 Patient recruitment for Aim 2
M5 Second Draft Aim 1
M6 Draft on mediation analyses
M7 Final workshop

Gantt chart

gantt.pdf

5.11 Equipment and resources available

Facilities Available

The present project will be carried out at the Department of Epidemiology - Regional Health Service (ASL Roma 1), at the University of Turin, and at Azienda Ospedaliero Universitaria of Sassari.The researchers working at the Units have epidemiological training and different backgrounds.

The offices of all units are equipped with PCs and statistical software which allow for the analysis of large datasets, namely SAS, ArcGIS, R and Stata. Administrative data on hospital discharges, mortality, emergency visits, drug prescriptions, etc. are available.

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Researchers at Azienda Ospedaliero Universitaria of Sassari have full access to research facilities that are key to this project. These include microbiology laboratories fully equipped for a variety of biological samples management, proteins and DNA extraction and their analyses. To date, these facilities enabled the characterization of thousands of microbiota samples by omics technologies. Thanks to a specific program on the ¿Clinic of Microbiota¿, researchers have full access to a DNA sequencer specifically suited for small microbial genomes (MiSeq, Illumina). Further, researchers have access to mass spectrometers (including a Q Exactive, Thermo) for peptide (proteomic and metaproteomic) analyses.

Subcontract

External services will be required to perform DNAm analyses on bisulfite-converted DNA samples and to perform DNA methylation of 200 subjects. Supplies for DNA methylation will be acquired by UO2.

5.12 Desc. of the complementarity and sinergy of secondary collab. researchers

The team of the SEMM project is composed of several researchers that cover all the topics that are included in the proposal. Under the supervision of the unit coordinators and in collaboration with them, they will deal with the epidemiological, biological, statistical, and medical items that will be investigated in the project. All of them are experts in their field and they will work synergically for the advancement of the project. The team is gender-balanced and it will include young researchers already part of the units together with young researchers that will be recruited for the project. Those new researchers already have a good experience in scientific research (demonstrated by their publication track).
For the purpose of the project, other personnels will be also recruited for technical roles (e.g.: administrative coordination of the project, recall of the EPIC subjects). Moreover, some early-stage researchers will have also a part in the project and will be initiated to the research approach being involved in the SEMM team.

5.13 Translational relevance and impact for the national health system (SSN)

What is already know about this topic?

The association between SEP and the prevalence of chronic diseases is well established, but few studies have examined its association with multimorbidity. Moreover, most of the studies on inequalities in multimorbidity used cross-sectional approaches and single indicators of SEP. The association between SEP and -omic biomarkers, including methylation and gut microbiota has been investigated. In particular, GM alpha-diversity, which measures the variety of microbial species, has been found to increase as SEP increases, both at the individual level and at the neighbourhood level. Moreover, the composition of intestinal bacteria, generally measured through beta-diversity, has been found to differ among subjects with different SEP, with a greater abundance of some genera (e.g., Bacteroides) and lower abundance of others (e.g., Prevotella) in individuals with higher SEP.

Details on what is already know about this topic

Details can be found in the following references:

Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. The Lancet 2012;380:37-43. doi:10.1016/S0140-6736(12)60240-2

Fiorito G, McCrory C, Robinson O, et al.; BIOS Consortium; Lifepath consortium. Socioeconomic position, lifestyle habits and biomarkers of epigenetic aging: a multi-cohort analysis Aging (Albany NY). 2019 Apr 14;11(7):2045-2070.

Fiorito G, Pedron S, Ochoa-Rosales C, et al. The role of epigenetic clocks in explaining educational inequalities in mortality: a multi-cohort study and meta-analysis. J Gerontol A Biol Sci Med Sci. 2022 Feb 17:glac041. doi: 10.1093/gerona/glac041

What this reasearch adds?

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We will use a longitudinal approach to study the association between several dimensions of SEP (individual, area-based, and time-varying indicators) and multimorbidity. We will investigate the mechanisms through which each indicator of SEP influences multimorbidity, disentangling the role of lifestyles, living context, work environment, and biological pathways. In particular, blood biomarkers will allow us to identify earlier markers of multimorbidity risk. The role of occupational exposure in the relationship between SEP and multimorbidity will be also analysed. The project will focus also on the interaction of multiple diseases and their severity and will allow to better understand the complex biological mechanisms underlying the relationship between SEP and healthy ageing. We will analyse microbiota and omics as a potential mediator of the relationship between SEP and multimorbidity, taking into account the effect of exposure to lifestyle and environmental risk factors

Details on what this reasearch adds

Details can be found in:

Vineis P, Delpierre C, Castagné R, Fiorito G, McCrory C, Kivimaki M, Stringhini S, Carmeli C, Kelly-Irving M. Health inequalities: Embodied evidence across biological layers. Soc Sci Med. 2020 Feb;246:112781. doi: 10.1016/j.socscimed.2019.112781. Epub 2019 Dec 27. PMID: 31986347.

Kelly-Irving M, Vineis P. Life-course approach: from socioeconomic determinants to biological embodiment. In: Vaccarella S, Lortet-Tieulent J, Saracci R, Conway DI, Straif K, Wild CP, editors. Reducing social inequalities in cancer: evidence and priorities for research. Lyon (FR): International Agency for Research on Cancer; 2019. Chapter 13.. PMID: 33534479.

Vineis P & Perera F 2007. Molecular epidemiology and biomarkers in etiologic cancer research: the new in light of the old. Cancer Epidemiol Biomarkers Prev, 16, 1954¿65

What are the implications for public health, clinical practice, patient care?

The project will contribute to identifying lifestyle habits, blood biomarkers, and gut microbiota features that could be monitored to build fairer strategies and tailored interventions for subjects at higher risk of unhealthy ageing. The increasing prevalence of multimorbidity has a severe impact on patients' families and health systems regarding resources and costs. Hence, policymakers and health governments should focus on this critical population. The results from this project will support the development of new strategies to identify early risk factors at the individual and contextual level for the incidence of multimorbidity. In addition, the results will give impetus to the scientific and medical community to develop recommendations for the management and treatment of multimorbidity for the patients and their families.

Details on what are the implications for public health, clinical practice, patient care

Details can be found in:

Vaccarella S, Weiderpass E, Vineis P. Present and future of health inequalities: Rationale for investing in the biological capital. EClinicalMedicine. 2020 Feb 4;19:100261. doi: 10.1016/j.eclinm.2020.100261. PMID: 32055791; PMCID: PMC7005444.

Wallenborn JT, Vonaesch P. Intestinal microbiota research from a global perspective. Gastroenterol Rep (Oxf). 2022 Apr 11;10:goac010. doi: 10.1093/gastro/goac010. PMID: 35419206; PMCID: PMC8996373.

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6 - Budget

Total proposed budget (Euro)				
Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	175.000,00	175.000,00	not permitted	0,00
2 Researchers' Contracts	455.000,00	0,00	455.000,00	50,47
3a.1 Equipment (Leasing -	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	177.000,00	0,00	177.000,00	19,63
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts *	3.000,00	0,00	3.000,00	0,33
5 Patient Costs	140.000,00	0,00	140.000,00	15,53
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	13.500,00	0,00	13.500,00	1,50
8 Publication Costs	22.500,00	0,00	22.500,00	2,50
9 Dissemination	11.000,00	0,00	11.000,00	1,22
10 Overheads *	58.779,00	0,00	58.779,00	6,52
11 Coordination Costs	20.703,00	0,00	20.703,00	2,30
Total	1.076.482,00	175.000,00	901.482,00	100,00

* percentage calculated as average value between all the Operating Units.

Report the Co-Funding Contributor:

UO1 Lazio: 3 Senior researchers: 1.5 months/person/year for two years
UO2 Turin: 2 Senior researchers and 2 young researchers: 1.5 months/person/year for two years
UO3 Sassari: 1 Senior researchers: 2 months/person/year for two years

Budget Justification	
1 Staff Salary	Senior and junior researchers' salary
2 Researchers' Contracts	7 units personnel (2 for UO1, 2 for UO2, 3 for UO3)
3a.1 Equipment (Leasing - Rent)	none
3a.2 Equipment (buying)	none
3b Supplies	Reagents for laboratory analyses

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3c Model Costs	none
4 Subcontracts	External services will be required to perform DNA methylation of 200 subjects
5 Patient Costs	Cost for the recall of 500 EPIC Turin subjects (invitation letters, questionnaires, materials for blood retrieval, insurance, standard blood analyses that will provided to patients, faecal occult blood test, ...)
6 IT Services and Data Bases	none
7 Travels	Travels for meeting and conferences participation
8 Publication Costs	Publication fees for open access journals
9 Dissemination	Conferences fees
10 Overheads	Administrative costs
11 Coordination Costs	Coordination, meeting organization, final workshop organization

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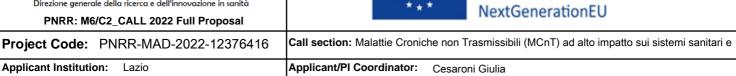|	
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Proposed total budget UO1 Institution: Department of Epidemiology-Regional Health Service, ASL Roma 1 (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	60.000,00	60.000,00	not permitted	0,00
2 Researchers' Contracts	145.000,00	0,00	145.000,00	74,17
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	0,00	0,00	0,00	0,00
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	4.500,00	0,00	4.500,00	2,30
8 Publication Costs	7.500,00	0,00	7.500,00	3,84
9 Dissemination	5.000,00	0,00	5.000,00	2,56
10 Overheads	12.789,00	0,00	12.789,00	6,54
11 Coordination Costs	20.703,00	0,00	20.703,00	10,59
Total	255.492,00	60.000,00	195.492,00	100,00

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Budget Justification

1 Staff Salary	3 Senior researchers: 1.5 months/person/year for two years
2 Researchers' Contracts	Cost of 2 units of personnel that will be in charge of data management and analyses of the Lazio Region Longitudinal Study
3a.1 Equipment (Leasing - Rent)	none
3a.2 Equipment (buying)	none
3b Supplies	none
3c Model Costs	none
4 Subcontracts	none
5 Patient Costs	none
6 IT Services and Data Bases	none
7 Travels	Participation to meetings for the project and to national and international conferences
8 Publication Costs	Publication costs for open-acces journals
9 Dissemination	participation to conference for presenting the results
10 Overheads	administrative costs
11 Coordination Costs	Organization of meetings and workshops, including final workshop

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Proposed total budget UO2 Institution: University of Turin (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	80.000,00	80.000,00	not permitted	0,00
2 Researchers' Contracts	120.000,00	0,00	120.000,00	36,79
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	27.000,00	0,00	27.000,00	8,28
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	3.000,00	0,00	3.000,00	0,92
5 Patient Costs	140.000,00	0,00	140.000,00	42,93
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	4.500,00	0,00	4.500,00	1,38
8 Publication Costs	7.500,00	0,00	7.500,00	2,30
9 Dissemination	3.000,00	0,00	3.000,00	0,92
10 Overheads	21.140,00	0,00	21.140,00	6,48
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	406.140,00	80.000,00	326.140,00	100,00

Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Budget Justification

1 Staff Salary	2 Senior researchers and 2 young researchers: 1.5 months/person/year for two years
2 Researchers' Contracts	Cost of 2 units of personnel (1 full-time and 1 part-time) that will take care of recruitment of EPIC subjects, shipment of samples, maintenance of the EPIC-Turin cohort (including follow-up)
3a.1 Equipment (Leasing - Rent)	none
3a.2 Equipment (buying)	none
3b Supplies	Reagents for the analysis of methylation to investigate epigenetic clock (200 subject)
3c Model Costs	none
4 Subcontracts	External services will be required to perform DNA methylation of 200 subjects
5 Patient Costs	Cost for the recall of 500 subjects (invitation letters, questionnaires, materials for blood retrieval, insurance, standard blood analyses that will provided to patients, faecal occult blood test, ...)
6 IT Services and Data Bases	none
7 Travels	Participation to meetings for the project and to national and international conferences
8 Publication Costs	Publication costs for peer-reviewed open-acces journals
9 Dissemination	Conference fees
10 Overheads	administrative costs
11 Coordination Costs	none

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Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Proposed total budget UO3 Institution: Azienda Ospedaliera di Sassari (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	35.000,00	35.000,00	not permitted	0,00
2 Researchers' Contracts	190.000,00	0,00	190.000,00	50,02
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	150.000,00	0,00	150.000,00	39,49
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	4.500,00	0,00	4.500,00	1,18
8 Publication Costs	7.500,00	0,00	7.500,00	1,97
9 Dissemination	3.000,00	0,00	3.000,00	0,79
10 Overheads	24.850,00	0,00	24.850,00	6,54
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	414.850,00	35.000,00	379.850,00	100,00

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	Finanziato dall'Unione europea NextGenerationEU
Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Budget Justification

1 Staff Salary	1 Senior researchers: 2 months/person/year for two years
2 Researchers' Contracts	Cost of 2 young adjunct collaborators that will be hired according to the art. 7, comma 2, letter d). Giovanni Fiorito and Marcello Abbondio have been evaluated in the triage stage at time of L.O.I. submission.30.000€ will cover a lab collaborator.
3a.1 Equipment (Leasing - Rent)	none
3a.2 Equipment (buying)	none
3b Supplies	Reagents for DNA and protein extraction from fecal samples, DNA libraries preparation and V4 sequencing (n = 500 samples), peptide samples preparation for LC-MS/MS analyses (n = 500 samples)
3c Model Costs	none
4 Subcontracts	none
5 Patient Costs	none
6 IT Services and Data Bases	none
7 Travels	Participation to meetings for the project and to national and international conferences
8 Publication Costs	Publication costs for open-acces journals
9 Dissemination	Conference fees
10 Overheads	Administrative costs
11 Coordination Costs	none

Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	**Finanziato dall'Unione europea** NextGenerationEU
Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Lazio	**Applicant/PI Coordinator:** Cesaroni Giulia

Principal Investigator Data

Cognome: Cesaroni
Nome: Giulia
Genere: F
Codice fiscale: CSRGLI65S50H501D
Documento: Passaporto, Numero: YB1488898
Data di nascita: 10/11/1965
Luogo di nascita: Roma
Provincia di nascita: RM
Indirizzo lavorativo: Via Cristoforo Colombo 112
Città: Roma
CAP: 00147
Provincia: RM
Email: giulia.cesaroni@yahoo.it
Altra email: g.cesaroni@deplazio.it
Telefono: +393476455995
Altro telefono: 3476455995
Qualifica: Dirigente Analista
Struttura: Dipartimento di Epidemiologia del Servizio Sanitario Regionale
Istituzione: ASL Roma1
Datore/ente di lavoro? Yes
Datore/ente di lavoro SSN? Yes
Nome datore/ente di lavoro non SSN:
Nome istituzione SSN: ASL Roma 1
Tipo contratto: Lavoro Subordinato a Tempo Indeterminato

Con l'invio della presente proposta si dichiara che la stessa o parti significative di essa non sono oggetto di altri finanziamenti pubblici o privati e che di conseguenza vi è assenza del c.d. doppio finanziamento ai sensi dell'art. 9 del Regolamento (UE) 2021/241, ossia che non ci sia una duplicazione del finanziamento degli stessi costi da parte di altri programmi dell'Unione, nonché con risorse ordinarie da Bilancio statale.

By submitting this proposal, I declare that no significant part or parts of it are recipient of any other public or private funding and that consequently there isn't any so-called double financing pursuant to art. 9 of Regulation (EU) 2021/241, i.e. that there is no duplication in the financing of the same costs by other Euopean Union programs or any other ordinary resources from the State budget.

![Ministero della Salute emblem] *Ministero della Salute* Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2022 Full Proposal**	![EU flag] **Finanziato** **dall'Unione europea** NextGenerationEU
Project Code: PNRR-MAD-2022-12376416	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
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Project validation result