1 - General information

Project code: PNRR-MAD-2022-12376584

Project topic: C1) Malattie croniche non trasmissibili, ad alto impatto sui sistemi sanitari e socio-assistenziali: fattori di rischio e prevenzione

PI / Coordinator: Sieri Sabina Assunta Giovanna

Applicant Institution: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano

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

Proposal title: Beyond BMI: external exposome, dysbiosis and systemic inflammation in the development of overweight-related chronic diseases in women

Duration in months: 24

MDC primary: Oncologia

MDC secondary: Cardiologia-Pneumologia

Project Classification IRG: Population Sciences and Epidemiology

Project Classification SS: Epidemiology of Cancer - EPIC

Project Keyword 1: Elucidation of the determinants of cancer and biomarkers of cancer by assembling groups of individuals to determine systematically whether the risk of disease/condition is different for individuals who are exposed or not exposed to specific factors (or combinations of factors) of interest. These may be either risk or protective factors and include genetic, epigenetic, molecular, behavioral, and environmental factors.

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

Project total financing request to the MOH: € 993.685

Free keywords: Metabolically unhealthy; metabolically healthy; inflammation; cancer; cardiovascular disease

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'.

Project Code: PNRR-MAD-2022-12376584	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	**Applicant/PI Coordinator:** Sieri Sabina Assunta Giovanna

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).	X
2) The Principal Investigator declares that the information contained in this proposal is correct and complete.	X
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).	X
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.	X

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

The ongoing COVID-19 pandemic has brought to light the underlying poor metabolic health in our society, with overweight/obesity-related chronic diseases associated with COVID-19 severity and worse outcome. Irrespective of metabolic health, overweight and obese people had higher risk than lean people to develop a chronic disease. However, recent data suggested that regardless of whether a person is normal weight, overweight or obese, the condition of being "Metabolically Unhealthy" (MU) leads to a higher risk of developing cardiovascular diseases (CVDs) and cancer if compared to "Metabolically Healthy" (MH) people.
We propose elucidating pathways underlying the association of overweight/obesity - comparing MU and MH overweight/obese (MUO and MHO) women and normal weight women - with CVDs (myocardial infarction and stroke) and overweight/obesity-related cancers. We hypothesize that gut dysbiosis and systemic inflammation may explain the different risk linked to MH or MU overweight/obesity and are involved in the occurrence of chronic-degenerative diseases linked to overweight/obesity. We will evaluate whether and how external exposome (diet, lifestyle and environment) influences overweight/obesity-related chronic disease risk through dysbiosis and systemic inflammation in a prospective observational and in an experimental design.
We will test our hypotheses by analyzing data from well-defined cohorts of thousands of women followed over long periods: the EPIC-Italy study. We propose to conduct a case-cohort study, nested within the EPIC-Italy cohort, focusing on CVDs and some main cancer sites such as the breast and colon-rectum. Metabolic and inflammation biomarkers will be used to compare dysbiosis and inflammatory profiles in normal weight healthy, normal weight unhealthy, MHO and MUO women from our cohort who do and do not develop overweight/obesity-related diseases.
We will evaluate if predictive risk pathways identified in the women from the EPIC-Italy cohort are modified by a preventive lifestyle intervention designed to reduce the incidence of chronic diseases through a secondary analysis of the randomized controlled Me.Me.Me. trial. The Me.Me.Me is based on a Mediterranean dietary intervention with a low-calorie restriction

and/or a fast-mimic diet drug (metformin).
Mechanisms linking MHO and MUO phenotypes and overweight/obesity-related chronic diseases through dysbiosis and inflammation are incompletely understood. Better understanding of the relation between external exposome, overweight/obesity, internal exposome (dysbiosis and inflammation markers) and cardiometabolic diseases will make it possible to identify the women who are at increased risk because of their cardiometabolic profile and to develop strategies (e.g. lifestyle, dietary or pharmacologic interventions) to disrupt dysbiosis and inflammatory process and hence reduce the risk of chronic diseases. Furthermore, if we find good evidence that a lifestyle/metformin intervention may modulate the identified dysbiosis and inflammatory markers, we will be able to effectively intervene on women at risk using target primary prevention actions.

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

Operative Units

Institution that perform as UO	CF Institution	Department / Division / Laboratory	Role in the project	Southern Italy	SSN
1 - Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	80018230153	Department of Research/Epidemiology and Prevention Unit	PI-Responsible of study design/management		X
2 - Istituto per lo Studio, la Prevenzione e la rete Oncologica (ISPRO), Firenze	94158910482	SC Epidemiologia dei Fattori di Rischio e degli Stili di vita	Recovery of blood samples, individual exposoma data and follow-up		X
3 - Università degli studi della Campania Luigi Vanvitelli, Napoli	06909360635	Dipartimento di Salute Mentale e Fisica e Medicina Preventiva	Responsible of the statistical analyses	X	
4 - Azienda Ospedaliera Universitaria Federico II, Napoli	02044190615	UOC Medicina Interna e Nutrizione Clinica	Recovery of blood samples and responsible for inflammatory markers assessment	X	X

Project Code: PNRR-MAD-2022-12376584	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	**Applicant/PI Coordinator:** Sieri Sabina Assunta Giovanna

Principal Research Collaborators

Key Personnel Name	Operative Unit	Role in the project
1 - Pasanisi Patrizia	Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	Co-PI - support of the PI into management of the study and coordination of the activities related to the MeMeMe data extraction and analyses
2 - Saieva Calogero	Istituto per lo Studio, la Prevenzione e la rete Oncologica (ISPRO), Firenze	Principal study's collaborator for the EPIC-Florence centre and coordination of the recovery of blood samples from the local biological bank and main individual data
3 - Chiodini Paolo	Università degli studi della Campania Luigi Vanvitelli, Napoli	Responsible of the statistical analyses
4 - PASANISI FABRIZIO	Azienda Ospedaliera Universitaria Federico II, Napoli	Principal study's collaborator for the EPIC-Naples centre and responsible of the inflammatory markers analyses
5 - Agnoli Claudia	Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	Responsible for the processing of laboratory data
6 Under 40 - bruno eleonora	Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	Responsible for ensuring the accuracy and integrity of the study data and supervision of study analyses in collaboration with the PI
7 Under 40 - Baldassari Ivan	Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	Assisting the PI in the planning for recover of biological samples and management.

Key Personnel Name	Co-PI	Resp. CE	Resp. Animal	Birth Date	Gender
1 - Pasanisi Patrizia	X			14/03/1974	F
2 - Saieva Calogero				22/10/1961	M
3 - Chiodini Paolo				18/09/1972	M
4 - PASANISI FABRIZIO				22/04/1957	M
5 - Agnoli Claudia				20/07/1981	F
6 Under 40 - bruno eleonora				20/12/1982	F
7 Under 40 - Baldassari Ivan				03/12/1992	M

Responsible who requests CE authorization: Sieri Sabina Assunta Giovanna

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 - MORLINO DELIA	Azienda Ospedaliera Universitaria Federico II, Napoli	28/06/1992	F	Support in the dietary and inflammation markers analyses	Bachelor's Degree: Biology Master's degree: Human Nutrition	Scholarship - Federico II, University, Naples Department of Clinical Medicine and Surgery, Naples
1 - CIOFFI IOLANDA	Azienda Ospedaliera Universitaria Federico II, Napoli	06/10/1985	F	Support in the nutritional data evaluation and analyses	Bachelor's degree: Dietetics Master's degree: Human Nutrition	Postdoc - Department Clinical Medicine and Surgery, Naples,

2.1 Administrative data of participating

Operative Unit Number 1:

Address: Via Giacomo Venezian, 1, Milano, 20133, Italy
PEC: epidemiologia.prevenzione@pec.istitutotumori.mi.it

Operative Unit Number 2:

Address: Via Cosimo Il Vecchio, 2, Firenze, 50139, Italy
PEC: ispro@postacert.toscana.it

Operative Unit Number 3:

Address: Via Luciano Armanni, 5, Napoli, 80138, Italy
PEC: dip.salutementalefisica@pec.unicampania.it

Operative Unit Number 4:

Address: Via Pansini 5, Napoli, 80131, Italy
PEC: aou.protocollo@pec.it

Operative Unit Number 5 (self financing):

Address:
PEC:

2.2 Principal Investigator (PI) Profile

Last Name: Sieri
First Name: Sabina Assunta Giovanna
Last name at birth:
Gender: F

Title: Principal investigator
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 07/03/1969
Place of Birth: Busto Arsizio

Official H index (Scopus or Web of Science): 61.0

Scopus Author Id:6603792079 **ORCID ID:**0000-0001-5201-172X **RESEARCH ID:**K-4667-2016

Contact address

Current organisation name: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano
Current Department / Faculty / Institute / Laboratory name: Department of Research/Epidemiology and Prevention Unit
Street: Via Venezian 1
Postcode / Cedex: 20133 **Town:** Milano
Phone:+393498608661 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan. Faculty of Medicine, Department of Biochemistry,Milan,Italy	Specialization / Specializzazione	Specialist in General Nutrition (70/70 cum laude)	1995	1999
University of Milan. Faculty of Biology, Milan, Italy	Single-cycle master's degree / Laurea magistrale a ciclo unico	Doctor in Biology	1990	1994

Personal Statement:

Dr. Sieri will serve as PI. Her research objective is to elucidate the pathways underlying the association of overweight/obesity (comparing metabolically unhealthy-MU and metabolically healthy-MH overweight/obese and normal-weight women) with cardiovascular disease and overweight-related cancer. She hypothesizes that gut dysbiosis and systemic inflammation may explain the different risks linked to MH or MU adiposity and are involved in the occurrence of chronic-degenerative diseases linked to overweight/obesity. She will be responsible for the overall design and conduction of this study including blood sample retrieval, dysbiosis markers analysis, and data analysis. She has been working in the area of the epidemiology of degenerative chronic diseases since 1996.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Fondazione IRCCS Istituto Nazionale dei Tumori	Department of Research, Epidemiology and Prevention Unit	Milan	Researcher	2002	2022
Fondazione IRCCS Istituto Nazionale dei Tumori	Department of Preventive and Predictive Medicine, Nutritional Epidemiology Unit	Milan	Researcher	1996	2001
University of Pavia	Human and Hereditary Pathology Department	Varese, Italy	Research Fellow	1994	1995

Other awards and honors

2014 National Italian Ministry of University Qualification as Associate Professor of Hygiene

Other CV informations

She has been involved in numerous international projects on nutrition and chronic diseases (EPIC, POOLING PROJECT, IDEFICS, INTERACT, PANACEA, EPIC-CVD, IMMIDIET). She is investigator in the ORDET study, where she has been specifically involved in the study of the association between diet, biomarkers and breast cancer risk. She has been involved in the large prospective EPIC study as responsible for Italian Food Frequency Questionnaire. She has been involved in the large EPIC-CVD study. She has published over 250 peer-reviewed publications including high impact journals.

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

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Dietary glycemic index, glycemic load and cancer: An overview of the literature	Review	18-31	27	2017	10.1016/j.numecd.2016.09.014	27986350	28	F
Associations of dairy product consumption with mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Italy cohort	Article	1220-1230	110	2019	10.1093/ajcn/nqz183	31435641	12	C
Metabolic syndrome and breast cancer risk: A case-cohort study nested in a multicentre Italian cohort	Article	e0128891	10	2015	10.1371/journal.pone.0128891	26030767	50	C
Adherence to a Mediterranean diet and long-term changes in weight and waist circumference in the EPIC-Italy cohort	Article	22	8	2018	10.1038/s41387-018-0023-3	29695712	46	C
Italian mediterranean index and risk of colorectal cancer in the Italian section of the EPIC cohort	Article	1404-1411	132	2013	10.1002/ijc.27740	22821300	63	C
Macronutrient composition of the diet and long-term changes in weight and waist circumference in the EPIC-Italy cohort	Article	67-75	31	2021	10.1016/j.numecd.2020.08.007	33097407	1	C
Colorectal cancer risk and dyslipidemia: A case-cohort study nested in an Italian multicentre cohort	Article	144-151	38	2014	10.1016/j.canep.2014.02.002	24636241	31	C

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Dietary cadmium and risk of breast cancer subtypes defined by hormone receptor status: A prospective cohort study	Article	2153-2160	144	2019	10.1002/ijc.32039	30515770	26	L
Dietary Glycemic Load and Glycemic Index and Risk of Cerebrovascular Disease in the EPICOR Cohort	Article	e62625	8	2013	10.1371/journal.pone.0062625	23717392	25	F
Dietary fat intake and development of specific breast cancer subtypes	Article	dju068	106	2014	10.1093/jnci/dju068	24718872	69	F
Toenail selenium and risk of type 2 diabetes: The ORDET cohort study	Article	145-150	29	2015	10.1016/j.jtemb.2014.07.017	25169979	16	L
Dietary glycemic index and glycemic load and risk of colorectal cancer: Results from the EPIC-Italy study	Article	2923-2931	136	2015	10.1002/ijc.29341	25403784	40	F
Micronutrients involved in one-carbon metabolism and risk of breast cancer subtypes	Article	e0138318	10	2015	10.1371/journal.pone.0138318	26376452	23	L
Plasma riboflavin and vitamin B-6, but not homocysteine, folate, or vitamin B-12, are inversely associated with breast cancer risk in the european prospective investigation into cancer and nutrition-varese cohort	Article	1227-1234	146	2016	10.3945/jn.115.225433	27121532	23	L
Dietary glycemic index, glycemic load, and cancer risk: Results from the EPIC-Italy study	Article	9757	7	2017	10.1038/s41598-017-09498-2	28851931	44	F
Glycemic index, glycemic load, and risk of coronary heart disease: A pan-European cohort study	Article	631-643	112	2020	10.1093/ajcn/nqaa157	32619242	9	F

* 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.**
Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis	Article	597	11	2020	10.1038/s41467-020-14389-8	32001714	36
Biomarkers of inflammation and breast cancer risk: A case-control study nested in the EPIC-Varese cohort	Article	12708	7	2017	10.1038/s41598-017-12703-x	28983080	39
Ovarian cancer risk factors by histologic subtype: An analysis from the Ovarian Cancer Cohort Consortium	Article	2888-2898	34	2016	10.1200/JCO.2016.66.8178	27325851	155
Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: The European prospective investigation into cancer and nutrition study (EPIC)	Article	613-621	101	2015	10.3945/ajcn.114.100065	25733647	216
Dietary fat intake and development of specific breast cancer subtypes	Article	dju068	106	2014	10.1093/jnci/dju068	24718872	69
Fruit and vegetable intake and risk of breast cancer by hormone receptor status	Article	219-236	105	2013	10.1093/jnci/djs635	23349252	111

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: Results from the European Prospective Investigation into Nutrition and Cancer cohort study	Article	1107-1120	97	2013	10.3945/ajcn.112.049569	23553166	98
Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: A large prospective cohort study	Article	R76	14	2012	10.1186/bcr3186	22583394	71
Impact of cigarette smoking on cancer risk in the European prospective investigation into cancer and nutrition study	Article	4550-4557	30	2012	10.1200/JCO.2011.41.0183	23169508	91
Prospective study on the role of glucose metabolism in breast cancer occurrence	Article	921-929	130	2012	10.1002/ijc.26071	21413010	75

** Autocertificated

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Associazione Italiana per la Ricerca sul Cancro	Fondazione IRCCS Istituto Nazionale dei Tumori	2015-2017	Role of inorganic xenoestrogens and their binding proteins in risk of developing breast cancer subtypes	Coordinator	279.000,00	https://www.istitutotumori.mi.it/web/guest/s.c.-epidemiologia-e-prevenzione
Italian Ministry of Health	Fondazione IRCCS istituto nazionale dei tumori	2011-2014	Role of nutrients involved in one-carbon metabolism in the development of different molecular subtypes of breast cancer in the ORDET cohort	Coordinator	308.228,00	https://www.istitutotumori.mi.it/web/guest/s.c.-epidemiologia-e-prevenzione
Italian Ministry of Health	Fondazione IRCCS Istituto Nazionale dei Tumori	2019	Metabolic syndrome and risks of breast cancer and cardiovascular disease: a systems biology approach applied to epidemiological studies to identify predictive biomarkers and pathological molecular pathways	Coordinator	449.491,00	https://www.istitutotumori.mi.it/web/guest/s.c.-epidemiologia-e-prevenzione

2.3 CO-PI Profile

Last Name: Pasanisi
First Name: Patrizia

Last name at birth:
Gender: F

Title: Co-PI - support of the PI into management of the study and coordination of the activities related to the MeMeMe data extraction and analyses

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Roma

Nationality: Italy
Date of birth: 14/03/1974

Official H index (Scopus or Web of Science): 18.0

Scopus Author Id:6603594296 **ORCID ID:**0000-0001-6278-3491 **RESEARCH ID:**F-4908-2017

Contact address

Current organisation name: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano
Current Department / Faculty / Institute / Laboratory name: Department of Research/Epidemiology and Prevention Unit
Street: Via Venezian 1
Postcode / Cedex: 20133 **Town:** Milano
Phone:+393394423378 **Phone 2:** 0223903513

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Università degli Studi "La Sapienza", Roma, Italy	Specialization / Specializzazione	Hygene and Preventive Medicine	1998	2002
Università degli Studi "La Sapienza", Roma, Italy	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine & Surgery	1992	1998

Personal Statement:
She is a medical doctor with a Master in Epidemiology and a Master in Nutrition and her research activity is mainly focused in studying the associations between diet, metabolic and hormonal factors and cancer. The goal of this study is to understand the pathways underlying the variation in the individual risk of developing obesity-associated chronic disease thus opening target strategies for prevention. Given her long experience in the design, management and analysis of prevention clinical randomized trials she will support the PI in all the phases of this study and in statistical epidemiological analyses. Furthermore, she has the responsibility of the Me.Me.Me trial and she will be responsible of all the activities included into the aim 3 of the present proposal.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Fondazione IRCCS Istituto Nazionale dei Tumori	Department of Research, Epidemiology and Prevention Unit	Milano, Italy	Senior Researcher,tenured	2009	2022
Fondazione IRCCS Istituto Nazionale dei Tumori	Department of Research, Epidemiology and Prevention Unit	Milano, Italy	Research Assitant	2003	2009
Fondazione IRCCS Istituto Nazionale dei Tumori,	Department of Research, Epidemiology Unit	Milano, Italy	Post graduate fellow	1999	2002

Other awards and honors

Year 2005 winner of the Young Researcher Award, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Other CV informations

Dr. Patrizia Pasanisi has a wide experience in nutritional epidemiology and dietary intervetnion trials. She works at the S.C. Epidemiology and Prevention, Fondazione IRCCS Istituto Nazionale dei Tumori in Milan since 1999 and since 2009 as senior researcher. She has been involved for over 15 years in dietary intervention studies. She had the responsibility of the WCRF systematic literature review on the role of diet in the aetiology of breast, cervix and ovarian cancer. Currently, she is the PI of a large prospective trial on BRCA women to investigate the role of diet in the penetrance of genetic breast cancer and she is the coordinator of a randomized trial of Mediterranean diet and Metformin for primary prevention of age-related diseases in over 2000 people with metabolic syndrome.

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

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Metformin decreases circulating androgen and estrogen levels in nondiabetic women with breast cancer	Article	433-438	13	2013	10.1016/j.clbc.2013.08.012	24267731	36	L
Life-style and metformin for the prevention of endometrial pathology in postmenopausal women	Article	119-124	29	2013	10.3109/09513590.2012.706671	22946682	21	L
Metabolic syndrome and breast cancer prognosis	Article	159-165	147	2014	10.1007/s10549-014-3076-6	25104441	71	L
Adherence to WCRF/AICR cancer prevention recommendations and metabolic syndrome in breast cancer patients	Article	237-244	138	2016	10.1002/ijc.29689	26175188	24	L
A Pilot Low-Inflammatory Dietary Intervention to Reduce Inflammation and Improve Quality of Life in Patients With Familial Adenomatous Polyposis: Protocol Description and Preliminary Results	Article	1534735419846400	18	2019	10.1177/1534735419846400	31055940	3	F
Monitoring vitamin B<inf>12</inf> in women treated with metformin for primary prevention of breast cancer and age-related chronic diseases	Article	1020	11	2019	10.3390/nu11051020	31067706	4	L

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
A mediterranean dietary intervention in female carriers of brca mutations: Results from an italian prospective randomized controlled trial	Article	1-13	12	2020	10.3390/cancers12123732	33322597	2	L
Adherence to dietary recommendations after one year of intervention in breast cancer women: The diana-5 trial	Article	2990	13	2021	10.3390/nu13092990	34578868	3	L
Recruitment in randomized clinical trials: The MeMeMe experience	Article	e0265495	17	2022	10.1371/journal.pone.0265495	35333878	0	L
The Impact of Mediterranean Dietary Intervention on Metabolic and Hormonal Parameters According to BRCA1/2 Variant Type	Article	820878	13	2022	10.3389/fgene.2022.820878	35356420	0	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
Italian Ministry of Health	Fondazione IRCCS istituto nazionale dei tumori	2010-2014	A randomized controlled trial of diet and physical activity in BRCA mutation carriers	Coordinator	218.000,00	https://www.istitutotumori.mi.it/web/guest/s.c.
Associazione Italiana per la Ricerca sul cancro (AIRC)	Fondazione IRCCS istituto nazionale dei tumori	2015-2019	Lifestyle and the penetrance of BRCA mutation	Coordinator	201.600,00	https://www.istitutotumori.mi.it/web/guest/s.c.-epidemiologia-e-prevenzione

2.3 Research Collaborators n. 2

Last Name: Saieva
First Name: Calogero

Last name at birth:
Gender: M

Title: Principal study's collaborator for the EPIC-Florence centre and coordination of the recovery of blood samples from the local biological bank and main individual data

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Agrigento

Nationality: Italiana

Date of birth: 22/10/1961

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

Scopus Author Id:7003814439 **ORCID ID:**0000-0002-0117-1608 **RESEARCH ID:**AAC-2611-2019

Contact address

Current organisation name: Istituto per lo Studio, la Prevenzione e la rete Oncologica (ISPRO), Firenze

Current Department / Faculty / Institute / Laboratory name: SC Epidemiologia dei Fattori di Rischio e degli Stili di vita

Street: via cosimo il vecchio 2

Postcode / Cedex: 50139 **Town:** firenze

Phone:+393392743892 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Florence, Florence	Specialization / Specializzazione	Hygene and Preventive Medicine	1996	2000
University of Florence, Florence	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine & Surgery	1980	1991

Personal Statement:

Senior Investigator in the EPIC study. He is responsible for the recovery of blood samples from the local biological bank, and for the recovery of the main individual data related to diet, lifestyle and clinical follow-up.
The main responsibility and goal in this project is in defining and validate the health status of the EPIC-Florence study participants. He will collaborate with the PI for the statistical analyses focused on the main study's objectives, interpretation of results, and scientific papers preparation and dissemination of results.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Institute for cancer research, prevention and clinical network (ISPRO)	Cancer Risk Factors and Lifestyle Epidemiology Unit	Florence	Medical Epidemiologist	2018	2022
Cancer Research and Prevention Institute (ISPO)	Cancer Risk Factors and Lifestyle Epidemiology Unit	Florence	Medical Epidemiologist	2008	2017
Center for Study and Cancer Prevention (CSPO)	Molecular and Nutritional Epidemiology Unit	Florence	Medical Epidemiologist	2002	2008

Other awards and honors

None

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Bando Ricerca Salute 2018 Regione Toscana	ISPRO, Florence Italy	2020	Lifestyle determinants and biomarkers of heavy metals exposure in a sample of a large prospective study in Tuscany: temporal trends, comparison with other local populations, and association with cancer risk (EPI METAL)	Collaborator	376.000,00	https://www.regione.toscana.it/-/bando-ricerca-salute-2018

2.4 Research Collaborators n. 3

Last Name: Chiodini
First Name: Paolo
Last name at birth:
Gender: M

Title: Responsible of the statistical analyses
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 18/09/1972
Place of Birth: Cuggiono

Official H index (Scopus or Web of Science): 46.0

Scopus Author Id:24586672300 **ORCID ID:**0000-0003-0139-2264 **RESEARCH ID:**E-7290-2014

Contact address

Current organisation name: Università degli studi della Campania Luigi Vanvitelli, Napoli
Current Department / Faculty / Institute / Laboratory name: Dipartimento di Salute Mentale e Fisica e Medicina Preventiva
Street: Via Luciano Armanni, 5
Postcode / Cedex: 80138
Town: Napoli
Phone:+393492649186
Phone 2: 0815666021

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Università degli Studi di Milano	Specialization / Specializzazione	Medical Statistics	2002	2007
Università degli Studi di Milano	Single-cycle master's degree / Laurea magistrale a ciclo unico	Statistics	1995	2002

Personal Statement:

Dr. Chiodini's main research fields are cardiovascular and cancer epidemiology, development and validation of prognostic models, statistical methods for clinical research and clinical trials, conduction and analysis of Systematic reviews, meta-analyses and individual patient data meta-analyses. In the present proposal he will be involved into the study design, the definition of the cases and controls to be included into the case-cohort analyses and will be responsible of the statistical analyses. He will also manage the analyses to test whether the external exposome influences adiposity-related chronic disease risk through dysbiosis and inflammation.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Università degli Studi della Campania "Luigi Vanvitelli"	Dipartimento di Salute Mentale e Fisica e Medicina Preventiva	Napoli, Italy	Full Professor	2020	2022
Università degli Studi della Campania "Luigi Vanvitelli"	Dipartimento di Salute Mentale e Fisica e Medicina Preventiva	Napoli, Italy	Associate Professor	2017	2020
Seconda Università degli Studi di Napoli	Dipartimento di Salute Mentale e Fisica e Medicina Preventiva	Napoli, Italy	Researcher	2006	2017
Regione Campania	Agenzia Regionale Sanità	Napoli, Italy	Research Fellow	2004	2006
Istituto Superiore di Sanità	Epidemiologia	Milano, Italy	Research Fellow	2003	2003

Other awards and honors

Visiting Senior Lecturer in the Centre for Primary Care and Public Health within the Blizard Institute, Queen Mary University of London from march 2019 to february 2021

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministero dell'Università e della Ricerca	Seconda Università degli Studi di Napoli	2007	2007 PRIN Coordinatore Unità Locale	Coordinator	20.000,00	ttps://prin.mur.gov.it/Pages/Index/8120000

2.5 Research Collaborators n. 4

Last Name: PASANISI
First Name: FABRIZIO

Last name at birth:
Gender: M

Title: Principal study's collaborator for the EPIC-Naples centre and responsible of the inflammatory markers analyses

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Napoli

Nationality: Italiana
Date of birth: 22/04/1957

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

Scopus Author Id:7003329259 **ORCID ID:**0000-0003-4224-7821 **RESEARCH ID:**L-7437-2015

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Federico II, Napoli
Current Department / Faculty / Institute / Laboratory name: UOC Medicina Interna e Nutrizione Clinica
Street: Via Pansini 5
Postcode / Cedex: 80131 **Town:** Napoli
Phone:+393388757940 **Phone 2:** 3388757940

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Federico II University Naples, Italy	Specialization / Specializzazione	Internal Medicine	1986	1990
University of Glasgow, Dept of Medicine Glasgow, UK	PhD	Clinical Pharmacology and Therapy	1982	1986
Federico II University Naples,Italy	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1976	1981

Personal Statement:

He is currently involved in research studies on the pathophysiology and treatment of obesity and malnutriton. In the present proposal he is principal study's collaborator for the EPIC-Naples centre and with his laboratory team will be responsible for the metabolic mechanistic part of the study. He will be responsible for the inflammatory markers determination and analyses and will participate into the dietary analyses.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Federico II University Hospital	Internal Medicine and Clinical Nutrition	Naples, Italy	Director	2020	2022
Federico II University Hospital	Dept of Internal Medicine	Naples, Italy	Consultant Physician	2015	2020
Federico II University Hospital	Dept of Clinical Medicine and Surgery	Naples, Italy	Associate Professor	2010	2015

Other awards and honors

Member of the collaborating center for obesity management of the European Association for the Study of Obesity (EASO-COM). Member of the steering committee of the Italian Federation of Nutrition Scientific Societies (FESIN). Past-President of the Campania Regional Section of the Italian Society of Obesity (SIO). Director of the Interuniversity (Naples and Milan) Center for the Study of Obesity and Eating Disorders (CISRODCA).

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministero dell'Università e della Ricerca	Fedrico II University Naples	2012	PRIN	Coordinator	30.000,00	https://www.mur.gov.it/it/aree-tematiche/ricerca/programmi-di-finanziamento/prin
Ministero dell'Università e della ricerca	Federico II University Hospital	2008	PRIN	Coordinator	40.000,00	https://www.mur.gov.it/it/aree-tematiche/ricerca/programmi-di-finanziamento/prin

2.6 Research Collaborators n. 5

Last Name: Agnoli
First Name: Claudia
Last name at birth: Agnoli
Gender: F

Title: Responsible for the processing of laboratory data
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 20/07/1981
Place of Birth: Fiorenzuola d'Arda

Official H index (Scopus or Web of Science): 47.0

Scopus Author Id:25959868900 **ORCID ID:**0000-0003-4472-1179 **RESEARCH ID:**K-5916-2016

Contact address

Current organisation name: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano
Current Department / Faculty / Institute / Laboratory name: Department of Research/Epidemiology and Prevention Unit
Street: Via Venezian, 1
Postcode / Cedex: 20133
Town: Milano
Phone:+393487294402
Phone 2: 3487294402

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Parma	Single-cycle master's degree / Laurea magistrale a ciclo unico	Degree in Food Science and Technology	2000	2005

Personal Statement:

Investigator in the EPIC study. She has been working in the area of the epidemiology of degenerative chronic diseases for more than 16 years and she has a Master in Epidemiology. She is responsible for the recovery of blood samples from the Varese biological bank, and for the analysis and processing of the Varese laboratory data. She will collaborate with the PI for the statistical analyses focused on the main study objectives, interpretation of results, and scientific papers preparation and dissemination of results.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Fondazione IRCCS Istituto Nazionale dei Tumori	Department of Research, Epidemiology and Prevention Unit	Milan, Italy	Researcher	2006	2022

Other awards and honors

2016: collaborator of a grant funded by Italian Ministry of Health: "Epigenetics and prediction of Breast Cancer Risk: the role

of circulating miRNA and the interaction with metabolic abnormalities".
2012: winner of the "Premio Maccacaro" for young researcher conferred by Associazione Italiana di Epidemiologia (AIE).
2011: winner of the "Premio Giovani Ricercatori" for young researcher conferred by Fondazione IRCCS Istituto Nazionale dei Tumori, Milano.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Italian Ministry of Health	Fondazione IRCCS istituto nazionale dei tumori	2019	The role of diet in low-grade chronic inflammation and risk of cancer and major chronic degenerative disease: a prospective study	Coordinator	433.660,00	https://www.istitutotumori.mi.it/web/guest/s.c.-epidemiologia-eprevenzione

2.7 Research Collaborators n. 6 - Under 40

Last Name: bruno
First Name: eleonora

Last name at birth:
Gender: F

Title: Responsible for ensuring the accuracy and integrity of the study data and supervision of study analyses in collaboration with the PI

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Maglie

Nationality: Italiana
Date of birth: 20/12/1982

Official H index (Scopus or Web of Science): 13.0

Scopus Author Id:37008981900 **ORCID ID:**0000-0002-9605-9482 **RESEARCH ID:**D- 4093-2017

Contact address

Current organisation name: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano
Current Department / Faculty / Institute / Laboratory name: Department of Research/Epidemiology and Prevention Unit
Street: FONDAZIONE IRCCS Istituto Nazionale dei Tumori, Via G. Venezian 1
Postcode / Cedex: 20133 **Town:** Milano
Phone:+393288364970 **Phone 2:** 0223903512

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Study University of Milan	PhD	Integrated Biomedical Research	2014	2017
Study University of Milan	Master's Degree / Laurea Magistrale	Food quality and safety (Nutrition Science)	2005	2007
Study University of Milan	Bachelor Degree / Laurea Triennale	Food Science and technology	2001	2005

Personal Statement:

She is a researcher with a PhD in Integrated Biomedical Research and a master in epidemiology. She is involved for almost 14 years in observational studies about the relevance of nutrition and lifestyle in breast cancer and in randomized dietary intervention studies for primary prevention of cancer and for the prevention of cancer recurrences. In the present proposal she will be responsible for ensuring the accuracy and integrity of the study data and will supervise the study analyses in collaboration with the PI.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Fondazione IRCCS Istituto Nazionale dei Tumori	Department of Research, Epidemiology and Prevention Unit	Milano, Italy	Researcher	2019	2022
Fondazione IRCCS Istituto Nazionale dei Tumori	Department of Research, Epidemiology and Prevention Unit	Milano, Italy	Research Assitant	2008	2019

Other awards and honors

HONOR: FONDAZIONE AIACE 2021

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
NONE	NONE	0	NONE	Collaborator	0,00	NONE

2.8 Research Collaborators n. 7 - Under 40

Last Name: Baldassari
First Name: Ivan

Last name at birth:
Gender: M

Title: Assisting the PI in the planning for recover of biological samples and management.

Nationality: Italy

Date of birth: 03/12/1992

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Milano

Official H index (Scopus or Web of Science): 2.0

Scopus Author Id:57203807566 **ORCID ID:**0000-0002-8537-9691 **RESEARCH ID:**U-2197-2018

Contact address

Current organisation name: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano

Current Department / Faculty / Institute / Laboratory name: Department of Research/Epidemiology and Prevention Unit

Street: Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian, 1

Postcode / Cedex: 20133 **Town:** Milano

Phone:+393280723036 **Phone 2:** 3280723036

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Università degli Studi di Milano	Master's Degree / Laurea Magistrale	Alimentazione e Nutrizione Umana (LM61)	2014	2016
Università degli Studi di Milano	Bachelor Degree / Laurea Triennale	Agrotecnologie per l'ambiente e il territorio	2011	2014

Personal Statement:

He has experience in conducting of randomized dietary intervention trials, both in cancer patients and at healthy people in high metabolic risk of cancer.
Here, he will support the PI in the planning for recover of biological sample and management.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI	Department of Research, Epidemiology and Prevention Unit	Milano	Researcher	2016	2022

Other awards and honors

N.A.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
NONE	NONE	0	NONE	Collaborator	0,00	NONE

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

Last Name: MORLINO
First Name: DELIA
Last name at birth:
Gender: F

Title: Support in the dietary and inflammation markers analyses
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 28/06/1992
Place of Birth: Napoli

Official H index (Scopus or Web of Science): 2.0

Scopus Author Id:57205197065 **ORCID ID:**0000-0002-3158-450X **RESEARCH ID:**ACG-1620-2022

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Federico II, Napoli
Current Department / Faculty / Institute / Laboratory name: UOC Medicina Interna e Nutrizione Clinica
Street: Via Sergio Pansini, 5
Postcode / Cedex: 80131
Town: Napoli
Phone:+393333276435
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Federico II University, Naples, Italy	PhD	Advanced biomedical and surgical therapies	2018	2022
Federico II University, Naples, Italy	Master's Degree / Laurea Magistrale	Human Nutrition	2014	2016
Federico II University, Naples, Italy	Bachelor Degree / Laurea Triennale	Biology	2010	2014

Personal Statement:
She has experience into the collection and management of dietary data, collected through food frequency questionnaire, according to different nutritional score present in the literature. She has been already involved in the management of biological samples for inflammation/dismetabolism markers evaluation. In the present project she will support the handling of the biological sasamples stored in biobanks and the laboratory analysis and data processing for metabolic- and inflammatory-related biomarkers.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Federico II University, Naples, Italy	Department of Clinical Medicine and Surgery	Naples, Italy	Scholarship	2019	2020
Federico II University, Naples, Italy	Department of Clinical Medicine and Surgery	Naples, Italy	Scholarship	2021	2022

Other awards and honors

Travel grant-32° SISA Congress

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
NONE	NONE	0	NONE	Collaborator	0,00	NONE

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

Last Name: CIOFFI
First Name: IOLANDA
Last name at birth:
Gender: F

Title: Support in the nutritional data evaluation and analyses
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 06/10/1985
Place of Birth: Vico Equense

Official H index (Scopus or Web of Science): 8.0

Scopus Author Id:56274662300 **ORCID ID:**0000-0002-1408-209X **RESEARCH ID:**Q-1023-2019

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Federico II, Napoli
Current Department / Faculty / Institute / Laboratory name: UOC Medicina Interna e Nutrizione Clinica
Street: Via S Pansini, 5
Postcode / Cedex: 80131
Town: Napoli
Phone:+393382941867
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
School of Medicine, Federico II University, Naples, Italy	PhD	Human Nutrition and Food Science	2012	2015
School of Medicine, Federico II University, Naples, Italy	Master's Degree / Laurea Magistrale	Human Nutrition	2009	2011
School of Medicine, Federico II University, Naples, Italy	Bachelor Degree / Laurea Triennale	Dietetics	2004	2009

Personal Statement:

She has experience into the evaluation of nutritional status and dietary data assessment. She will participate into the assessment of the individual lifestyle (e.g.physical activity), environment (e.g.tobacco consumption) and clinical follow-up data. The results obtained will be discussed and interpreted by all members of the multidisciplinary team.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Federico II University	Naples, Italy	Departement Clinical Medicine and Surgery	Postdoc	2021	2022
Federico II University	Departement Clinical Medicine and Surgery	Naples, Italy	Postdoc	2019	2021
Federico II University	Department Clinical Medicine and Surgery	Naples, Italy	Researcher	2018	2019

Other awards and honors

Research grant award for the research project 'Resting energy expenditure in patients with Crohn's disease' by the Italian Society of Artificial Nutrition and Metabolism (SINPE).

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
NONE	NONE	0	NONE	Collaborator	0,00	NONE

2.17 Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Baldassari Ivan	Recruitment in randomized clinical trials: The MeMeMe experience	Article	1-11	17	2022	10.1371/journal.pone.0265495	35333878	0	F
MORLINO DELIA	Prevalence of Sarcopenia in Women with Breast Cancer	Article	1839	14	2022	10.3390/nu14091839	35565806	0	F
Pasanisi Patrizia	A mediterranean dietary intervention in female carriers of brca mutations: Results from an italian prospective randomized controlled trial	Article	1-13	12	2020	10.3390/cancers12123732	33322597	2	L
Saieva Calogero	Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-florence trial	Article	4175-4183	38	2020	10.1200/JCO.20.00650	32840419	80	O
Chiodini Paolo	Impact of chronic liver disease upon admission on COVID-19 in-hospital mortality: Findings from COVOCA study	Article	e0243700	15	2020	10.1371/journal.pone.0243700	33301529	8	C
Pasanisi Patrizia	Monitoring vitamin B12 in women treated with metformin for primary prevention of breast cancer and age-related chronic diseases	Article	1020	11	2019	10.3390/nu11051020	31067706	4	L
CIOFFI IOLANDA	Intermittent versus continuous energy restriction on weight loss and cardiometabolic outcomes: A systematic review and meta-analysis of randomized controlled trials	Article	371	16	2018	10.1186/s12967-018-1748-4	30583725	52	F
bruno eleonora	Effect of aerobic exercise intervention on markers of insulin resistance in breast cancer women	Article	e12617	27	2018	10.1111/ecc.12617	27925359	18	F
Saieva Calogero	Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study	Article	K934	361	2018	10.1136/bmj.k934	29844013	33	O
Agnoli Claudia	Separate and combined associations of obesity and metabolic health with coronary heart disease: A pan-European case-cohort analysis	Article	397-406	39	2018	10.1093/eurheartj/ehx448	29020414	139	O

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Agnoli Claudia	Oxidative stress and inflammation mediate the effect of air pollution on cardio- and cerebrovascular disease: A prospective study in nonsmokers	Article	234-246	59	2018	10.1002/em.22153	29114965	40	O
PASANISI FABRIZIO	Prediction and evaluation of resting energy expenditure in a large group of obese outpatients	Article	697-705	41	2017	10.1038/ijo.2017.34	28163316	24	L
PASANISI FABRIZIO	Dietary protein content for an optimal diet: a clinical view	Article	345-348	8	2017	10.1002/jcsm.12176	28444858	21	L
bruno eleonora	Adherence to WCRF/AICR cancer prevention recommendations and metabolic syndrome in breast cancer patients	Article	237-244	138	2016	10.1002/ijc.29689	26175188	25	F
Saieva Calogero	Dietary and lifestyle determinants of malondialdehyde DNA adducts in a representative sample of the Florence City population	Article	475-480	31	2016	10.1093/mutage/gew012	26961145	14	F
PASANISI FABRIZIO	Orexin-A represses satiety-inducing POMC neurons and contributes to obesity via stimulation of endocannabinoid signaling	Article	4759-4764	113	2016	10.1073/pnas.1521304113	27071101	36	O
Saieva Calogero	General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition	Article	646-657	137	2015	10.1002/ijc.29432	25598323	57	O
Chiodini Paolo	A journey into a Mediterranean diet and type 2 diabetes: A systematic review with meta-analyses	Article	e008222	5	2015	10.1136/bmjopen-2015-008222	26260349	209	O
Agnoli Claudia	Metabolic syndrome and breast cancer risk: A case-cohort study nested in a multicentre Italian cohort	Article	e0128891	10	2015	10.1371/journal.pone.0128891	26030767	50	F
Agnoli Claudia	Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer	Article	858-871	60	2014	10.1002/hep.27016	24443059	116	O
Pasanisi Patrizia	Metabolic syndrome and breast cancer prognosis	Article	159-165	147	2014	10.1007/s10549-014-3076-6	25104441	71	L
Pasanisi Patrizia	Life-style and metformin for the prevention of endometrial pathology in postmenopausal women	Article	119-124	29	2013	10.3109/09513590.2012.706671	22946682	21	L

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Agnoli Claudia	Hormonal, metabolic, and inflammatory profiles and endometrial cancer risk within the EPIC cohort - A factor analysis	Article	787-799	177	2013	10.1093/aje/kws309	23492765	94	O
Pasanisi Patrizia	Metformin decreases circulating androgen and estrogen levels in nondiabetic women with breast cancer	Article	433-438	13	2013	10.1016/j.clbc.2013.08.012	24267731	36	L
Chiodini Paolo	Metabolic syndrome and risk of cancer: A systematic review and meta-analysis	Article	2402-2411	35	2012	10.2337/dc12-0336	23093685	597	O

* 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?	No
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
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
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

Obese people had higher risk than lean people to develop a chronic disease. However, the condition of being Metabolically Healthy (MH) or Unhealthy (MU) obese may change disease risk. We aim elucidating pathways underlying the variation of chronic disease risk by comparing MU and MH overweight/obese and normal-weight women. Our hypothesis is that gut dysbiosis and systemic inflammation may explain the different risk linked to MH or MU adiposity and that are involved in the occurrence of obesity-related chronic diseases. We will also evaluate whether and how external exposome (diet, lifestyle, environment) affects chronic disease risk through dysbiosis and inflammation. The project has four elements: the well-defined EPIC-ITALY cohort with long follow-up; metabolic and inflammatory biomarkers to identify pathways; diet, lifestyle and environment data to prospectively evaluate the effect of external exposome; secondary analysis of the Me.Me.Me. randomized controlled trial.

Background / State of the art

Chronic diseases are the leading causes of mortality accounting for 87% of deaths in Europe (PM:24886110), and obesity has a key role in their pathogenesis. Reducing BMI by 1% was estimated to save 179000-202000 incident cases of type-2 diabetes, 122000 of cardiovascular diseases and 32000-33000 of cancer over 20 years (PM:21872750).
However, there is a large variation in the individual obesity-related disease risk that cannot simply be explained by the extent of adiposity. The observation that some obese people have lower disease risk than others has led to the concept of metabolically healthy versus metabolically unhealthy overweight/obese (MHO,MUO)(PM:32128581). MHO exhibit a

favorable metabolic and inflammatory profile, remaining insulin-sensitive. In contrast, MUO are characterized by increased secretion of inflammatory cytokines resulting in chronic low-grade inflammation, insulin resistance and contributing to their metabolic impairment and higher risk of chronic diseases. MHO prevalence is higher in women than in men (PM:32128581). Obesity may lead to gut dysbiosis and consequent metabolic endotoxemia. Our hypothesis is that this is the critical factor in inducing adipose tissue chronic-low grade inflammation that characterizes MUO and it is associated with chronic diseases. Diet and lifestyle affect the microbiota and the inflammatory profile, however this topic is still relatively unknown (PM:34680216), thus we intend to investigate it in this proposal.

Description and distribution of activities of each operating unit

The research team has an established collaboration since 30 years on the management of the EPIC-Italy cohort study that favors the synergy of the group. This collaboration has led to the publication of numerous scientific articles on the association between diet, lifestyle, biomarkers, and cancer and CVDs risk in the Italian population. One of the strengths of this project is the nature of the team, involving different figures, all with consolidated role in data analyses, metabolic and inflammatory biomarkers analyses and prevention clinical randomized trials.

The Epidemiology and Prevention Unit (UO1-INT) has long been concerned with elucidating how diet and hormones influence disease aetiology and how this knowledge can be used in disease prevention. The UO1-INT has been involved in prospective studies (ORDET and EPIC) since 1987 and intervention studies (DIANA and Me.Me.Me.) since 1996.
UO1-INT will be responsible of overall design and conduct of the study. UO1-INT will coordinate and supervise the dysbiosis analyses of its laboratory, which has long expertise in these kind of analyses from biological samples taken in the course of large-scale epidemiological studies. UO1-INT will be involved in EPIC-Varese and Me.Me.Me biological bank management.

ISPRO (UO2) has been involved in the EPIC study from its beginning (1992). UO2 will be involved in the recovery of blood samples from the local biological bank (EPIC-Florence), main individual data related to diet, lifestyle, and clinical follow-up.

The Medical Statistics Unit of the University of Campania (UO3) is involved in several collaborative epidemiological and clinical research projects including the EPIC study. The mission is to serve as a source of expertise for clinical research and epidemiology and to promote the use of rigorous quantitative methods in the biomedical sciences. UO3 will be involved into the study design, the definition of the cases and controls to be included into the case-cohort analyses and will be responsible of the statistical analyses. UO3 will also manage the analyses to test whether the external exposome influences adiposity-related chronic disease risk through dysbiosis and inflammation.

Azienda Ospedaliera Universitaria Federico II (UO4) will be involved in the recovery of blood samples for the EPIC-Naples centre and with his laboratory team will be responsible for the mechanistic part of the study. UO4 will be responsible for the inflammatory markers determination and analyses and will participate into the dietary analyses.

All the project collaborators will be actively involved in the various project phases. The results obtained will be discussed and interpreted by all members of the multidisciplinary team. Periodic meetings (at least every 6 months) will ensure smooth project management and will allow to discuss any difficulties and to assess project progress.

5.4 Specific Aims and Experimental Design

Specific aim 1

To elucidate the pathways (via dysbiosis and inflammation) underlying the different risk associations between the incidence of chronic diseases and the status of being MHO or MUO women. The definition of MU will be given on the basis of the

baseline information about waist circumference, blood pressure, therapy for dyslipidemia and diabetes of the women participant into the EPIC-Italy cohort. This aim will be achieved by a case-cohort study, nested within the EPIC-Italy cohort, focusing on chronic diseases strongly related to obesity, i.e. CVDs (myocardial infarction and stroke) and some main cancer sites such as the breast and colon-rectum.
Metabolic- and inflammatory-related biomarkers will be used to improve the understanding of the mechanisms through which dysbiosis and consequent low-grade chronic inflammation influence increased risk of overweight/obesity-related cancers and CVDs. To do this we will compare systemic endotoxemia (defined as a condition of elevated plasma lipopolysaccharide at levels 10-50 times lower than during septic conditions) and inflammatory profiles in normal weight healthy, normal weight unhealthy, MHO, and MUO women from our EPIC-Italy cohort who do and do not develop obesity-related cancers or CVDs.
A preliminary analysis on a subset of EPIC-Varese postmenopausal women showed that leptin and C-reactive protein (CRP) were significantly higher, while adiponectin was significantly lower, in overweight/obese than in normal weight women and in those with abdominal obesity than in those who had not it (see picture of preliminary data, Tables 1 and 2). Furthermore, high lipopolysaccharide levels were associated with increased breast cancer risk (see picture of preliminary data,Table 3). Also, overweight/obese women with abdominal obesity of the EPIC-Italy cohort had increased breast cancer risk; the risk increase was stronger among postmenopausal women (see picture of preliminary data,Table 4).
These observations led us to hypothesize that systemic endotoxemia and inflammation may explain the different risk of adiposity and are involved in the occurrence of overweight/obesity-related chronic diseases.
EPIC-Italy is the Italian section of a larger project known as EPIC (European Prospective Investigation into Cancer and Nutrition), a prospective study on diet and cancer carried out in 10 European countries. Between 1992-1997, EPIC-Italy recruited 47,749 volunteers (15,171 men, 32,578 women, aged 35-65 years) in 5 centers: Varese and Turin in the Northern part of the country; Florence in Central and Ragusa and Naples in Southern Italy, respectively. Participants have been followed up for a median of about 14 years. These centers are now involved in the present proposal of investigation.

Specific aim 2

To determine whether and how external exposome (diet, lifestyle and environment) influences obesity-related chronic disease risk through dysbiosis and systemic inflammation in a prospective observational design.
To do this we will characterize different phenotypes of women on the basis of their BMI and their metabolic health (normal weight healthy, normal weight unhealthy, MHO, and MUO) to evaluate if and how their diet (investigated by food frequency questionnaire), lifestyle (e.g. physical activity) and environment (evaluated from tobacco consumption and atmospheric pollution data modelled by using information derived from satellite and monitoring station) may act on disease risk through modulation of dysbiosis and chronic inflammation.
For 76% of women recruited in EPIC Varese cohort (n=7407), lifestyle, dietary information, anthropometric measurements and blood samples were taken twice: in 1987-1992, and 1993-1997. This will allow us to prospectively evaluate the association between external exposome and the development of MUO/MHO in those women who were normal weight at the first measurement and how dysbiosis and inflammation influence the incidence of obesity phenotypes.

Specific aim 3

To test if the predictive risk pathways identified in the women from the EPIC-Italy cohort are modified by a preventive lifestyle intervention designed to reduce the incidence of age-related chronic disease.
To answer to this specific aim we will perform a secondary analysis on women included into the Me.Me.Me. prospective randomized intervention trial (NCT02960711) (PMID:35333878,28740367,28106245, 30794607,32921035). Me.Me.Me. stands for Metabolic syndrome, Mediterranean diet and Metformin. The Me.Me.Me. included a Mediterranean dietary intervention with moderate calorie and protein restriction, physical activity recommendations and/or a treatment with metformin, a low-cost fast-mimic diet drug. Me.Me.Me. involved people at higher risk of development of chronic diseases

because of age (50-74 years at recruitment) and the presence of the metabolic syndrome (central adiposity, hyperglycaemia, dyslipidemia, and hypertension) defined according the International Diabetic Federation (PMID: 19805654). The study had a 2 × 2 factorial design involving 1600 volunteers (about 60% women) randomized into 4 groups (400 each): metformin (1,700 mg/day) + Mediterranean dietary intervention; placebo + Mediterranean dietary intervention, metformin (1,700 mg/day) alone; placebo alone. The metformin/placebo component was double-blind. Volunteers randomized to the Mediterranean dietary intervention were invited to participate in dietary activities with common lunch/dinner and kitchen classes at least once a month in the first year. Anthropometric variables, blood samples, lifestyle information, and dietary and exercise data were collected at baseline and once/year for each of the 5 years of the study. Among the 942 Me.Me.Me. women properly randomized, 244 were allocated in the metformin (1,700 mg/day) + Mediterranean dietary intervention arm, 240 in the placebo + Mediterranean dietary intervention, 242 in the metformin (1,700 mg/day) alone and 216 in the placebo alone.
The risk pathways identified in the women from the EPIC-Italy cohort will be evaluated in a sample of women participants into the Me.Me.Me. from each of the four randomized groups by profiting of their blood samples at baseline and after one year of intervention.

Experimental design aim 1

We will assess the association of different obesity phenotypes with risk of breast (BC) and colorectal cancer (CRC), acute myocardial infarction (MI), and stroke and whether these associations are mediated by inflammatory, dysbiosis, and nonalcoholic fatty liver disease biomarkers. To do this, we will perform a case-cohort study nested in the EPIC-Italy cohort. At next follow-up (end of 2012 for both cancer and CVD), we expect to have 1200 BC and 379 CRC; 409 stroke and 496 MI in women. A center-stratified random subcohort of 1000 women will be obtained by sampling from the 22,494 women recruited to EPIC-Italy. These women will be classified based on their obesity phenotype into normal weight (i.e. BMI less than 25), MHO (i.e. BMI of 25 or more, systolic BP less than 130 mm Hg, no BP-lowering medication, waist circumference below the median value of the women's cohort, and no self-reported diabetes) (PMID: 33961036), and MUO (i.e. BMI of 25 or more and systolic BP at least 130 mm Hg, BP-lowering medication, waist circumference above the median value of the women's cohort or self-reported diabetes).
The following biomarkers will be measured in plasma samples:
-CRP, TNF-alpha, IL-6, leptin, PAI-1, IL-1beta, IFN-gamma, IL-8, IL-12 (proinflammatory cytokines), and adiponectin and IL-10 (anti-inflammatory cytokines) to assess chronic low-grade inflammation that characterizes dismetabolic obesity. Indeed, an aspect that has been hypothesized to differentiate MUO from MHO is the presence of chronic low-grade inflammation, which has been purported to be a cause of insulin-resistance (PMID: 29328913, 7678183). These biomarkers will be measured by an automated Immunoassay platform;
-LPS and zonulin to assess dysbiosis. LPS has been hypothesized to potentiate both chronic low-grade inflammation and insulin resistance that led to the development of metabolic complications (PMID:22728514), while zonulin is a marker of intestinal permeability (PMID: 25162769). They will be measured using ELISA kits;
-ceramides as biomarkers of insulin resistance and inflammation linked to adipose tissue (PMID: 24749054, 11557309). They will be measured with a semi-targeted lipidomic analysis by a liquid chromatography-high resolution mass spectrometry platform (HPLC-HRMS) after solvent samples extraction, followed by ceramides identification with the Lipid Search software;
-triglycerides, and gamma-glutamyl transferase (GGT) to evaluate the presence of nonalcoholic fatty liver disease (NAFLD), which is linked to abnormalities of lipid metabolism potentially involved in the progression of obesity-induced disease (PMID: 35630058). They will be measured on automated analyzer using reagent kits from standard companies.
We will then perform Cox models with appropriate weights for the case-cohort design to evaluate the association of obesity phenotype and NAFLD, inflammatory and dysbiosis biomarkers as well as with risks of BC, CRC, stroke, and MI. Finally, we will perform mediation analysis to evaluate whether the associations between obesity phenotype and diseases risks are mediated by NAFLD, inflammatory and dysbiosis biomarkers

Tasks
1.1 Update of follow-up
1.2 Dataset preparation for case-cohort study (UNIT 3)
1.3 Retrieval of blood samples of selected subjects in each EPIC center (UNIT 1,2,4)
1.4 Laboratory analysis to determine inflammatory and NAFLD-biomarkers at laboratory of UNIT 4
1.5 Laboratory analysis to determine ceramides and dysbiosis biomarkers at laboratory of UNIT 1
1.6 Dataset preparation for statistical analyses of EPIC-Italy cohort
1.7 Statistical analyses

Experimental design aim 2

We will study the influence of external exposome on the relationship between change in obesity phenotype and incidence of CRC, BC, stroke and MI in women, using a prospective design. We will evaluate the effect of external exposome on the incidence of MHO or MUO phenotype in EPIC women who updated (after a median of 10 years from recruitment) anthropometric, blood pressure and diabetes information by filling in mail questionnaires or by telephone interview (n=22,400). We will assess how external exposome at baseline may influence disease risk both directly and through change in obesity phenotype.
Among the EPIC -Varese women who gave a dietary, lifestyle, anthropometric information and a blood sample twice we will set up a nested case-control study to evaluate how change in obesity phenotype may be influenced by external exposome and how it may influence the development of BC through modulation of inflammation and metabolic endotoxemia.
The abovementioned associations will be evaluated using survival models, including when appropriate, mediation models. In the models we will evaluate the risk due to dietary and lifestyle (smoking, occupation, physical activity) information collected in the five EPIC-Italy centers through questionnaire, together with information derived from and connection to satellite data for pollution and data on dysbiosis markers and disease status. For the EPIC-Varese subsample a conditional logistic regression model will be applied.
Tasks
2.1 Datasets preparation for statistical analyses of the EPIC-Italy cohort with the updated anthropometric and lifestyle information of EPIC-Italy follow-up
2.2 Dataset preparation for case-control study in the EPIC-Varese subsample with information and blood samples collected twice
2.3 LPS, zonulin and inflammatory biomarkers analyses in 250 blood samples of women who were measured twice in the EPIC-Varese cohort. The analyses will be performed with ELISA kits for LPS and zonulin at the laboratory of the same Unit of the PI (UNIT 1) and at the laboratory of UNIT 4 for inflammatory biomarkers
2.4 Georeferencing of the cohort through individual address and connection to satellite data (UNIT 4)
2.5 Statistical analyses (UNIT 3)

Experimental design aim 3

We will test whether the inflammatory, dysbiosis and NAFLD markers involved in the association between obesity phenotype and diseases risk may be modulated by a preventive intervention based on Mediterranean diet and metformin treatment. To evaluate this aspect we will study the MUO women included into the Me.Me.Me randomized controlled trial (NCT02960711). According to the Me.Me.Me protocol, women participants had to provide a fasting 20-mL blood sample (to measure plasma glucose, triglycerides, total, LDL and HDL cholesterol and liver transaminases) at baseline, at the end of the first year of the study, and once/year for each of the 5 years of the study in a sample of study participants.

Out of the 942 Me.Me.Me. women properly randomized, we will randomly select a subsample of women with BMI of25

kg/m2 or above and complete metabolic data after the first year of intervention.
In detail, we will profit of blood samples from baseline and at the end of the first year of the study:
100 women allocated in the metformin (1,700 mg/day) + Mediterranean dietary intervention arm
100 in the placebo + Mediterranean dietary intervention
100 in the metformin (1,700 mg/day) alone and
100 in the placebo alone.

Measurements of the previously described inflammatory and dysbiosis markers will be assessed from these samples. The effect of the intervention (diet/metformin or both) on biomarkers will be analyzed evaluating differences over time among interventions by means of mixed effect regression models.

Tasks

3.1 Retrieval of plasma samples of selected subjects
3.2 Dysbiosis markers and ceramides analyses will be performed by UNIT 1
3.3 Shipment of plasma samples to the lab of UNIT 4 for inflammatory markers analyses
3.4 Dataset preparation for statistical analyses of the Me.Me.Me study
3.5 Statistical analyses to test whether and how the proposed intervention modulates the biomarkers under study (UNIT 3)

Picture to support preliminary data

dati_preliminari_16_05_2022.pdf

Hypothesis and significance

The overarching aim of our study is to provide updated, relevant and innovative evidence for underpinning future strategies for the targeted disease prevention and clinical interventions that address the issue of obesity heterogeneity acting on the external (i.e. diet, environment, lifestyle) and internal (i.e. dysbiosis and inflammation) exposome determinants of obesity phenotypes.
We propose to elucidate pathways underlying the association of MUO and MHO and major overweight/obesity-related chronic diseases.
Our hypotheses are that dysbiosis and consequent proinflammatory profiles will enable the identification of pathways underlying different overweight/obesity phenotypes that lead to the development of chronic diseases and that these identified clinical/molecular predictive pathways of risk might be modified by lifestyle/metformin interventions.
The success of this study may open new 'target' preventive intervention to reduce the risks of the major chronic diseases.
The project has four elements: (i) a well-defined cohort of thousands of women followed over long periods (EPIC-ITALY cohort); (ii) inflammation and dysbiosis markers to determine molecular level characteristics of unhealthy and healthy obese women and hence identify pathways; (iii) diet, lifestyle and environment information to evaluate their influence (via dysbiosis and inflammation) on the development of obesity/overweight-related chronic disease; (iv) secondary use of the randomized controlled Me.Me.Me. trial based on a Mediterranean diet intervention with a low-calorie restriction and/or a low-cost fast-mimic diet drug (metformin).

5.5 Methodologies and statistical analyses

Methods of data collection

Dietary and lifestyle data were collected by questionnaires. Anthropometric and blood pressure measurements were taken by trained personnel.

Environmental data: in recent years the use of satellite data to define exposure in environmental epidemiology has become more widespread. Satellite data have the advantage of providing greater spatial coverage compared to ground monitoring networks, better spatial resolution/characterization of space, good temporal coverage and limited costs. DEP Lazio developed a model to predict PM2.5 and PM10 concentrations using data from satellite images, monitored data, meteorological parameters and spatial data. Addresses of subjects will be geocoded to estimate environmental exposure. The environmental data will be available daily in the period 2006-2015, but availability of data in other time periods will be explored.
Follow up will be performed trough linkage to mortality, hospital discharge databases and cancer registry.
Laboratory data
The eleven inflammation biomarkers (CRP, TNF-alpha, IL-6, leptin, PAI-1, IL-1beta, IFN-gamma, IL-8, IL-12, adiponectin, IL-10) will be measured by automated microfluidic immunoassay cartridges on ProteinSimple Ella (Bio-Techne, Milan, Italy), in accordance with the manufacturer's instructions.
LPS and zonulin will be measure using by ELISA kits.
Ceramides will be determined in LC-MS and LC-MS/MS using an Orbitrap machine equipped with a HESI ion source and operating in high resolution mode. The data will be processed to identify molecular structures using Thermo XCalibur and Lipid Search softwares (PMID:27260449).
Triglycerides and gamma-glutamyl transferase (GGT) will be measured by specific standardized kits (Abbott Diagnostics, Rome, Italy) on an automated biochemistry analyzer (Architect ci 16200 Integrated System, Abbott Diagnostics, Rome, Italy).

Statistic plan

To evaluate associations within the EPIC-Italy study the case-cohort design will be used because evaluating all the markers in the entire cohort is not viable due to the cost consideration and because there is interest in several definitions of a case. Cohort sampling designs are used in follow-up studies when large cohorts are needed to observe enough cases but it is not feasible to collect data on all covariates for the whole cohort. The case-cohort design requires the evaluation of markers in (1) a random subsample of the original cohort (subcohort), selected independently of the definition of cases; and, (2) in all cases outside the subcohort, i.e. all members of the cohort developing any or all events of interest during the follow-up. The union of (1) and (2) is referred to as the case-cohort design. A distinct advantage of the case-cohort design is that the selected subcohort can be used for analysing several endpoints of interest. Furthermore, as the subcohort forms a random sample of the original cohort, it can be used to assess the marker distribution of the population. If the subcohort is selected efficiently, the statistical power of tests is not substantially reduced compared to the alternative where the full cohort is considered. In this study, a subcohort of 1000 subjects will be used.
To evaluate associations in the EPIC-Varese subsample, a nested case-control study will be designed. For each case, one matched control will be chosen, using an incidence density sampling protocol, from appropriate risk sets consisting of the Varese-cohort members alive and free of cancer at the time of diagnosis of the index case.
Power calculation
Considering the most powerful analysis, i.e. that on breast cancer, we expect 1200 cases, and assuming statistical power 0.80 and alpha-error 0.05 (2-tailed test), two groups (exposed/unexposed) of equal size, the minimum detectable HR will be 1.23. For the least powerful analysis (that on colon cancer) we expect 379 cases, and assuming statistical power 0.80 and alpha-error 0.05 (2-tailed test), two groups (exposed/unexposed) of equal size, the minimum detectable HR will be 1.34

Statistical analysis

To achieve AIM 1, we will use the Prentice weighted approach to Cox model in order to adapt it to a case-cohort design. In fact, because of the overrepresentation of cases in a case-cohort analysis, a modified version of Cox regression should be used in which the partial likelihood is replaced by a pseudolikelihood, where cases inside and outside the subcohort are weighted differently. Among the various weighting schemes proposed we will use that proposed by Prentice, in which all

members of the subcohort are given equal weight, while cases outside the subcohort are only weighted (and hence included in the risk set) at their event time.
Moreover, we will use a mediation analysis in order to disentangle the total effect of the exposure on a certain outcome in natural indirect and pure direct effects. The natural indirect effect can be defined as the effect of the exposure on the outcome operating through the mediators, while the pure direct effect expresses changes in the outcome due to the exposure, but operating through other mechanisms, independent of the considered mediator. Analyses will be performed through the counterfactual approach (PMID: 25580377) that allows the presence of nonlinearities and interactions between exposure and mediator. Counterfactual methods have been already developed for the most common types of outcome in epidemiology, such as continuous, binary, and survival variables (VanderWeele 2015). For non-rare time-to-event outcomes or when multiple mediators not necessarily independent will be of interest, counterfactual approaches involving specific weights will be used (PMID: 30689682). To make results more comprehensible, pure direct and natural indirect effects 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(s) (VanderWeele 2015). To be able to give a causal interpretation to direct and indirect effects, the aforementioned approaches require all the confounders of the associations exposure-outcome, exposure-mediator(s), and mediator(s)-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.
To evaluate the effect of external exposome on the development of MUO/MHO in the EPIC-Varese subsample conditional logistic regression models will be applied (AIM 2)
The effect of the intervention (diet/metformin or both) on biomarkers (AIM 3) will be analyzed by means of mixed effect regression models that use all available data over follow-up and can properly account for correlation between repeated measures. Time, intervention and their interaction will be included in the model as covariates.

Timing of analysis data

In the first phase of the project (first year), follow-up of EPIC-Italy volunteers, recruited in 1993-1998, will be updated until 2013. Volunteers were followed- up through the local population-based cancer registries in Florence, Ragusa, Turin and Varese (a median of follow-up of 14 years) until 2009/2010. In Naples data were obtained by means of an active follow-up procedure and/or record linkage with regional computerized file of hospital discharge forms until 2010. Georeferencing of the cohort will be also finalized in the first year of the study. The analyses on exposome will be finalized in the second year together with inflammatory and dysbiosis biomarkers.

5.6 Expected outcomes

The results of the project are expected to provide an improved knowledge on the complex biological mechanisms by which unhealthy obesity phenotype leads to increased risk of obesity-related cancers and CVDs, increasing our understanding of the causes of these diseases. This is of particular importance to confirm that unhealthy obesity is a causal factor of chronic diseases and not only a condition that shares the same lifestyle factors with these diseases.
Furthermore, the project will allow us to better understand interactions between external exposome and inflammation and dysbiosis biomarkers in their role in causing unhealthy obesity. If we find that external exposome exerts its effect by increasing incidence of unhealthy obesity, this will be of enormous importance since external exposome can be modified, making it feasible to reduce risk.
Furthermore, we will analyze how these risk profiles will be modified by dietary intervention with moderate calorie and protein restriction and/or a treatment with a low-cost fast-mimic diet drug dietary.

5.7 Risk analysis, possible problems and solutions

Precise measurement of inflammation biomarkers can be challenging, due to their relatively low concentration in healthy

participants. To solve this problem, we will use high-sensitive kits. Moreover, this approach has already been used to measure some of these cytokines in EPIC blood samples, producing satisfactory results (PMID: 28983080). The use of environmental data will be challenging due to lack of fine spatial and temporal resolution in air pollution assessment. The use of satellite data will override this problem estimating daily pollution concentrations at 1X1 km resolution.

5.8 Significance and Innovation

Previous studies probing associations of obesity with BC, CRC and CVDs mainly considered obesity as a single entity and not as a phenotypically heterogeneous condition. Taking advantage of the prospective design and large sample size of the EPIC-Italy cohort, the present proposal will allow to investigate the role of external exposome on incidence of unhealthy obesity and how dysbiosis and inflammation biomarkers mediated the risk of developing overweight/obesity-related disease. Furthermore, the study population, is highly characterized in terms of exposures (diet, lifestyle, environment), thus permitting extensive evaluation of the risk factors and their potential interaction with obesity and biomarkers.
Deeper understanding of the obesity heterogeneity has important clinical implications and may lead to personalized therapy and cost-effective public health intervention.

5.9 Bibliography

PMID: 24886110: Divajeva D, et al. BMC Public Health. 2014;14:456.
PMID: 21872750: Wang YC, et al. Lancet. 2011;378(9793):815-25.
PMID: 32128581: Blüher M. Endocr Rev. 2020; 41(3):bnaa004.
PMID: 34680216: Eibl G, et al. Cancers (Basel). 2021;13(20):5067.
PMID: 35333878: Baldassari I, et al. PLoS One. 2022;17(3):e0265495.
PMID: 28740367: Cortellini M et al. Patient Prefer Adherence. 2017;11:1127-32.
PMID: 28106245: Pasanisi P, et al. Tumori. 2018;104(2):137-142.
PMID: 30794607: Cortellini M et al. PLoS One. 2019;14(2):e0212475.
PMID: 32921035: Bruno E, et al. Epidemiol Prev. 2020;44(4):288-94.
PMID: 19805654: Alberti KG, et al. Circulation. 2009;120(16):1640-5
PMID: 33961036: Zembic A, et al. JAMA Netw Open. 2021;4(5):e218505
PMID: 29328913: Lee YS, et al. Cell 2018;172(1-2):22-40.
PMID: 7678183: Hotamisligil GS, et al. Science. 1993;259(5091):87-91.
PMID: 22728514: Vrieze A, et al. Gastroenterology. 2012;143(4):913-6.e7.
PMID: 25162769: Jialal I, et al. Metab Syndr Relat Disord. 2014 ;12(9):454-6.
PMID: 24749054: Larsen PJ, et al. Mol Metab. 2014 ;3(3):252-60.
PMID: 11557309: Andrieu-Abadie N, et al. Free Radic Biol Med. 2001 ;31(6):717-28.
PMID: 35630058: Petrescu M et al, Medicina. 2022 May 6;58(5):641.
PMID: 27260449: Tang H, et al. Talanta. 2016;156-157:163-71.
PMID: 25580377: VanderWeele TJ, et al. Epidemiol Methods. 2014 ;2(1):95-115.
VanderWeele TJ. 2015 (book) ISBN 978-0-19-932587-0
PMID: 30689682: Fasanelli F, et al. Am J Epidemiol. 2019 May 1;188(5):967-74.
PMID: 28983080: Agnoli C, et al. Sci Rep. 2017;7(1):12708.
PMID: 29506361: Badaloni C,et al. Epidemiol Prev. 2018 Jan-Feb;42(1):46-59.
PMID: 24126480: Karelis AD, et al.Nat Rev Endocrinol. 2013;9(12):694-5.
PMID: 31524630: Smith GI, et al. J Clin Invest. 2019;129(10):3978-89.
PMID: 24622321: Stefan N et al. Lancet Diabetes Endocrinol.2013;1(2):152-62.
PMID: 26133659: Boutagy NE, et al. Biochimie. 2016;124:11-20.

PMID: 30185915: Man SM. Nat Rev Gastroenterol Hepatol. 2018;15(12):721-37.

5.10 Timeline / Deliverables / Payable Milestones

In the first year of the study, we will update follow-up (UO1, UO2, and UO4), retrieve samples in each EPIC center, begin the geolocation of the EPIC-Italy cohort (UO1, UO2, UO4), measure dysbiosis markers in the EPIC-Varese subsample (UO1) and start measuring dysbiosis and inflammatory biomarkers on EPIC samples. In the second year, we will perform all other analyses on dysbiosis, inflammatory biomarkers and NFLD on the EPIC-Italy cohort and Me.Me.Me study (UO1, UO4) and perform mediation analysis on the EPIC-Italy case-cohort dataset (UO1, UO3). We will also perform the laboratory and statistical analysis to assess the complex relationships between external exposome, obesity phenotype, biomarkers, and subsequent disease onset (UO1 and UO3).

Milestones 12 month

After 12 months we will have identified all new CRC, BC, IM and stroke cases and performed the analyses on the Varese subcohorts to determine LPS and zonulin in relation to BC incidence. We will further have geolocalized all EPIC participants. External exposome data will be ready for statistical analyses.

Milestones 24 month

Dysbiosis and inflammatory biomarkers and ceramides analyses of EPIC-ITALY and Me.Me.Me samples will be finished. Publication of scientific papers illustrating study results will be prepared.

Gantt chart

GANTT.pdf

5.11 Equipment and resources available

Facilities Available

UO1-INT has a long and successful history of population-based research and intervention studies. Biological samples of study participants have been stored by experienced personnel since the 1980s. Blood samples from EPIC-Varese participants (stored 30 years) are available for analysis, as are blood samples from MeMeMe study participants. In the UO1 is located the Molecular Epidemiology Laboratory that is fully-equipped to process biological material and do analyses in: clinical biochemistry; LC-high resolution MS (Orbitrap), LC-MS (triple quadrupole) and GC-MS spectrometry for metabolomics, and ICP-MS for elemental analyses.
Office spaces are available at Unit 1, 2 and 3 with personal computers equipped with software to set up data analyses and to perform statistical analyses. Specific resources are available as software environments for statistical computing and analysis (i.e. Stata, SAS, R)
In the UO4 is located the laboratory CEINGE-Biotecnologie Avanzate that operates in the field of molecular biology and advanced biotechnology applied to Human Health. The laboratory is fully equipped with instrumentations for molecular and biochemical analyses. In particular, an innovative automated microfluidic immunoassay system (ProteinSimple Ella, Bio-Techne) for a high-throughput analysis of cytokines and other protein biomarkers is already available.

Subcontract

Department of Clinical and Biological Sciences (CLINBIO), University of Turin and The Department of Epidemiology (DEP) in Rome will be subcontractors of the project. The role of CLINBIO will be to perform the follow-up of the EPIC cohorts of Turin under the supervision of Prof Fulvio Ricceri and to provide the biological samples needed for the project. He will perform the follow-up of mortality and CRC/BC incidence until 31/12/2013 through the municipalities, cancer registries,

hospital discharge databases, cause-specific mortality registries and/or active follow up. He has a strong experience in follow-up procedures of epidemiological studies. For logistic reasons the follow up of the Turin cohort cannot be performed by the three UNITS of the present project.
The role of DEP Lazio will be to provide daily environmental data starting from geocoded data of all subjects. The DEP Lazio has a strong experience in the evaluation of the environmental data using satellite data and including spatio-temporal parameters and other important spatial predictors (PMID: 29506361).

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

Project feasibility is ensured by collaboration between a team of young researchers that work under the supervision of experienced scientists. These collaborators are young nutritionists adept in dietary assessment and evaluation of adherence to dietary patterns, of anthropometric characteristics and physical activity level. They have been already involved in observational epidemiological studies on lifestyle and chronic disease risk, moreover they will work in close contact with senior researchers involved in EPIC-Italy study.
Under the supervision of their mentor (Prof. Pasanisi F), they will be enabled to gain experience in handling biological samples stored in biobanks, and support lab analysis and data processing for metabolic- and inflammatory-related biomarkers.
The young researchers will also have the possibility of collaborating with Prof. Chiodini, thus they will be involved in the design and conduction of epidemiological studies and in the implementation of complex exposome data analyses.

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

What is already know about this topic?

CVDs and cancer are the main chronic diseases in terms of disease burden and premature mortality (PM:24886110). Epidemiologic studies have identified that high BMI is a major risk factor for these chronic diseases (PM:21872750). However, obesity is a heterogeneous condition associated with a varying spectrum of metabolic risk from the MHO to MUO phenotype, with a subgroup of MHO who may be protected from obesity-related cardiometabolic diseases or may be at a significantly lower risk than individuals with the same adiposity but presenting a dismetabolic profile (PM:32128581).

Details on what is already know about this topic

Inflammation of the adipose tissue points the link between obesity and metabolic abnormalities (PMID:24126480). Some obese/overweight people display chronic, low-grade inflammation, which has been purported to be a cause of insulin resistance (PMID:31524630). These people show visceral and ectopic fat accumulation, including liver fat storage (PMID:24622321). Gut dysbiosis may contribute to the metabolic imbalance driving an increase in intestinal permeability and promoting metabolic endotoxemia, a life-threatening condition associated with systemic inflammation and obesity-linked diseases (PMID:26133659). LPS activates inflammatory cytokine production thus increasing insulin resistance (PMID:30185915).
Better understanding of the factors that distinguish MHO from MUO phenotype and of the effect of environmental and lifestyle factors on metabolic complications of adiposity could produce new insights into mechanism underlying metabolic dysfunction and obesity-related diseases.

What this reasearch adds?

Mechanisms linking the incidence of chronic-degenerative diseases and the status of being MHO or MUO through dysbiosis and related systemic low-grade inflammation are incompletely understood (PM:32128581). Better understanding of the relation between obesity, dysbiosis and inflammation markers with cardiometabolic diseases and the further influence of external exposome will allow:

-to identify the women who are at increased risk because of their cardiometabolic profile;
-to develop strategies (e.g. lifestyle, dietary or pharmacologic interventions) to disrupt dysbiosis and inflammatory process and
-to reduce the risk of a future chronic disease.
Furthermore, if we find good evidence that a lifestyle/metformin intervention may modulate the identified dysbiosis and inflammatory markers, we will be able to effectively intervene on women at risk using target primary prevention actions.

Details on what this reasearch adds

The precise mechanisms responsible for preserved metabolic health in people with MHO or the increased risk for obesity relate-disease in people with MUO are not known. EPIC-Italy is a well-characterized cohort, with its high-quality data on diet and lifestyle factors that will allow to explore the relationships with overweight/obese related diseases in MHO or MUO compared to normal weight people. Metabolic health may deteriorate with ageing. Hence, MHO might have a high prevalence in premenopausal women and lower frequencies with increasing age. EPIC-Italy cohort could allow to investigate the progress of this condition. Finally, the influence of the gut microbiome on metabolic health is a rapidly emerging area of research. The EPIC-Italy cohort with its stored blood samples (baseline and some years later for a subsample) will allow to evaluate if these abnormalities are a cause or a consequence of the metabolic dysfunction and if they are associated with obesity-related diseases.

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

Over a third of Europeans over age 15 suffer from a chronic condition and two-thirds of those reaching retirement age have at least two chronic illnesses. The costs of effective cancer treatments are increasing sharply while for several cancers effective treatments do not exist. Therefore, a rational approach to cancer control must pass through prevention. The prevention of CVDs and diabetes is a further essential element in the control of these diseases. Our study expects to show that cost-effective measures (modification of diet and/or assumption of a low-cost drug) have the potential to reduce the burden of these diseases. Moreover, demonstrating that these measures are effective for the primary prevention of more than a single disease, our study will impact not only on one, but on several leading causes of morbidity and mortality, thus helping to relieve overstretched health and social services from the huge pressure due to large human, social and economic costs of these diseases.

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

The heterogeneity in the metabolic complications associated with obesity has important clinical implications, particularly in the current era of precision medicine and cost-effectiveness. The classification of obesity by BMI status alone does not provide adequate insight into current health status and disease risk. The available data suggest that more intensive, and presumably more expensive, weight management therapies should be prioritized for those with MUO over those with MHO to reduce the incidence of obesity related disease. There is a great need to prevent or treat obesity. A balance between approaches - reducing or preventing obesity and breaking the link between obesity and related diseases - is required. An intermediate approach, targeting common points in the link (such as insulin resistance) is also possible. We expect to show if heterogenous adiposity conditions may differently influence disease risk and how they may be counteracted with cost-effective measure.

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	232.000,00	232.000,00	not permitted	0,00
2 Researchers' Contracts	305.000,00	0,00	305.000,00	30,69
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	530.000,00	0,00	530.000,00	53,34
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts *	62.600,00	0,00	62.600,00	6,30
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	19.500,00	0,00	19.500,00	1,96
8 Publication Costs	7.000,00	0,00	7.000,00	0,70
9 Dissemination	4.000,00	0,00	4.000,00	0,40
10 Overheads *	60.585,00	0,00	60.585,00	6,10
11 Coordination Costs	5.000,00	0,00	5.000,00	0,50
Total	1.225.685,00	232.000,00	993.685,00	100,00

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

Report the Co-Funding Contributor:

Co-founding : Staff salary for UO1 (1 Senior Epidemiologist and 1 Epidemiologist) and the researcher's contract of the PI will be funded by Fondazione IRCCS Istituto Nazionale dei Tumori. Staff salary for UO2 (1 Medical doctor) will be funded by ISPRO
Staff salary for UO3 (1 Senior Statistitian) will be funded by University of Campania.
Staff salary for UO4 (1 Medical doctor) will be funded by Azienda Ospedaliera Universitaria Federico II.

Budget Justification

1 Staff Salary	1 Senior Researcher 3,6 P/M/Y for 2 yrs, 1 Senior Epidemiologist, MD 2,4 P/M/Y for 2 yrs, 1 Epidemiologist 4,8 P/M/Y for 2 yrs (UO1), 1 MD 1,2 P/M/Y for 2 yrs (UO2), 1 Senior Statistician 1,8 P/M/Y for 2 yrs (UO3), 1 MD 1,2 P/M/Y for 2 yrs (UO4).

2 Researchers' Contracts	U1:1 Senior Epidemiologist, 30% for 2 ys-3,6 P/M/Y-co-founded; 1 young-researcher, 25% for 2 ys-3.0 P/M/Y for 2 ys-co-founded; 1 Fellow(lab),100% for 2 ys-12 P/M/Y; U2:1 Fellow 12P/M/Y for 2 ys; U3:1 Fellow 12P/M/Y for 2 yrs; U4: 2 researchers to hire
3a.1 Equipment (Leasing - Rent)	none
3a.2 Equipment (buying)	none
3b Supplies	Kits for LPS, zonulin, CRP, TNF-alpha, IL-6, leptin, PAI-1, IL-1beta, IFN-gamma, IL-8, IL-12, adiponectin, IL-10, triglycerides and GGT. Reagents for automated microfluidic immunoassay and LC-MS.Analytical standards for ceramides.Columns for LC-MS.
3c Model Costs	none
4 Subcontracts	Follow-up update and retrieval of biological samples in Turin EPIC centre. Georeferencing of the cohort through individual address and connection to satellite data
5 Patient Costs	none
6 IT Services and Data Bases	none
7 Travels	Travels and subsistence costs for participation in national and international scientific meetings to present the results of the project
8 Publication Costs	Payment of publication costs in Open Access journals
9 Dissemination	Registration fees for participation in national and international scientific meetings to present the results of the project
10 Overheads	Institutional overheads (max 7%)
11 Coordination Costs	Costs Organization of kick off, mid-term and final meetings between participating units to discuss data analysis. Shipping costs for blood samples.

Proposed total budget UO1 Institution: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano (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	147.000,00	147.000,00	not permitted	0,00
2 Researchers' Contracts	105.000,00	0,00	105.000,00	32,45
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	155.000,00	0,00	155.000,00	47,90
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	23.800,00	0,00	23.800,00	7,36
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	1,39
8 Publication Costs	7.000,00	0,00	7.000,00	2,16
9 Dissemination	4.000,00	0,00	4.000,00	1,24
10 Overheads	19.285,00	0,00	19.285,00	5,96
11 Coordination Costs	5.000,00	0,00	5.000,00	1,55
Total	470.585,00	147.000,00	323.585,00	100,00

Budget Justification

1 Staff Salary	1 Senior Researcher, biologist (PI) (30% per year for 2 years - 3,6 P/M/Y for 2 years) 1 Senior Epidemiologist, MD (Co-PI) (20% per year for 2 years - 2,4 P/M/Y for 2 years), 1 Epidemiologist (40% per year for 2 years - 4,8 P/M/Y for 2 years)
2 Researchers' Contracts	1 Senior Epidemiologist, 30% per y for 2 yrs -3,6 P/M/Y for 2 yrs-co-founded; 1 young researcher, 25% for 2 yrs-3.0 P/M/Y for 2 yrs-co-founded; 1 Fellows(lab),100% for 2 yrs- 12 P/M/Y
3a.1 Equipment (Leasing - Rent)	none
3a.2 Equipment (buying)	none
3b Supplies	Elisa Kits for LPS and zonulin for about 4400 blood samples. Analytical standards for ceramides. Columns and reagents for LC-MS analyses.
3c Model Costs	none
4 Subcontracts	Follow-up update and retrieval of biological samples in EPIC-Italy centre of Turin
5 Patient Costs	none
6 IT Services and Data Bases	none
7 Travels	Travels and subsistence costs for participation in national and international scientific meetings to present the results of the project
8 Publication Costs	Payment of publication costs in Open Access journals
9 Dissemination	Registration fees for participation in national and international scientific meetings to present the results of the project
10 Overheads	Istitutional overheads
11 Coordination Costs	Costs Organization of kick off, mid-term and final meetings between participating units to discuss data analysis. Shipping costs for blood samples

Proposed total budget UO2 Institution: Istituto per lo Studio, la Prevenzione e la rete Oncologica (ISPRO), Firenze (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	19.000,00	19.000,00	not permitted	0,00
2 Researchers' Contracts	50.000,00	0,00	50.000,00	84,96
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	5.000,00	0,00	5.000,00	8,50
8 Publication Costs	0,00	0,00	0,00	0,00
9 Dissemination	0,00	0,00	0,00	0,00
10 Overheads	3.850,00	0,00	3.850,00	6,54
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	77.850,00	19.000,00	58.850,00	100,00

Budget Justification	
1 Staff Salary	1 Medical Doctor (10% per year for 2 years - 1,2 P/M/Y for 2 years)
2 Researchers' Contracts	1 Fellows(lab),100% for 2 yrs- 12 P/M/Y
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	Travels and subsistence costs for participation in national and international scientific meetings to present the results of the project
8 Publication Costs	none
9 Dissemination	none
10 Overheads	Istitutional overheads
11 Coordination Costs	none

Proposed total budget UO3 Institution: Università degli studi della Campania Luigi Vanvitelli, Napoli (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	31.000,00	31.000,00	not permitted	0,00
2 Researchers' Contracts	50.000,00	0,00	50.000,00	84,96
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	5.000,00	0,00	5.000,00	8,50
8 Publication Costs	0,00	0,00	0,00	0,00
9 Dissemination	0,00	0,00	0,00	0,00
10 Overheads	3.850,00	0,00	3.850,00	6,54
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	89.850,00	31.000,00	58.850,00	100,00

Budget Justification	
1 Staff Salary	1 Senior Statistician (15% per year for 2 years - 1,8 P/M/Y for 2 years)
2 Researchers' Contracts	1 Fellows(lab),100% for 2 yrs- 12 P/M/Y
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	Travels and subsistence costs for participation in national and international scientific meetings to present the results of the project
8 Publication Costs	none
9 Dissemination	none
10 Overheads	Istitutional overheads
11 Coordination Costs	none

Proposed total budget UO4 Institution: Azienda Ospedaliera Universitaria Federico II, Napoli (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	100.000,00	0,00	100.000,00	18,10
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	375.000,00	0,00	375.000,00	67,89
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	38.800,00	0,00	38.800,00	7,02
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	5.000,00	0,00	5.000,00	0,91
8 Publication Costs	0,00	0,00	0,00	0,00
9 Dissemination	0,00	0,00	0,00	0,00
10 Overheads	33.600,00	0,00	33.600,00	6,08
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	587.400,00	35.000,00	552.400,00	100,00

Project Code: PNRR-MAD-2022-12376584	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	**Applicant/PI Coordinator:** Sieri Sabina Assunta Giovanna

Budget Justification

1 Staff Salary	1 Medical Doctor, Head of the Internal Medicine and Clinical Nutrition Unit (10% per year for 2 years - 1,2 P/M/Y for 2 years)
2 Researchers' Contracts	2 researchers to hire (1 for the lab),100% for 2 yrs- 12 P/M/Y
3a.1 Equipment (Leasing - Rent)	none
3a.2 Equipment (buying)	none
3b Supplies	Kits for CRP, TNF-alpha, IL-6, leptin, PAI-1, IL-1beta, IFN-gamma, IL-8, IL-12, adiponectin, IL-10 for about 4400 blood samples. Reagents for automated microfluidic immunoassay system (ProteinSimple Ella). Kits for Triglycerides and GGT
3c Model Costs	none
4 Subcontracts	Georeferencing of the cohort through individual address and connection to satellite data
5 Patient Costs	none
6 IT Services and Data Bases	none
7 Travels	Travels and subsistence costs for participation in national and international scientific meetings to present the results of the project
8 Publication Costs	none
9 Dissemination	none
10 Overheads	Institutional overheads
11 Coordination Costs	none

Principal Investigator Data

Cognome: Sieri
Nome: Sabina Assunta Giovanna
Genere: F
Codice fiscale: SRISNS69C47B300H
Documento: Carta d'identità, Numero: AV6032491
Data di nascita: 07/03/1969
Luogo di nascita: Busto Arsizio
Provincia di nascita: VA
Indirizzo lavorativo: Via Venezian 1
Città: Milano
CAP: 20133
Provincia: MI
Email: sieris@libero.it
Altra email: sabina.sieri@istitutotumori.mi.it
Telefono: +393498608661
Qualifica: Ricercatore Sanitario
Struttura: Sc Epidemiologia e Prevenzione
Istituzione: Fondazione IRCCS Istituto Nazionale dei Tumori
Datore/ente di lavoro? Yes
Datore/ente di lavoro SSN? Yes
Nome datore/ente di lavoro non SSN:
Nome istituzione SSN: Fondazione IRCCS Istituto Tumori Milano
Tipo contratto: Lavoro Subordinato a Tempo Determinato - Piramide DS6

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.

Project Code: PNRR-MAD-2022-12376584	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Fondazione Istituto Nazionale per lo studio e la cura dei tumori - Milano	**Applicant/PI Coordinator:** Sieri Sabina Assunta Giovanna

Project validation result