Nutrition and Metabolism Branch (NME)

Branch head
Dr Marc Gunter (until January 2023)
Dr Pietro Ferrari (acting)

Deputy branch heads
Dr Mazda Jenab
Dr Sabina Rinaldi

Scientists
Dr Laure Dossus
Dr Heinz Freisling
Dr Inge Huybrechts
Dr Pekka Keski-Rahkonen
Dr Neil Murphy
Dr Augustin Scalbert (until July 2022)
Dr Vivian Viallon

Senior visiting scientists
Dr Marc Gunter
Dr Elio Riboli (until September 2022)
Dr Guri Skeie

Visiting scientists
Dr Kristin Benjaminsen-Borch (until June 2022)
Dr Sheila Coelho Soares Lima (until June 2022)
Dr Elodie Faure
Dr Agnès Fournier
Dr Mohamed Khalis
Dr Tomohiro Matsuda
Dr Norie Sawada

Research assistants
Dr David Achaintre (until June 2022)
Ms Carine Biessy
Ms Corinne Casagrande (until March 2023)
Mr Bertrand Hémon
Ms Vanessa Neveu
Ms Geneviève Nicolas
Ms Nivonirina Robinot
Ms Béatrice Vozar

Laboratory technicians
Ms Audrey Gicquiau (until September 2022)
Ms Anne-Sophie Navionis

Secretariat
Ms Sally Moldan (until February 2023)
Ms Karine Racinoux
Ms Sarah Sherwood
Ms Tracy Wootton
Ms Karina Zaluski

Postdoctoral fellows
Dr Adam Amara (until December 2022)
Dr Jessica Blanco Lopez
Dr Felix Boekstegers
Dr Manon Cairat (until July 2022)
Dr Chrysovalantou Chatziioannou (until August 2023)
Dr Emeline Courtois
Dr Charlotte Debras (until September 2023)
Dr Niki Dimou
Dr Esther Gonzalez Gil
Dr Rhea Harewood
Dr Mathilde His (until December 2022)
Dr Inarie Jacobs
Dr Rola Jaafar
Dr Anna Jansana Riera
Dr Ruhina Laskar (until September 2023)
Dr Matthew Lee
Dr Azam Majidi
Dr Shiny Lizia Manohar
Dr Komodo Matta
Dr Ana-Lucia Mayen-Chacon (until September 2022)
Dr Mira Merdas
Dr Yahya Mahamat Saleh
Dr Sabine Naudin
Dr Nikolaos Papadimitriou
Dr Jodi Rattner (until June 2023)
Dr Martina Recalde (until July 2022)
Dr Sanam Shah
Dr Daniel Tolossa
Dr Sabrina Wang
Dr James Yarmolinsky (until May 2022)

Doctoral students
Ms Inmaculada Aguilero (until May 2023)
Ms Aline Al Nahas
Mr Christian Antoniussen (until August 2023)
Mr Jeroen Berden
Ms Marie Breeur
Ms Carlota Castro-Espin (until June 2023)
Mr Alberto Catalano (until June 2023)
Ms Bernadette Chimera
Ms Emma Fontvieille
Mr Quan Gan
Ms Emine Koc Camak (until November 2023)
Ms Kim Maasen (until June 2022)
Ms Alessandra Macciotta (until June 2023)
Mr Pablo Marcos Lopez (until January 2023)
Ms Maria Matias de Pinho (until July 2022)
Ms Fernanda Morales Berstein (until May 2022)
Ms Julie Neau (until November 2022)
Ms Laia Peruchet-Noray
Ms Martina Recalde (until June 2022)
Ms Fanélie Vasson
Ms Diana Wu
Ms Yuhan Zhang (until August 2023)
Ms Yadi Zheng

Trainees
Mr Loïc Abed (until July 2022)
Mr Pablo Marcos Lopez (until July 2022)
Ms Fanélie Vasson (until August 2023)
Mr Maxime Vincent (until March 2022)
Mr Wendyam Yameogo (until August 2023)
Ms Julie Neau (until August 2022)

The Nutrition and Metabolism Branch (NME) places a strong emphasis on the implementation and coordination of epidemiological studies on cancer to identify causal relationships between nutrition, metabolism, and cancer and inform on cancer prevention. The activities of NME largely focus on three major research themes: (i) understanding the role of obesity and metabolic dysfunction in cancer development; (ii) research on the role of diet and lifestyle factors in cancer, including identification of biomarkers of diet and nutrition and their application within studies of cancer etiology; and (iii) multimorbidity and biological pathways common to cancer, diabetes, and cardiovascular diseases.

Research in NME aims to exploit methodological advances in molecular profiling techniques, epidemiology, and biostatistics to implement an integrated, multidisciplinary programme of research. Given the potential for advances in molecular profiling to help overcome methodological challenges in nutrition and cancer research and to discover the underlying biological pathways, emphasis has been placed on conducting molecular epidemiological research that integrates –omics data (see the text box), including metabolomics, hormone measurements, and genomics, within population-based cohorts and intervention studies. In addition to NME's work within established cohorts such as the European Prospective Investigation into Cancer and Nutrition (EPIC) and the UK Biobank and across cohort consortia, NME has devoted considerable resources to the development of studies in low- and middle-income countries, such as South Africa and Morocco, and in Latin America where, because of the epidemiological transition, cancers linked to diet and lifestyle are increasing in incidence. Over the past 5 years, NME scientists have also initiated small-scale intervention studies, primarily focused on biomarker discovery or to understand mechanisms linking obesity, diet, and cancer.

NME's studies are inherently multidisciplinary and typically involve collaborations with multiple partners. Significant cancer research activities from the six NME teams are reported here.

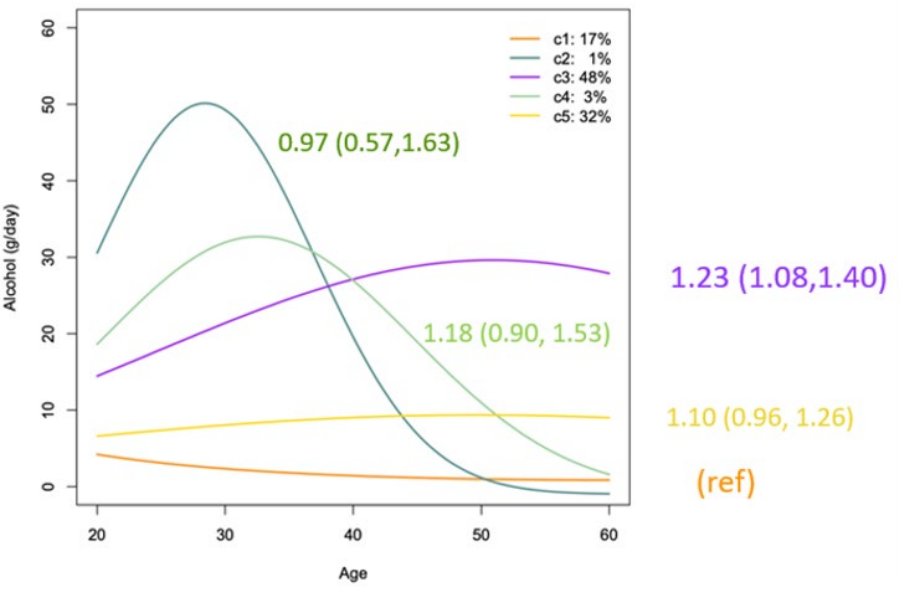
Biostatistics and Data Integration Team (BDI)

Data are at the core of cancer epidemiology, and tasks related to (i) data management, including data centralization, harmonization, and dissemination, and (ii) application of cutting-edge statistical methods are essential. During the 2022–2023 biennium, BDI continued the centralization and harmonization of laboratory data acquired within EPIC. BDI was in charge of the dissemination of EPIC data and data available in recently funded large-scale projects, such as Discovering the Causes of Three Poorly Understood Cancers in Europe (DISCERN) and PROMINENT: Discovering the molecular signatures of cancer PROMotion to INform prevENTion, co-led by the Genomic Epidemiology Branch (GEM). In line with recommendations for international data protection regulations, data dissemination and analysis have been seamlessly conducted via the IARC Scientific IT platform, which was developed by the Information Technology Services (ITS) team to follow the Open Science principle that data should be "as open as possible and as closed as necessary".

Methodological developments were conducted to assess and improve the performance of several statistical methods, including extensions of the lasso and dimension-reduction techniques, which are valuable for the analysis of –omics data in cancer epidemiology (Etiévant and Viallon, 2022a; Ballout et al., 2023). A data-shared lasso analysis of pre-diagnostic metabolite concentrations measured in blood in several nested case–control studies identified nine metabolites associated with cancer risk across multiple cancer sites (Breeur et al., 2022).

Leveraging the availability of longitudinal exposure assessments within EPIC participants, a research programme was developed to investigate the impact of changes in modifiable lifestyle factors on cancer risk and mortality. Adherence to the healthy lifestyle index, a composite score based on smoking, alcohol consumption, obesity, and physical activity, was inversely associated with risk of colorectal cancer (Botteri et al., 2023), risk of lifestyle-related cancers, and all-cause mortality. Trajectory profiles of alcohol intake during early and mid-adulthood showed that consistent moderate to elevated exposures to alcohol intake throughout adulthood were associated with risk of colorectal cancer (Mayén et al., 2022) (Figure 1).

Figure 1. Trajectory profiles of alcohol intake (c1 to c5) during adulthood in men in the European Prospective Investigation into Cancer and Nutrition (EPIC), and associated estimates of colorectal cancer hazard ratio (95% confidence interval). Reproduced from Mayén et al. (2022), © 2022, Springer Nature.



Lifestyle Exposure and Intervention Team (LEI)

New dietary and lifestyle indicators were generated and validated in cohort studies, enabling the investigation of novel diet–cancer associations. Databases on dietary fatty acid isomers were compiled in cohort and case–control studies (Huybrechts et al., 2022). Fatty acid isomers and industrial trans fatty acids were positively associated with colorectal cancer risk in the Iran Opium and Cancer (IROPICAN) study (Seyyedsalehi et al., 2022a, 2022b) and in the NutriNet-Santé cohort (Wendeu-Foyet et al., 2023). In addition, food processing was investigated in relation with cancer risk via the NOVA classification. Results in EPIC showed inverse relationships between the consumption of fresh or minimally processed foods and overall cancer risk, whereas consumption of processed and ultra-processed foods was positively related to the risk of several cancer types (Kliemann et al., 2023).

In collaboration with scientists in the Hormones and Metabolism Team (HorM), the role of food processing in breast cancer etiology was evaluated in countries in epidemiological transition. Consumption of ultra-processed foods was positively associated with colorectal cancer risk in a study conducted in Morocco (El Kinany et al., 2022). Results from the PRECAMA study (525 case–control pairs) indicated that consumption of ultra-processed foods may be related to the risk of breast cancer in young women in Latin America (Romieu et al., 2022). Results from a study in Black women in Soweto, South Africa (the South Africa Breast Cancer [SABC] study) (396 case–control pairs) indicated that the intake of unprocessed or minimally processed foods may reduce the risk of breast cancer (Jacobs et al., 2022a). Food processing may play a role in breast cancer etiology in these populations.

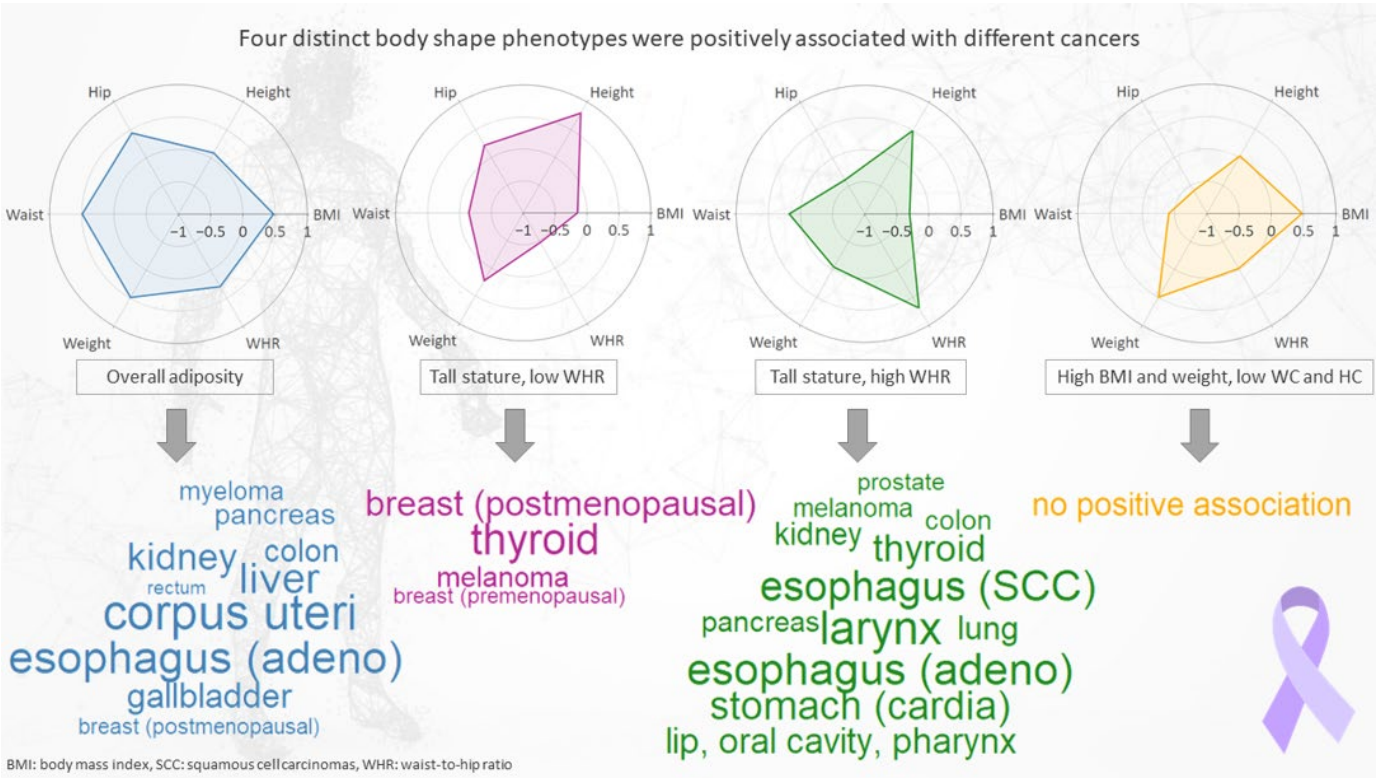
An intervention study to promote changes in lifestyle behaviours was designed within the colorectal cancer screening programme in France (ClinicalTrials.gov identifier: NCT05273931). The Lifestyle Intervention After Colonoscopy (LIFE-SCREEN) study involved 30 hospitals (15 in the control arm and 15 in the intervention arm), and 20 participants were recruited in each hospital.

Nutrition, Cancer, and Multimorbidity Team (NCM)

In a large prospective study in 2 645 885 Catalonian individuals, using the Information System for Research in Primary Care (SIDIAP) electronic health record database, body mass index (BMI) across the participants' lifetime was investigated. Anthropometric indicators, such as overweight and obesity duration, intensity, and onset age, were found to be linked with 18 cancer types, five more than previously thought. Some of the novel cancer types that were identified are leukaemia, non-Hodgkin lymphoma, and bladder cancers, particularly in people who never smoked (Recalde et al., 2023a).

To investigate the role of anthropometry in a more comprehensive way beyond BMI, a multivariate dimension-reduction technique was used to derive participants' body shapes from height, weight, BMI, waist circumference, hip circumference, and waist-to-hip ratio. Four distinct body

Figure 2. Cancer risk associations with four distinct body shape phenotypes derived in the European Prospective Investigation into Cancer and Nutrition (EPIC). Reproduced from Sedlmeier et al. (2023). © 2023, Sedlmeier et al.



shapes were identified and captured the heterogeneous distribution of adiposity compared with single anthropometric traits. In an EPIC study of 340 152 men and women from nine European countries, the four distinct body shapes were positively associated with the risk of overall cancer and 17 site-specific cancers (Sedlmeier et al., 2023) (Figure 2). Using genetic variants related to these body shapes, associations with breast cancer risk were reported (Peruchet-Noray et al., 2023). In a study of 159 045 European adults, among 1045 patients with colorectal cancer and 1620 patients with breast cancer, both cumulative BMI and cardiometabolic diseases had a direct link to survival outcomes, independently of each other (Kohls et al., 2022).

Metabolic Epidemiology Team (MET)

Studies leveraging genetic and tumour marker data were conducted to investigate associations of body size and diabetes with colorectal cancer. In a pooled observational analysis that included more than 11 000 colorectal cancer cases with tumour molecular marker data, BMI was positively associated with colorectal cancer risk for cases with Jass types 1–4 colorectal cancer but not for cases with Jass type 5 colorectal cancer (considered familial-like/Lynch syndrome) (Murphy et al., 2023) (Figure 3). The lack of association observed for Jass type 5 suggests that BMI is not a risk factor for the development of colorectal cancer for individuals with Lynch syndrome.

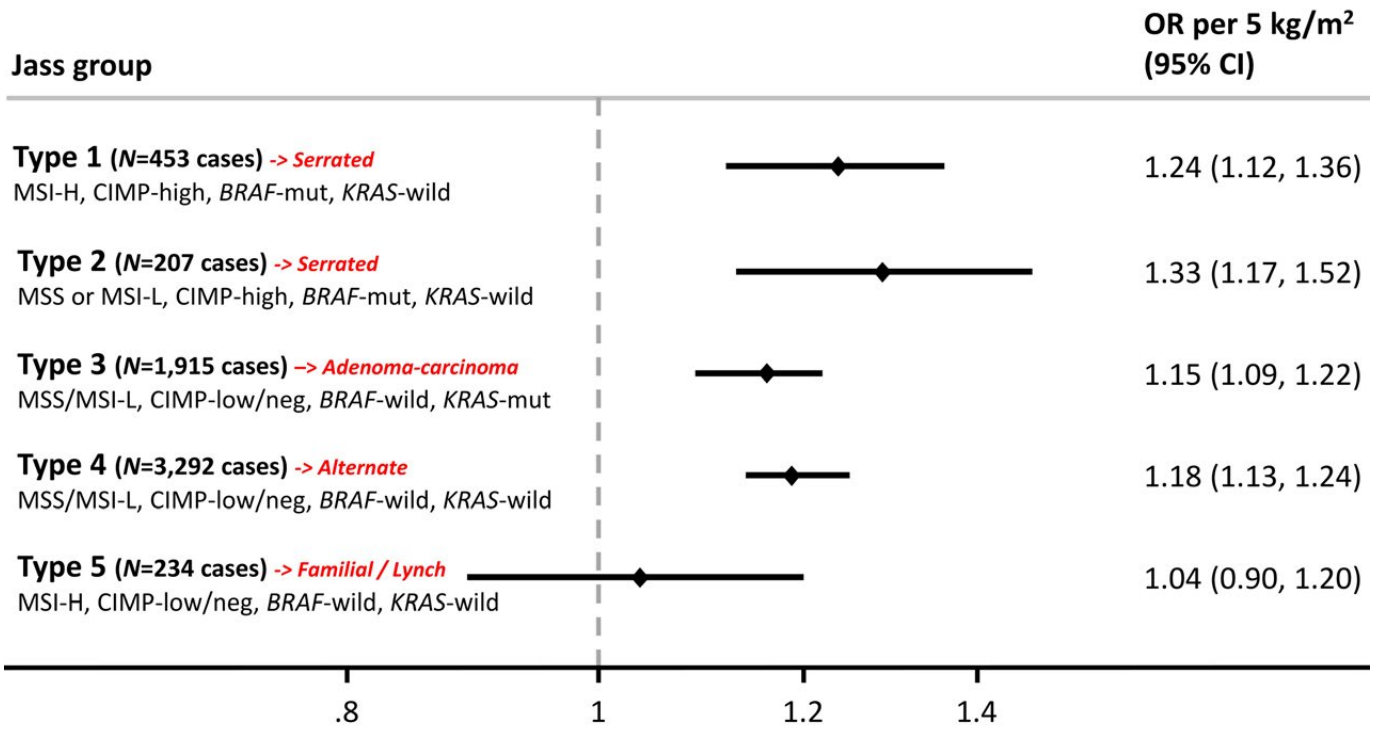
Mendelian randomization was used to separate the effects of early-life and later-life adiposity on colorectal cancer risk (Papadimitriou et al., 2023). Genetically predicted early-life body size was estimated to increase the odds of colorectal cancer. However, after accounting for adult body size using multivariable Mendelian randomization, effect estimates for early-life body size were attenuated towards the null. These findings suggest that the influence of early-life body size on colorectal cancer development is largely mediated through later-life body size.

In a genome-wide gene–environment interaction (GxE) analysis including 31 318 colorectal cancer cases and 41 499 controls, a significant interaction was found between diabetes status and the variants rs3802177 in *SLC30A8*, a gene that regulates phosphorylation of the insulin receptor and phosphatidylinositol 3-kinase (PI3K) activity, and rs9526201 in *LRCH1*, a gene that regulates T-cell migration, with colorectal cancer risk (Dimou et al., 2023). These results suggest that variation in genes related to insulin signalling and immune function may modify the relationship between diabetes and colorectal cancer.

Hormones and Metabolism Team (HorM)

The associations of inflammatory biomarkers with breast cancer risk were evaluated in the EPIC study (1600 case–control pairs) and in the Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women (PRECAMA) study (453 case–control pairs). Inflammatory biomarkers were measured in the NME laboratory. In EPIC, leptin, the leptin-to-adiponectin ratio, and C-reactive protein (CRP) levels were borderline inversely associated with breast cancer risk in premenopausal women, and positively associated with risk in postmenopausal women (Cairat et al., 2022). In PRECAMA, levels of interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) were positively associated with breast cancer risk overall, with some

Figure 3. Observational associations between body mass index and Jass classified types and inferred pathways (in red) of colorectal cancer. CI, confidence interval; OR, odds ratio. © IARC.



evidence of heterogeneity by estrogen receptor status and according to tumour size (Fontvieille et al., 2022) (Figure 4). The findings suggested that systemic inflammation may play a modest role in breast cancer development.

Onco-Metabolomics Team (OMB)

Leveraging the acquired expertise in the high-throughput profiling of biospecimens from population-based studies within the NME laboratories, research conducted by OMB indicated that metabolic signatures expressing adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations were inversely associated with colorectal cancer in EPIC (Rothwell et al., 2022b). These results indicate the potential of metabolic profiling for risk stratification. Also, metabolic syndrome, a marker of poor metabolic health, was positively related to the risk of gastrointestinal cancers (Rothwell et al., 2022a). A metabolomics study focusing on early-life obesity, which is a candidate risk factor for several cancer types, examined the mediating role of metabolites measured in cord blood between different prenatal exposures and postnatal growth and propensity towards childhood overweight (Alfano et al., 2022). The results suggested a mediating role of cholestenone, a microbial catabolite of cholesterol, in the relationship between maternal exposures and postnatal growth.

Higher total blood concentrations of bile acids, particularly taurine- and choline-conjugated bile acids, were positively linked to risk of hepatocellular carcinoma in a nested case–control study in EPIC, indicating a role of bile acid metabolism and liver function in this cancer type (Stepien et al., 2022).

In a study of the metabolic impacts of metformin treatment versus placebo in 373 randomized breast cancer survivors who were overweight or obese (Bellerba et al., 2022), metformin increased levels of branched chain amino acids, proline, 3-methyl-2-oxovalerate, 4-methyl-2-oxovalerate, alanine, and indoxyl sulfate, and reduced levels of long-chain unsaturated phosphatidylcholines, among others (Bellerba et al., 2022) (Figure 5). OMB scientists wrote a review on the role of the gut microbiome and microbiome-derived metabolites in hepatobiliary cancer development.

Figure 4. Associations between inflammatory biomarkers and breast cancer, by estrogen receptor (ER) status and in triple-negative (TN) tumours. Odds ratios (ORs) are per standard deviation (SD) increase in log-transformed biomarker concentration. P-homogeneity ER compares ER-negative and ER-positive tumours. P-homogeneity TN compares TN and non-TN tumours. CI, confidence interval; IFN, interferon; IL, interleukin; TNF, tumour necrosis factor. Reproduced from Fontvieille et al. (2022). © 2022, Fontvieille et al.

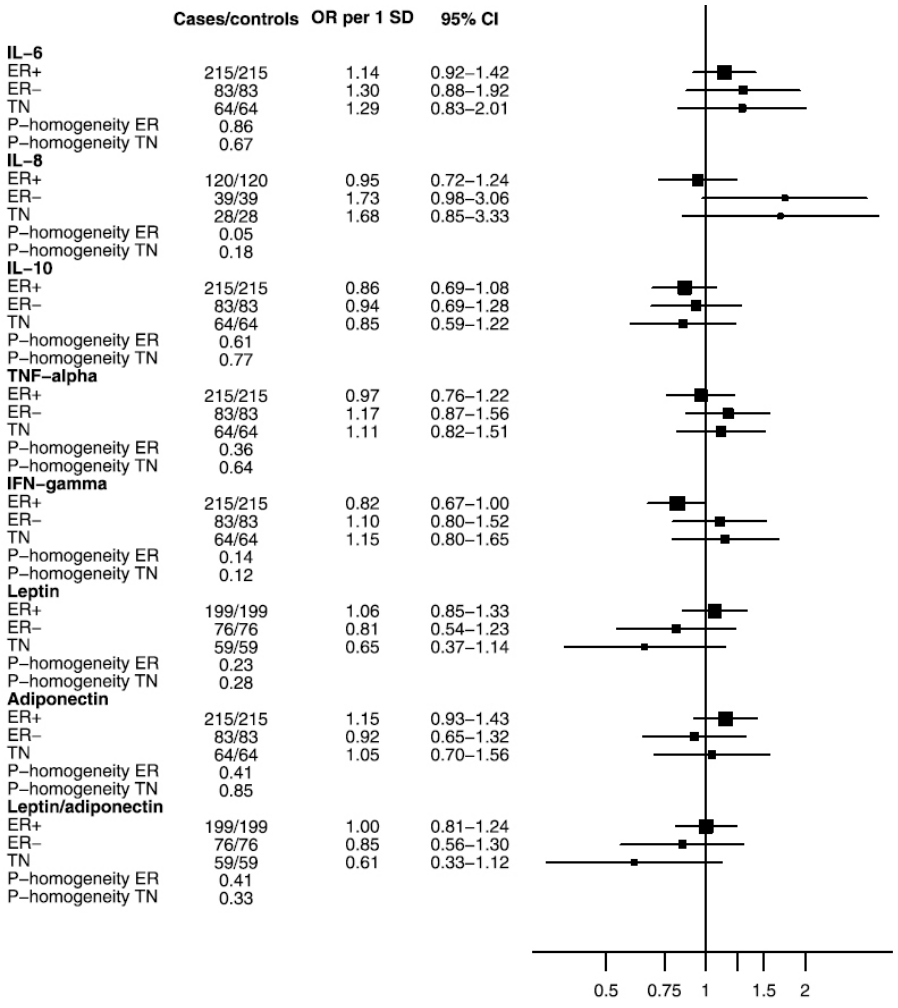
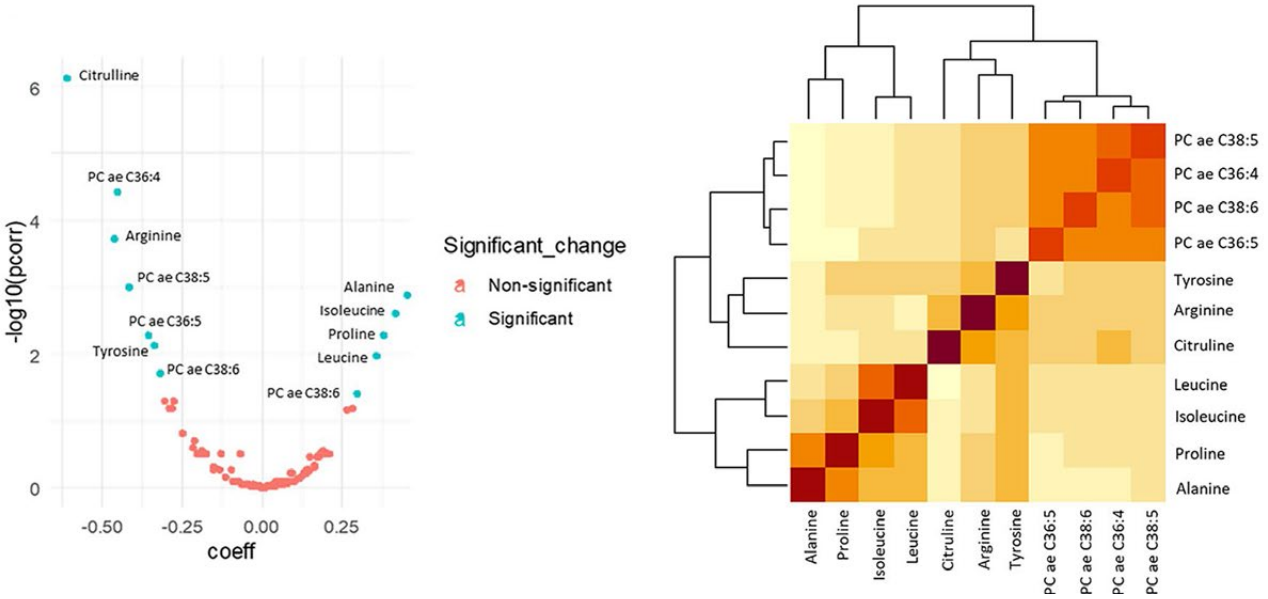
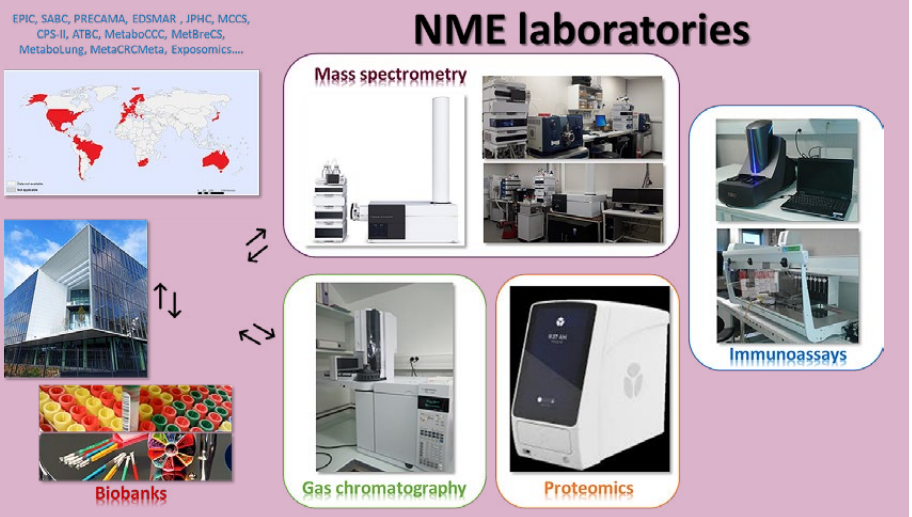


Figure 5. A volcano plot (left) and a heatmap (right) showing changes in plasma metabolite concentrations after metformin treatment in breast cancer survivors who were overweight or obese (Biocrates AbsoluteIDQ p180 targeted metabolomics; *n* = 194 metformin, *n* = 197 placebo). The volcano plot shows the beta regression coefficients of the treatment effect on the horizontal axis and the $-\log_{10}$(false-discovery rate [FDR]-corrected *P* values) on the vertical axis. PC, phosphatidylcholine. Reproduced from Bellerba et al. (2022). © 2022, Bellerba et al.



NME laboratory activities

The laboratories of NME have been set up to suit the needs of epidemiological studies. Analytical methods have been specifically developed to be applicable to large series of samples, to be fast, and to need low sample volume, because the quantity of samples in biobanks is often limited. This specificity of NME laboratories has enabled the Branch to work with many collaborators and projects worldwide. © IARC. Building: © Kevin Buy.



Over the past few years, the NME laboratories have made relevant investments in methodology and technological capabilities. As a result, state-of-the-art biochemical profiling techniques were effectively applied to a large number of biological samples collected in cohort, case–control, and intervention studies. The NME laboratories are equipped with cutting-edge technology analytical instruments, including four liquid chromatography-mass spectrometry systems (SCIEX QTRAP 5500, Triple Quadrupole 4500, Agilent Q-TOF 6550, and Thermo Q Exactive), all coupled to ultra-high-performance liquid chromatographs, a multiplexing electrochemiluminescence reader (Meso Scale Discovery), two gas chromatographs with flame ionization detectors (FID) (Agilent), and, very recently, the Signature Q100 machine from Olink for targeted proteomics. Automated liquid handling systems are also available to speed up sample preparation for applications to large-scale projects. Major applications include untargeted and targeted (Biocrates AbsoluteIDQ p180 kit) metabolomics, analyses of hormones (including sex steroids), biomarkers of inflammation, fatty acids, and polyphenols. Plasma, serum, and urine samples were mainly analysed. During the 2022–2023 biennium, this technology was used to analyse about 20 000 biospecimens, originating from more than 20 different countries, and created invaluable opportunities for scientific collaborations with several local and international partners.