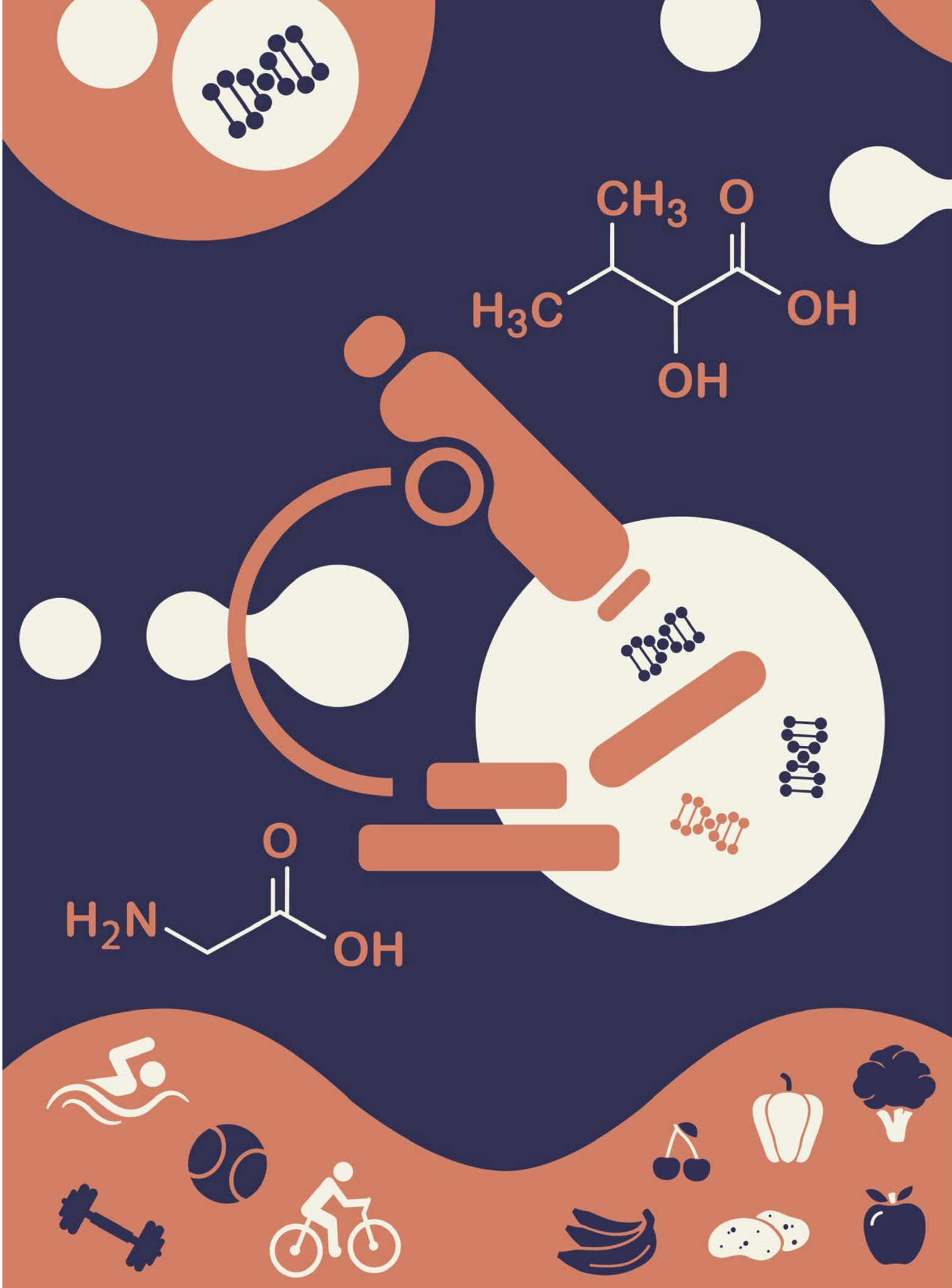
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The Section of Nutrition and Metabolism (NME) comprises three highly integrated groups: the Biomarkers Group (BMA), the Nutritional Epidemiology Group (NEP), and the Nutritional Methodology and Biostatistics Group (NMB). The Section combines large-scale population-based studies with laboratory and biostatistical expertise to identify causal links between nutrition, metabolic factors, and cancer. The goal of the Section is to provide robust evidence of the role of nutrition in cancer development that can be translated to clinical interventions and public health policy. NME aims to go beyond what may be considered the traditional domains of nutrition in cancer research and to fully exploit methodological advances in –omics and molecular profiling techniques to implement an integrated, multidisciplinary programme of research. The overall strategic vision of NME is based on three major research themes: (i) understanding the role of obesity and metabolic dysfunction in cancer development, (ii) identification of biomarkers of diet and nutrition and their application within studies of cancer, and (iii) multimorbidity and biological pathways common to cancer, diabetes, and cardiovascular disease. Within these themes, NME focuses on a core set of cancer sites, primarily gastrointestinal cancers, as well as hormone-related cancers such as breast cancer and endometrial cancer. A particular emphasis is placed on cancer types that have clear links to nutrition and metabolic abnormalities and for which much remains to be discovered about disease etiology.

With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, NME was renamed as the Nutrition and Metabolism Branch.

Establishing an epidemiological study in Afghanistan: Kandahar Obesity Research

As a result of rapid economic, social, and cultural changes, the prevalence of obesity in Afghanistan is increasing and dietary habits are shifting from the traditional pattern to a pattern more typical of industrialized countries, with concomitant increases in the incidence of noncommunicable diseases (NCDs).

A population-based cross-sectional study was designed in Kandahar city, and data were collected on sociodemographic characteristics, health history, anthropometry, physical activity, and diet. NME used stratified sampling to recruit an equal number of participants in the normal-weight, overweight, and obese categories. Body fat composition was analysed using bioelectric impedance analysis, and dried blood, urine, and stool samples were collected for biomarker analyses.

The study included 712 participants (411 men and 301 women); 92% lived in urban areas, 73% were married, 42% were aged 20–30 years, 51% were not formally educated, 79% were never-smokers, and 68% had central obesity. With respect to NCDs, 38% were hypertensive, 18% were diabetic, 30% had dyslipidaemia, 36% had fatty liver disease, and 50% were symptomatic for anxiety and/or depression.

This is the first study that will assess dietary patterns, lifestyle factors, and their association with obesity and metabolic health in Afghanistan. The data collected will be an invaluable resource for future studies on biomarkers or the microbiome, and could be used to train future public health scientists in Afghanistan.

Kandahar Obesity Research. © IARC.

Biomarkers Group (BMA)

Metabolomics reveals new biomarkers for intake of processed meat

Processed meat has been associated with a higher risk of colorectal cancer; however, identification of the etiologically relevant components of this heterogeneous food group remains challenging. The Biomarkers Group (BMA) applied an untargeted metabolomic approach to identify novel biomarkers of intake for processed meat products in a randomized cross-over dietary intervention and in 474 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Several pepper-derived alkaloids were positively associated with intake of sausage and processed meat and may be used as biomarkers to improve assessment of intake of processed meat in epidemiological studies (Figure 1) (Wedekind et al., 2021).

New data on biomarkers of exposure and their associations with disease risk collected in the Exposome-Explorer database

The Exposome-Explorer database (http://exposome-explorer.iarc.fr) provides detailed information on more than 1000 biomarkers of dietary and pollutant exposures as measured in various populations. New information on their associations with cancer risk in relevant epidemiological studies, derived from more than 300 scientific papers, has now been collated (Neveu et al., 2020).

Identification of biomarkers to explore novel etiological hypotheses in breast cancer

BMA applied targeted metabolomics to identify novel metabolites associated with breast cancer, breast density, and potential modifiable determinants.

In premenopausal Mexican women from the Mexican Teachers Cohort, sphingomyelin (SM) C16:1 and phosphatidylcholine (PC) ae C30:2 were inversely associated with percentage mammographic density and were positively associated with cholesterol and metabolic syndrome components (His et al., 2021a).

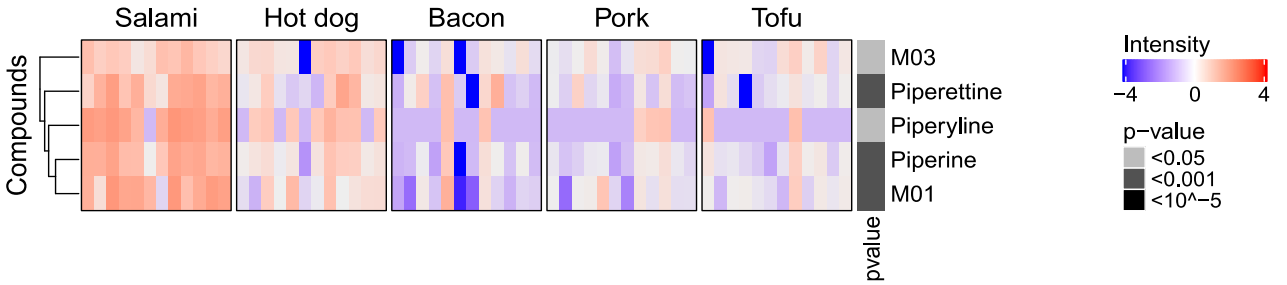
As part of the EPIC study, BMA observed novel associations between circulating concentrations of acetylcarnitine, arginine, asparagine, and PCs, and breast cancer. Correlates of these biomarkers were investigated (His et al., 2021b), and PCs were observed to be inversely associated with adiposity and positively associated with total and saturated fat intakes. PC ae C36:2 was inversely associated with alcohol consumption and positively associated with healthy lifestyle. Asparagine was inversely associated with adiposity. These findings suggest possible mechanisms for novel etiological hypotheses on breast cancer.

Obesity and endometrial cancer: disentangling underlying mechanisms

Obesity is a major risk factor for endometrial cancer, but the underlying pathways and their relative contribution are still unclear. In a study conducted as part of EPIC, pathways characterized by reduced adiponectin and increased inflammatory biomarkers, insulin, and estrogen explained about 70% of the association between endometrial cancer and obesity (Dashti et al., 2021).

Using metabolomics, BMA discovered alterations in concentrations of glycine, serine, SM C18:0, and free carnitine associated with endometrial cancer (Figure 2) (Dossus et al., 2021). BMA also identified a metabolic signature of obesity among more than 4000 EPIC participants that was more predictive of endometrial cancer risk than anthropometric measures (Kliemann et al., 2021).

Figure 1. Scaled relative intensities of pepper alkaloid metabolites in plasma samples associated with intake of several processed food products in a dietary intervention study (*n* = 12). Reproduced from Wedekind et al. (2021). © John Wiley & Sons.



Circulating tryptophan metabolites and risk of colon cancer

Dysregulation of tryptophan metabolism has been linked to the development of colorectal cancer, but few epidemiological studies have addressed this hypothesis. BMA studied associations between tryptophan metabolites and colon cancer risk in the ColoCare, Colorectal Cancer Study of Austria (CORSA), and EPIC cohorts (Papadimitriou et al., 2021). Tryptophan levels were inversely associated and serotonin levels positively associated with colon cancer risk (Figure 3). These results support earlier studies on the role of tryptophan metabolism in colon cancer and offer new insights into changes in the metabolic flux of tryptophan before and after diagnosis of colon cancer.

Figure 2. Odds ratios (ORs) and *P* values for the associations between metabolites and risk of endometrial cancer in models adjusted for body mass index (BMI). ORs are estimated per standard deviation (SD) increase in log-transformed metabolite concentrations, from logistic regression conditional on matching variables. The figure shows statistical significance based on *P* values (significant metabolites above the dotted line). SM, sphingomyelin. Reproduced from Dossus et al. (2021). © 2021, Published by Elsevier Inc.

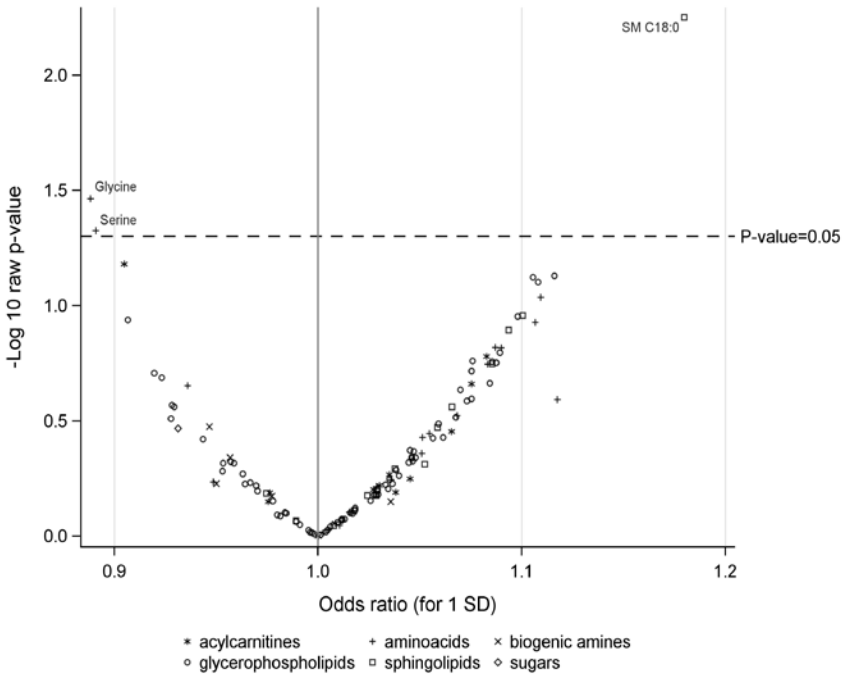
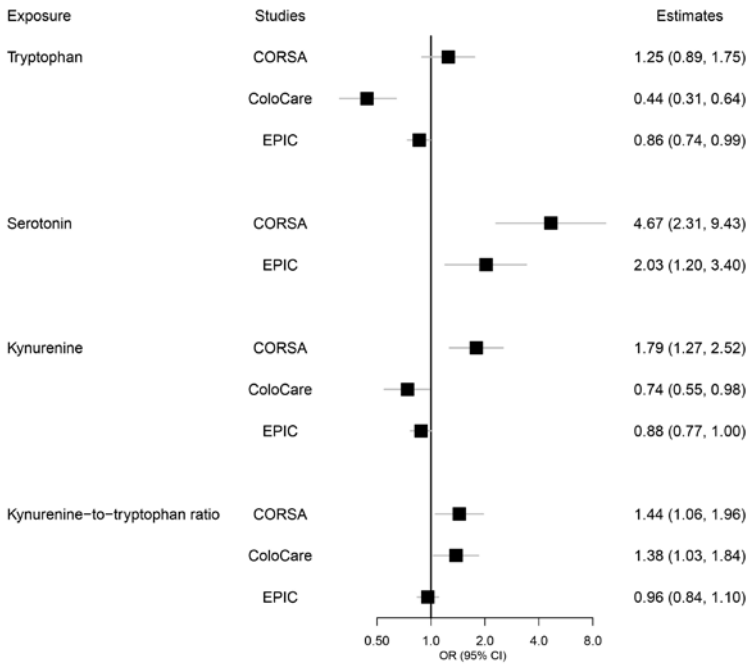


Figure 3. Associations of tryptophan, serotonin, kynurenine, and kynurenine-to-tryptophan ratio with colon cancer in the Colorectal Cancer Study of Austria (CORSA), ColoCare, and European Prospective Investigation into Cancer and Nutrition (EPIC) studies. The odds ratios (ORs) correspond to a 1 standard deviation difference in concentration levels of the biomarkers, except for serotonin where the comparison was made between detectable and undetectable concentration levels. CI, confidence interval. Reproduced with permission from Papadimitriou et al. (2021a), John Wiley & Sons.



Nutritional Epidemiology Group (NEP)

Insulin, insulin-like growth factors, and breast and colorectal cancers

Experimental and epidemiological evidence has implicated the insulin and insulin-like growth factor (IGF) axis in breast and colorectal cancer development, but causality of these relationships is uncertain. In observational and Mendelian randomization (MR) analyses, the Nutritional Epidemiology Group (NEP) investigated the role of circulating IGF-1 and fasting insulin in breast and colorectal cancer development. In the UK Biobank, higher IGF-1 concentrations were associated with greater breast (hazard ratio [HR] per 5 nmol/L, 1.11; 95% confidence interval [CI], 1.07–1.16) and colorectal cancer risk (HR per 1 standard deviation [SD], 1.11; 95% CI, 1.05–1.17). In MR analyses, genetically predicted IGF-1 concentrations were positively associated with breast (odds ratio [OR] per 5 nmol/L, 1.05; 95% CI, 1.01–1.10) and colorectal cancer risk (OR per 1 SD increment, 1.08; 95% CI, 1.03–1.12). Genetically predicted fasting insulin levels were positively associated with colorectal cancer risk (OR per 1 SD, 1.65; 95% CI, 1.15–2.36) (Murphy et al., 2021a). These results support probable causal relationships and suggest that targeting the insulin–IGF axis may be beneficial in preventing breast and colorectal tumorigenesis (Murphy et al., 2020a, 2020b).

Exploring the role of iron in colorectal cancer

Iron is hypothesized to play a role in colorectal tumorigenesis; however, epidemiological evidence is limited. NEP examined the association between dietary and circulating iron and colorectal cancer via genetically predicted circulating iron using MR in 58 221 cases of colorectal cancer and 67 694 controls, and dietary total, haem, and non-haem iron assessed using dietary questionnaires within the EPIC cohort (6162 cases of colorectal cancer, 450 101 non-cases). A positive association was observed for genetically predicted circulating iron and colon cancer risk (OR per SD, 1.08; 95% CI, 1.00–1.17; *P* value, 0.05) (Tsilidis et al., 2021). In the EPIC study, haem iron was positively associated with colorectal cancer in men (HR Q5 vs Q1, 1.13; 95% CI, 0.99–1.29) but not in women. These findings support a possible causal association between circulating iron and haem iron and the development of colorectal cancer.

Food processing and cancer risk and mortality

Global industrialization has increased the consumption of ultra-processed foods (UPFs) while reducing food biodiversity. Recent analyses by NEP as part of the EPIC cohort examined the associations between processed food consumption and cancer risk. Positive associations between UPFs and several cancer sites were found, and an inverse association was observed for minimally processed foods in relation to most of the cancer outcomes.

Evidence suggests that UPFs may increase cancer risk via their obesogenic properties and their poor nutritional value, as well as through exposure to potentially carcinogenic compounds such as certain food additives and neoformed processing contaminants. The increase in UPF consumption parallels a steady decrease in food biodiversity as a result of industrialization. The continuing studies of NEP have already demonstrated an increased risk of premature death and cancer risk with lower species diversity in the diet (Hanley-Cook et al., 2021).

Metabolic profiling and colorectal cancer

Risk of colorectal cancer can be lowered by adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines. NEP derived metabolic signatures of adherence to these guidelines and tested their associations with colorectal cancer risk as part of the EPIC cohort. Higher WCRF/AICR scores were characterized by metabolic signatures of increased odd-chain fatty acids, serine, glycine, and specific PCs. These signatures were more strongly inversely associated with colorectal cancer risk (OR, 0.62 per unit change; 95% CI, 0.50–0.78) than the WCRF/AICR score (OR, 0.93 per unit change; 95% CI, 0.86–1.00) overall. Measuring a specific panel of metabolites representative of a healthy or unhealthy lifestyle may identify strata of the population at higher risk of colorectal cancer.

Nutritional Methodology and Biostatistics Group (NMB)

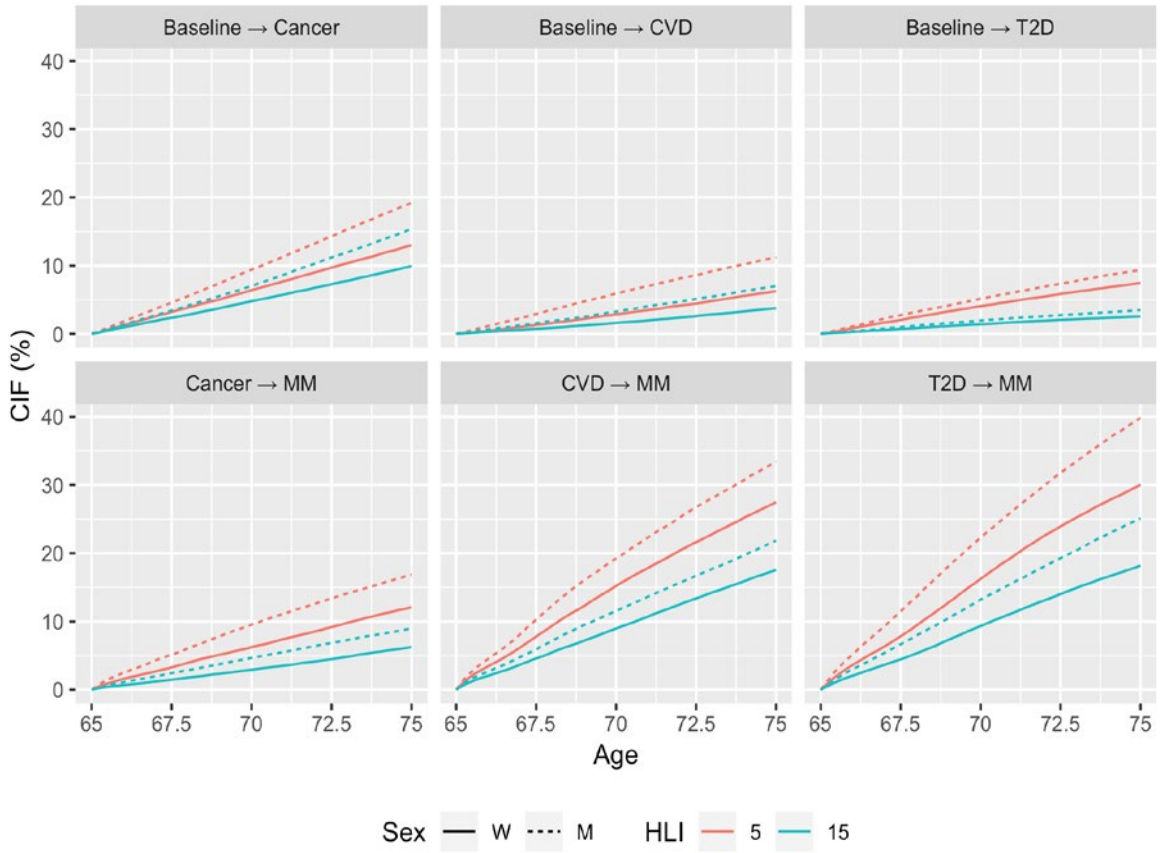
Biostatistical activities

The increasing availability of molecular data in large epidemiological studies requires the development and application of ad hoc statistical methodology. The Nutritional Methodology and Biostatistics Group (NMB) has implemented a new pipeline for the normalization and pooling of metabolomics data (Viallon et al., 2021). A new machine-learning method based on an extension of the lasso penalty was developed to analyse large-dimension data in (nested) case–control studies with several disease subtypes (Ballout et al., 2021). In line with recent developments in the field of causal inference, NMB applied modern causal mediation analysis to investigate the biological processes underlying the carcinogenic effect of obesity and alcohol (Assi et al., 2020; Dashti et al., 2021), and MR analysis was applied to investigate the causality of bilirubin on cancer occurrence (Seyed Khoei et al., 2020a, 2021).

Lifestyle and risk of multimorbidity

Improvements in longevity have increased the likelihood of an individual developing two or more diseases, referred to as multimorbidity. Cardiovascular diseases, type 2 diabetes, and cancer are the most common NCDs and represent major causes of morbidity, disability, and impaired quality of life. Limited evidence exists on how established risk factors for single NCDs are related to the clustering

Figure 4. Cumulative incidence functions (CIFs) describing the development of cancer, cardiovascular disease (CVD), and type 2 diabetes (T2D), and subsequent cancer–cardiometabolic multimorbidity (MM). Cancer refers to first malignant tumours at any site excluding non-melanoma skin cancer. CIFs are plotted for men (dotted) and women (continuous) aged 65 years for healthy lifestyle index (HLI) values of 15 (healthy, 85th percentile in green) and 5 (unhealthy, 4th percentile in red). HLI ranges from 0 to 20 units; higher scores indicate healthier lifestyles. Reproduced from Freisling et al. (2020a). © 2020, Freisling et al.



of NCDs within individuals. Within a large cohort of 300 000 participants from seven European countries, NMB showed that favourable lifestyle habits reduced the risk of incident multimorbidity from cancer and cardiometabolic diseases (Freisling et al., 2020a). In particular, NMB's absolute risk model assessed the burden of multimorbidity among participants who experienced a first disease, and quantified the preventive potential of healthy lifestyle habits with regard to multimorbidity of cancer and cardiometabolic diseases. For example, after diagnosis with type 2 diabetes, the 10-year absolute risks of multimorbidity were 40% for men and 30% for women with an unhealthy lifestyle, and 25% for men and 18% for women with a healthy lifestyle (Figure 4) (Freisling et al., 2020a).

Alcohol and cancer

Modest associations between alcohol consumption and cancer, particularly for light and moderate intakes, may be missed as a result of measurement error in self-reported assessments. NMB identified 2-hydroxy-3-methylbutyric acid as a novel biomarker of alcohol consumption in the EPIC study and the Alpha-Tocopherol, Beta-Carotene Cancer (ATBC) study (Loftfield et al., 2021). Higher levels of 2-hydroxy-3-methylbutyric acid were positively associated with risk of hepatocellular carcinoma, pancreatic cancer, and liver disease mortality. These metabolites could help advance the study of alcohol and cancer risk in population-based studies.

In a pooled analysis of EPIC and Melbourne Cohort Collaborative Study (MCCS) data, a novel positive association between lifetime alcohol intake and risk of noncardia stomach cancer was identified (Jayasekara et al., 2021).