



# ONCODIR



EVIDENCE-BASED PARTICIPATORY DECISION MAKING FOR CANCER PREVENTION  
THROUGH IMPLEMENTATION RESEARCH

Grant Agreement: 101104777

## D2.1 CRC Incidence factors and Barriers identification



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## Executive Summary

The ONCODIR project is dedicated to developing innovative tools aimed at enhancing cancer prevention and control through the integration of end-user feedback into the design and implementation processes. This document highlights the methodologies employed and the outcomes achieved in gathering insights from various stakeholders, including healthcare professionals, policy-makers, and citizen representatives.

A key focus of the project has been to establish a framework for continuously collecting and harmonizing end-user requirements. By engaging participants in design thinking workshops and interactive sessions, the project has successfully identified critical performance indicators that inform the development of tools tailored to users' needs. Input from citizen perception studies has further enriched this process, emphasizing the importance of community engagement in validating and refining the tools.

In addition to user engagement, a comprehensive analysis of colorectal cancer incidence factors was conducted. This analysis assessed risk factors associated with colorectal cancer, including genetic, socio-economic, and behavioral influences. The findings highlight major factors that drive the development of colorectal cancer, as well as well-being gaps within a person's lifestyle, providing actionable recommendations that align with Europe's Beating Cancer Plan.

Furthermore, the project explored the social and economic factors influencing citizens' health-related quality of life. Through focus groups and surveys, barriers to effective health interventions were identified, allowing for a deeper understanding of user preferences and needs. This holistic approach ensures that the ONCODIR tools are not only technically sound but also culturally and socially relevant, ultimately contributing to improved outcomes in cancer prevention and care.

This document outlines the insights gained throughout these efforts, reinforcing the commitment to a user-centered design approach in the ongoing development of ONCODIR tools.

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## Acronyms & Abbreviations

Term	Description
AI	Artificial Intelligence
AICR	American Institute for Cancer Research
BMI	Body Mass Index
CRC	Colorectal Cancer
EHR	Electronic Health Record
EU	European Union
FDEP	Food Patterns Equivalents Database
G	Grams
GCSE	General Certificate of Secondary Education
GED	General Educational Development Test
IBD	Inflammatory Bowel Disease
IT	Information Technologies
Kcal	Kilocalories
Kj	Kilojoules
LIT	Laboratory Integration Test
M	Month
M	Mean
MD	Mean Difference
ml	Milligrams
NHS	National Health Service (UK)
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SD	Standard Deviation
SMD	Standard Mean Difference
UK	United Kingdom
VR	Virtual Reality
WCRF	World Cancer Research Fund

# 1 Introduction

## 1.1 Overview

This deliverable outlines the key activities undertaken to gather and analyze end-user feedback on the ONCODIR tools, including the citizen app, the decision support system, and the analytics dashboard. Engaging end-users through structured workshops and feedback sessions is crucial for informing the iterative development process and ensuring that the tools are effectively tailored to meet the diverse needs of their intended users.

This deliverable also integrates findings from the comprehensive literature review and meta-analysis of colorectal cancer (CRC) incidence factors. This analysis examined various factors, including genetic, socio-economic, and behavioral risk factors associated with CRC, shedding light on the complexities of cancer prevention in different populations. The insights gained from this task provide a contextual framework that enhances our understanding of the specific needs and challenges faced by users in various demographics.

Furthermore, this deliverable also includes the findings of the work done to identify barriers to effective health interventions, including social, cultural, and economic factors impacting citizens' health-related quality of life. This task utilized targeted focus groups and surveys to uncover the obstacles that hinder access to preventive measures and treatment options. By understanding these barriers, we can better inform the design of the ONCODIR tools, ensuring they address not only the technical requirements but also the socio-cultural dynamics that influence user engagement and adherence to health recommendations.

Together, these findings create a holistic view of the landscape in which the ONCODIR tools will operate. This comprehensive approach aims to enhance usability and facilitate the successful implementation of the ONCODIR solutions in real-world settings, ultimately contributing to improved cancer prevention and control efforts.

## 1.2 Relation to other tasks and deliverables

The findings from the comprehensive literature review, meta-analysis of colorectal cancer incidence factors, user requirements sessions, and the identification of barriers to effective health interventions provide a foundational basis for the entire ONCODIR project. These insights are critical in shaping the development of the tools within the project, particularly those in Work Packages 3 and 4, ensuring their alignment with the needs and challenges faced by end-users.

By integrating the results from these tasks, the ONCODIR project aims to create tools that are not only technically sound, but also relevant and applicable in real-world contexts. The analysis of colorectal cancer incidence factors informs evidence-based practices that will enhance the effectiveness of the risk stratification engine (T4.1 / D4.1), while the identification of barriers highlights the social and economic challenges that must be addressed to improve health-related quality of life, insightful information for the data analytics dashboard (T4.4 / D4.1).

This holistic approach ensures that all components of the ONCODIR system are interconnected, facilitating a seamless flow of information and enhancing the overall impact of the project in its efforts to advance cancer prevention and control initiatives.

### 1.3 Structure of the deliverable

This deliverable is structured to provide a comprehensive overview of the ONCODIR project and its related activities, presenting valuable insights that will guide the development of tools aimed at enhancing cancer prevention and control.

- **Section 1:** Introduction - This section offers an introduction to the deliverable in the context of the ONCODIR project, outlining its objectives and purpose.
- **Section 2:** User Requirements and Sessions - This section focuses on the methodologies and outcomes of the user requirements sessions conducted with various stakeholders. It highlights the feedback gathered and its implications for tool development, ensuring that the ONCODIR solutions are tailored to meet the needs of end-users.
- **Section 3:** Literature Review and Meta-Analysis of Incidence Factors - Here, we present the findings from the comprehensive literature review and meta-analysis on colorectal cancer incidence factors. This analysis provides a contextual foundation that informs the design and functionality of the tools being developed.
- **Section 4:** Identification of Barriers - This section addresses the identification of barriers to effective health interventions. It explores the social, cultural, and economic factors that impact citizens' health-related quality of life, emphasizing the need for the tools to address these challenges effectively.

## 2 Adaptive framework for community-based context-sensitive research and scale-up implementation

### 2.1 Introduction

The Adaptive Framework centers on systematically gathering, reviewing, and incorporating feedback from end-user groups to define and refine the ONCODIR tools. This framework is designed to ensure that user requirements are accurately identified and validated, allowing the tools to be fully aligned with the needs and expectations of intended users. Through structured sessions with external stakeholders and consortium end-users, the Adaptive Framework serves as the foundation for defining and refining tool functionalities in preparation for further stages of development and implementation.

#### Key Elements of the Adaptive Framework

The Adaptive Framework provides a structured approach for collecting and synthesizing feedback from diverse end-user groups to guide ONCODIR tool development. It prioritizes systematic engagement with stakeholders to define precise user requirements and validate these with the technical capabilities of the tools.

The objective is to ensure that ONCODIR tools are designed to meet the specific needs and workflows of end-users, as defined by their direct feedback. This framework establishes a clear pathway from initial feedback collection to the final validation of requirements, creating a responsive and user-centered tool design process.

#### Workshop Plans and Roadmap

##### Workshops and E-Workshops

The initial plan for gathering feedback involved conducting regular workshops with external stakeholders at key project milestones (M4, M8, and M16) and supplementing these with remote e-workshops (M7 and M14) and 2 design thinking workshops, dedicated to efficiently delivering the ONCODIR tools to the end-users. However, to better align the feedback sessions with the tools' development stages, adjustments were made to the methodology and timeline. This allowed the sessions to reflect the tools' readiness and maturity more accurately, ensuring the relevance and usefulness of the collected insights.

- **First Session (Month 6):** The initial feedback session took place in Month 6, as the first drafts and concepts for the tools were taking shape. Held online and attended by consortium members, this session provided an opportunity to establish a structured approach for subsequent user requirement sessions. It also helped refine the methodology for engaging external stakeholders, particularly those with limited familiarity with the project's objectives.
- **First External Stakeholder Session (Month 7):** Building on insights from the initial session, and using the materials and videos developed, the first session with external stakeholders occurred in Month 7. Targeting healthcare professionals and policy-makers, this session provided essential feedback on the tools' usability and relevance from a practical perspective.
- **In-Person Consortium Session (Month 8):** An in-person session was conducted during the first Consortium Plenary. This hands-on workshop allowed consortium members to directly

exchange ideas of the tools in a roundtable discussion. Participants shared insights on potential improvements, new directions, and alignment with project objectives, which led to a detailed set of user requirements. These requirements were integrated and set as goals leading up to the first integration laboratory (LIT01) held in Month 13.

- **LIT01 User Requirements Session (Month 14):** After the tools achieved a significant level of maturity leading up to the First Laboratory Integration Test, and as part of the Laboratory itself, another user requirements session was conducted in Month 14. This session was hybrid, taking place both at the second Consortium Plenary and online. Based on feedback, it was determined that the tools would benefit from additional refinement before gathering further insights from external stakeholders.
- **Citizen Stakeholder Session (Month 17):** As part of the project's focus on community engagement, a dedicated session for citizen end-users took place in Month 17, with Lithuanian university students engaging with the citizen app, NELI. This session highlighted user preferences and functionality needs specific to a citizen demographic, providing valuable insights into the app's design and flow.
- **Policy-Maker Session in Brussels (Month 18):** The final session was held with the EUREGHA working group in Brussels, composed of healthcare professionals and policy-makers. This session focused on the policy-maker tool, DELI, gathering targeted feedback to ensure the tool's functionality and relevance align with policy and decision-making processes.

These sessions provided a structured approach to capturing detailed feedback directly from end-users, enabling the team to identify key preferences, pain points, and specific functional requirements critical to refining the tools.

### External Stakeholder Engagement

Engagement with external stakeholders, including healthcare professionals, patients, policy-makers, and other relevant community representatives, has provided essential insights into each tool's usability, functionality, and practical value. This feedback informs necessary modifications, ensuring that the tools are tailored to meet real-world expectations and serve the needs of diverse user groups effectively.

### Within-Consortium Sessions

In addition to external sessions, feedback was also gathered through sessions within the consortium. Consortium members who are end-users themselves have offered valuable insights that support both the scientific objectives of the project and the practical needs of end-users. This internal collaboration has contributed to a comprehensive view of user requirements, helping to align the tools with both practical application and project goals.

### Analysis and Integration of User Requirements

The feedback gathered from workshops and e-workshops is analyzed to establish key performance indicators (KPIs) that measure the effectiveness and usability of the tools, as well as objectives and functionalities to be added to the tools, if they don't include them. These KPIs, co-defined with end-users, serve as benchmarks for tool refinement and validation, ensuring that each tool aligns with

defined user needs. These KPIs were a primary indicator of the analysis for the success of the first Laboratory Integration Test of the project.

Feedback is processed in an iterative manner, with findings from each session guiding adjustments to the tools. This allows the framework to integrate evolving user needs, technical capabilities, and feedback cycles, ensuring continuous alignment between tool development and end-user expectations.

### Scalability for Future Implementation

While primarily focused on defining user requirements, the Adaptive Framework also provides a foundation for future scalability. By documenting feedback and establishing KPIs, it enables the tools to adapt to additional user groups and settings in future project phases. This approach supports the tools' eventual scale-up, with a solid, user-validated base to ensure relevance across regions.

## 2.2 Workshop Series with End-Users (Online and Physical)

### Workshop Objectives

The workshop series was designed to create a collaborative environment where end-users could share their insights and experiences regarding the ONCODIR tools. By facilitating both online and physical workshops, the project aimed to engage a diverse group of stakeholders, including healthcare professionals, policy-makers, and citizen representatives. The primary goal was to gather valuable feedback that would inform the iterative development of the tools, ensuring they meet the specific needs of the target audience.

Each workshop was structured around key objectives:

- **Gather User Insights:** Identify the needs, preferences, and pain points of end-users concerning the ONCODIR tools.
- **Validate Tool Concepts:** Present early drafts and prototypes of the tools to receive constructive feedback on their design and functionality.
- **Refine Tool Identity:** Collaboratively establish the identity and purpose of each tool's functions from the perspective of individuals who may utilize the tool regularly for personal or professional purposes.
- **Foster Collaboration:** Create a platform for dialogue and co-creation, allowing end-users to actively participate in the development process.

### Methodology, Feedback Collection and Follow-up Actions

The methodology for each session was tailored to maximize engagement and feedback quality. The approach included the following elements:

#### 1. Pre-Session Preparation:

- Participants were selected based on their relevance to the project, ensuring a diverse representation of perspectives from the end-user groups: citizens, healthcare professionals, and policy-makers.
- Presentations, prototypes, and discussion guides were prepared in advance to facilitate structured discussions.

#### 2. Session Format:

- Introduction: Each session began with an overview of the project objectives and contextualization of the tool within the project. Additionally, the role of user feedback in tool development is emphasized.
- Interactive Presentations: Stakeholders were presented with the current status of the tools, including demos of prototypes.
- Breakout Discussions: for the within-consortium sessions, participants were divided into smaller groups to discuss specific aspects of the tools, fostering deeper engagement and detailed feedback.

### 3. Feedback Collection Techniques:

- Surveys and Polls: Quick surveys were conducted during sessions to gather immediate feedback on specific features or functionalities.
- Discussion Notes: Facilitators documented key points from group discussions to capture insights and suggestions for within-consortium sessions.

### 4. Follow-Up Actions:

- Documentation of Feedback: All feedback was compiled and analyzed to identify common themes, preferences, and areas for improvement.
- Iterative Development: The feedback collected was used to refine tool functionalities and address any identified gaps or issues.

## Expected Outcomes

The workshop series was designed to achieve several critical outcomes:

- User-Centered Tool Design: The insights gained would ensure that the ONCODIR tools are aligned with user needs and expectations.
- Enhanced Tool Usability: Specific feedback on usability would guide refinements, leading to more intuitive and effective tools.

## Sessions and Outcomes

### First Session: Consortium Online Session (Month 6, 30th November 2023)

The initial feedback session took place in Month 6, as the first drafts and concepts for the tools were taking shape. This session was held online and attended by consortium members.

#### *Methodology Followed*

Participants were selected based on their roles in the consortium and tasked to provide user requirements to the tools that they were catered to: citizen representatives on NELI, healthcare professionals on DEPO, and policy-making representatives on DELI. Prototypes of the ONCODIR tools were presented if they were available. In the cases where the tool was still in development and had no tangible outputs, presentations focused on conceptual overviews and anticipated functionalities.

**Table 1. ONCODIR End user Groups**

End User Groups		
Citizens/Patients	Clinicians	Policy makers
ECPC	INCLIVA	EUREGHA
YCE	ESDO	MoHGR
POLA	IOB	MoH-LT
	LSMU	UNIRIOJA
	EFPC	RDFCM
		AReSS PUGLIA
		ICO
		EY

The session commenced with an overview of the project and the positioning of the tools within its framework, highlighting the critical need to gather initial user requirements for each tool to initiate their development. Interactive presentations and videos were utilized to provide updates on the current status of the tools and clarify their objectives.

Feedback from end-users was gathered using a structured spreadsheet document, categorizing responses for each showcased tool. An initial questionnaire was introduced based on the Task 2.3 literature review, which focused on prioritizing elements to be included for each end-user group. This questionnaire employed a 5-point Likert scale, where 5 indicated "Very Interesting" and 1 indicated "Not Interesting at All."

Some example questions included:

- For citizen representatives, questions addressed areas of interest regarding tool coverage, such as:
  - "1. What are the most significant risk factors for developing colorectal cancer?"
  - "6. How can I maintain a healthy weight to reduce the risk?"
- For clinician and healthcare professional representatives, questions focused on desired features in the tool, such as:
  - "3. What are the most effective education and awareness strategies to promote prevention?"
  - "8. What is the relationship between inflammatory bowel diseases and colorectal cancer?"
- For policy-maker representatives, questions aimed to assess interest in content relevant to public policy, such as:
  - "2. What are the most effective prevention strategies that can be implemented at the level of public policies?"
  - "7. What prevention programs are currently being implemented in at-risk populations?"



### Outcomes of the session

The outcomes of this session generated a substantial number of user requirements for tools that had progressed to a more advanced conceptual stage in the project, such as NELI, the citizen app, which featured a prototype demonstrating its intended appearance, using a sister project prototype as a reference. In contrast, tools still in the planning phase, like DELI, attracted fewer requirements, as participants found it difficult to understand their objectives due to the lack of a visual representation and a clear concept of how the tool would function.

The prioritization questionnaire proved to be less useful than anticipated, as the session outcomes indicated that the focus should be on defining the identity and essential features of each tool. Given the absence of preexisting material or content within these tools, there was no necessity to eliminate or prioritize any specific content.

THE ASK:				
In the table on the left write max 10 End-user requirements.				
End-user requirements = what technology should do and how it should do it				
Generic examples of end-user requirements:				
1. Verify distinction between healthy citizen and cancer patient with >95% s				
2. Non-invasive				
3. Intuitive graphical interface				
T4.2 Mobile App (NELI)				
NO	POIA	ECPC	YCE	EFPC
1	App should be available on android and apple	The mobile application should have an intuitive and	Chatbot should be available in the languages where pilots	easy to use
2	POIA patients should review UI (suggesting to set up	The app should offer easily accessible educational content	How will users receive access to Nutrinomics advices	different languages
3	App should be translated in languages of countries, where	It should empower patients through personalized feedback,	If as patient I am using NELI app, my physician should be	use info from other a
4	App should integrate activity (steps, calories burned from	The mobile app must ensure strict adherence to data		connect to medical/gp
5	Gamification (rewarding points) should be clearly explaind -			
6	Chatbot should be available in the languages where pilots			
7	How will users receive access to Nutrinomics advices			
8	If as patient I am using NELI app, my physician should be			
9	A text should be included in terms and conditions (legal			
10	A text should be included in the landing screen when			
11	Next to each question related to the recommendation to			

**Figure 1.** Part of the User Requirements provided by some of the partners for the Citizen Tool (NELI) (Annex C)

### Annexes

- Annex A: Agenda for Online Consortium User Requirements Session 30.11.2023 - Refer to this annex to know about the specifications and the agenda for the first Consortium User Requirements Session
- Annex B: Updated Agenda and Details for Online Consortium User Requirements Session 30.11.2023 - This annex document adds more information to the initial information shared in annex A.
- Annex C: Document for Collection of Consortium User Requirements 30.11.2023 - This annex document contains all the feedback collected from the Consortium Users on the showcased tools and the answers for the questionnaire from each of the Consortium Users.
- Annex D: ONCODIR Basic Tool Descriptions to support T2.1 and User Requirements Session - This annex document was shared by the Technical partners to the User partners to provide more context on the ONCODIR tools.

### Second Session: External Stakeholder Session (Month 7, 18th December 2023)

The first session with external stakeholders took place in Month 8, targeting healthcare professionals and policy-makers. This online session aimed to gather essential feedback on the usability and relevance of the ONCODIR tools.

### Methodology Followed

External stakeholders representing healthcare professionals and policy-makers in Thessaloniki, closely associated with the Aristotle University of Thessaloniki, were identified for these sessions. The three end-user tools were showcased, utilizing materials developed during the initial user requirements session. Interactive discussions were facilitated using Mentimeter, which encouraged real-time responses and engagement from all participants.

The sessions were held at the Nicholas Spyrou Lab, part of the Lab of Medical Physics & Digital Innovation (iMedPhys), part of the School of Medicine in Aristotle University of Thessaloniki (AUTH). This environment fostered collaboration and facilitated productive discussions.

Key project elements and objectives were presented through PowerPoint slides, structured to introduce the tools and lead into open discussions regarding user requirements. The sessions were conducted entirely in Greek to ensure fluid and natural conversations, as all participants were from Greece. Approximately 10 clinicians and medical researchers participated in the clinical session, while around 10 public health policy stakeholders attended the policy-maker session.

Feedback was gathered verbally during open discussions and structured through Mentimeter polls. A Mentimeter bar scale was utilized to assess the level of agreement on project planning and progression.

### Outcomes of the session

The majority of attendees expressed agreement with the project's approach, indicating alignment with the planning strategy. In the case of the verbal discussions, there was a designated person writing down the most important discussion points, which would be later translated into user requirements.

Partner	User Req ID	User requirement	Tech Req ID	Technical requirement	Difficulty to Implement	Comm before \ (CT
USER REQUIREMENT WORKSHOP USER REQUIREMENT WORKSHOP USER REQUIREMENT WORKSHOP USER REQUIREMENT WORKSHOP	52	Clinicians should have information about which groups of people are more vulnerable to develop CRC	52	Communication with DELI tool	Mid	
	54	Clinicians should know and have all the information about the risk factors of the development of CRC at hand	54	Risk factors identified in WP2 will be included in the dashboard.	Mid	
	55	Clinicians should have information on the most effective ways to promote prevention/should know how important their work is in prevention	55			
	56	Clinicians should be able to offer their patient different ways of prevention	56	tech_req_id_9	High	

**Figure 2.** Part of the User Requirements agreed by the External Stakeholders attending the session, for the Clinician Tool (DEPO) (Annex H)

### Annexes

- Annex E: Agenda for Clinician External Stakeholder User Requirement Session 18.12.2023 - Refer to this annex document to know more about the structure of the session dedicated to Clinical External Stakeholders.
- Annex F: Agenda for Policy-Maker External Stakeholder User Requirement Session 18.12.2023 - Refer to this annex document to know more about the structure of the session dedicated to Policy-maker External Stakeholders.

- Annex G: MoHGR - User Requirements for DELI (Policy-makers) - MoHGR documented feedback of their point of view after the Policy-maker session.
- Annex H: Document for Collection of Consortium User Requirements 23-24.01.2024 - Refer to this annex document to review the collected feedback from the User Requirements collected from the first External Stakeholder session, under the “User Requirement Workshop” tag. These Requirements were collected by hand and shared with the developers of each tool, and added with the collection document of the following User Requirements session.

### **Third Session: In-Person Consortium Session (Month 8, January 23-24th 2024)**

An in-person session was held during the first ONCODIR Consortium Plenary, allowing consortium members to engage directly with other stakeholders and have insightful conversations, as well as provide hands-on feedback. After the implementation of the first user requirements obtained during the first two sessions, new perspectives and insights from the consortium members were required to understand how to move forward with the development of the tools.

#### **Methodology Followed**

During the second and third days of the Plenary, a series of presentations showcased the current state of each tool, with one and a half hours allocated for the presentation of each tool. These sessions included open discussions with end-users, as well as a Q&A segment for developers to address any questions from the participants. All consortium members were present for the presentations of all tools.

On the second day, an end-user roundtable was held, lasting an hour and a half. This roundtable focused on discussing key issues and gaps identified by end-users, with the aim of finding solutions or strategies to manage their impact.

Feedback from end-users was collected over the two weeks following the session using a structured spreadsheet document that categorized responses for each showcased tool. End-users were also tasked with reviewing their original user requirements and providing feedback on how well these requirements have been integrated into the current state of the tools.

#### **Outcomes of the session**

The technical partners provided a clearer overview of the tools, which enabled end-users to generate a more refined and specific list of user requirements. The discussions that emerged during the plenary regarding the tools’ usability and alignment with their intended purposes helped many end-users gain a better understanding of what features should be prioritized for inclusion. Additionally, a designated facilitator documented the most critical pain points identified during these conversations, which would later be translated into actionable user requirements.

Partner	User Req ID	User requirement	Tech Req ID	Technical requirement	Difficulty to Implement	Comm before \ (CT
Cyprus_plenary	45	Need to have a "free text" field for the clinician to convey messages to citizens	45	Integrate a free text input field within DEPO for clinicians to compose messages	Low	▼
Cyprus_plenary	46	Notification about the citizen's state when changed	46			▼
Cyprus_plenary	47	Get information form free text from citizen about why citizen is doing "X"	47	If NELI provides this kind of information, DEPO will be able to retrieve them and demonstrate it.	Mid	▼

**Figure 3.** Part of the User Requirements collected by the session facilitator and agreed by the Consortium partners attending the session, for the Clinician Tool (DEPO) (Annex H)

## Annexes

- Annex H: Document for Collection of Consortium User Requirements 23-24.01.2024 - Refer to this annex document to review the collected feedback from the User on their Requirements for the state of the tools at this point in time.

### Fourth Session: LIT01 User Requirements Session, during the Second ONCODIR Consortium Plenary (Month 14, 1-2nd July 2024)

Building on the insights gained from the successful execution of LIT-01, this session aimed to further refine the development of the ONCODIR tools by actively engaging end-users in a collaborative dialogue.

#### Methodology Followed

The subsequent User Requirements session was held during the second ONCODIR Consortium Plenary, immediately following the successful completion of LIT-01 in Month 13 of the project. This timing was intentionally chosen to facilitate in-person discussions among end-users and enable dynamic feedback. The success of LIT-01 the previous month underscored the importance of integrating a significant portion of user requirements gathered from earlier sessions, which was one of the key performance indicators (KPIs) for the project.

The methodology for this session closely mirrored that of the previous end-user session; however, along creating new user requirements, participants were also tasked with evaluating how well all end-user's previous requirements had been integrated. They were encouraged to provide comments and adjust the prioritization of the requirements accordingly.

#### Outcomes of the session

The LIT01 User Requirements Session yielded a significant number of new user requirements for all tools discussed, extending beyond the main three ONCODIR tools to include the Fusion Engine tool as well. Participants actively engaged in evaluating the functionalities of each tool, providing insights that will enhance usability and effectiveness.

Partner	User Req ID	User requirement	Tech Req ID	Technical requirement	[INCLIVA] Priority	[INCLIVA] score 1: Not Implemented 2: Partially implemented 3: Fully implemented	[INCLIVA] Comments	[PO]
EUREGHA	PYRAMID_UR13	Have clear and standardised indicators to compare risk factors data across Europe			High	2. Partially Implemented	There are no standardised indicators, but general consensus that aligns with the risk factors used.	I
NEW REQUIREMENTS [User]		[New Requirement]						
INCLIVA		Provide an exact number for the risk stratification score, alongside of the level of risk.			High			I
INCLIVA		The Risk score "parameter" could have a pointer to indicate exactly where the person is within their own risk level (for example, I am at level 3, but my score is almost at level 4 so it should show that the pointer is going almost at 4, but still in the 3 level.			Mid			I
AreSS		The items must be translated in native language						

**Figure 4.** Part of the User Requirements by the Consortium partners attending the session, for the Risk Stratification Tool (PYRAMID) (Annex J)

## Annexes

- Annex I: Comprehensive guide to the User Requirements Workshop 01-02.07.2024 - This annex document is material created for Consortium Users to understand how to approach the User Requirements Session and the document to provide their feedback.
- Annex J: Document for Collection of Consortium User Requirements 01-02.07.2024 - Refer to this annex document to review the collected feedback from the Consortium Users on their Requirements for the state of the tools at this point in time.

## Fifth Session: Citizen Stakeholder Session (Month 17, 22nd October 2024)

A dedicated session for citizen end-users was held to engage Lithuanian university students aspiring to be doctors, with the citizen app, NELI. This session aimed to create a platform for young adults to interact directly with the app, providing valuable insights and feedback on its functionalities and user experience. By focusing on this demographic, the session sought to gather perspectives that reflect the preferences and needs of the younger public, particularly in the context of health and wellness.

### Methodology Followed

The session began with a brief welcome and explanation of the ONCODIR project, its goals and The session commenced with a brief welcome and an overview of the ONCODIR project, including its goals and significance. Participants were informed about the context of the tools and their roles within the ONCODIR data flow. An 11-minute video demonstration of the tool prototype showcased its key functionalities, enhancing participants' understanding of the app.

Conducted in a collaborative environment, the session encouraged the 24 student participants to ask questions and engage actively throughout. Feedback was collected via a structured survey designed to gather insights on the tool's usability and identify potential improvements to enhance the user experience.

### Outcomes of the session

The participants demonstrated a highly positive response to the prototype of the citizen app, NELI. Their feedback offered valuable insights and new perspectives that can greatly enhance the user experience. Many participants highlighted specific functionalities they found beneficial, as well as areas for improvement.

Marca temporal	How would you rate your overall impression	What is your initial reaction to the design and layout	How easy or difficult was it to understand	How likely do you see your Do you think it fulfills the objective
10/22/2024 16:24:59	Positive	good	Very easy	1 Somewhat clearly
10/22/2024 16:25:03	Very positive	Very nice.	Very easy	1 Clearly
10/22/2024 16:25:09	Positive	Great	Easy	1 Clearly
10/22/2024 16:25:34	Very positive	good	Neutral	2 Clearly
10/22/2024 16:26:06	Positive	good	Very easy	1 Clearly
10/22/2024 16:26:31	Very positive	Thats cool	Very easy	1 Clearly
10/22/2024 16:26:31	Very positive	So far everything is great!	Very easy	2 Clearly
10/22/2024 16:27:16	Very positive	very simple, easy to use	Very easy	2 Somewhat clearly
10/22/2024 16:27:17	Positive	Might be more aesthetic but it is fine	Easy	2 Clearly
10/22/2024 16:27:39	Very positive	Everything turned out to be very convenient and in	Neutral	2 Somewhat clearly
10/22/2024 16:27:59	Positive	convenient, simple, understandable	Very easy	1 Clearly
10/22/2024 16:28:10	Positive	positive	Easy	3 Clearly
10/22/2024 16:28:10	Very positive	Seems quite convenient as of now	Very easy	3 Clearly
10/22/2024 16:28:23	Very positive	It would be usefull	Very easy	1 Clearly
10/22/2024 16:29:02	Positive	Modern, easy to find everything	Easy	2 Somewhat clearly
10/22/2024 16:29:11	Very positive	Good, no too much of everything	Easy	1 Clearly
10/22/2024 16:29:12	Very positive	It is clear and intuitive	Easy	1 Clearly
10/22/2024 16:29:21	Very positive	positive	Easy	1 Clearly

**Figure 5.** Feedback collected from the survey from the External Stakeholders attending the session, for the Citizen Tool (NELI) (Annex L)

## Annexes

- Annex K: NELI ESUS Session Agenda and Structure Guide 22.10.2024 - Refer to this annex document to understand the structure and agenda of the session.
- Annex L: Document of Feedback of External Stakeholders User Requirements Session for Citizens Tool NELI 22.10.2024 - This annex document contains all the collected responses from the survey shared with the External Stakeholders that participated in the session.

## Sixth Session: Policy-Maker Session in EUREGHA's Working Group (Month 18, 6th November 2024)

The final session was conducted with the EUREGHA Working Group, with the participation of the tool developers, the ICCS team. The Working Group consists of professionals from both fields of healthcare and policy-making. This session aimed to gather targeted feedback on the policy-maker tool, DELI. Engaging with this diverse group of stakeholders was essential for ensuring that DELI effectively addresses the needs and expectations of policy-makers in the healthcare sector. The session provided a platform for in-depth discussions, allowing participants to share their insights and recommendations on how the tool can be refined to better support policy development and implementation.

### Methodology Followed

The session focused on contextualizing the DELI tool and its significance for policy-making. The participants had been sent the video demo and an access to the tool prior to the session, in order to have a personal experience with the tool.

In the session, participants were informed about the purpose of the event and the importance of their feedback in shaping the tool's development, followed by the viewing of a brief video demonstration highlighting DELI's key functionalities, enhancing the participants' understanding of its relevance to their work. A Q&A session with DELI's developers promoted clarity between the participants.

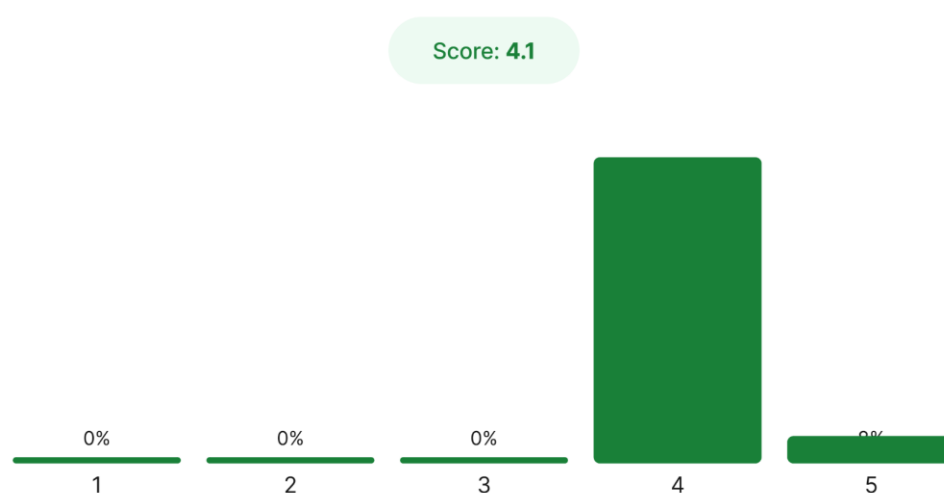
To gather actionable insights, attendees completed an interactive feedback survey designed to assess usability and identify areas for improvement. The survey link was shared in the chat, allowing participants to provide their thoughts and suggestions in real time. The session concluded with gratitude for their contributions, reinforcing the value of their input in refining the DELI tool.

### Outcomes of the session

The participants showed great engagement and a positive response to the showcased tool, DELI. The session concluded having in hand numerous insights and ideas on how to improve the experience of the tool, as well as shaping the path for DELI between the descriptive analytics tool environment.

★ What is your initial impression of the tool? (1 = Very negative; 2 = Negative; 3 = Neutral; 4 = Positive; 5 = Very positive)

Rating Poll ✓ 13 votes 👤 13 participants



slido

**Figure 6.** Dynamic representation of the survey answered by the External Stakeholders on the Policy-makers tool (DELI) (Annex O)

#### Annexes

- Annex M: DELI ESUS Session Agenda and Structure Guide 06.11.2024 - Refer to this annex document to understand the structure and agenda of the session.
- Annex N: Document of Feedback of External Stakeholders User Requirements Session for Citizens Tool DELI 22.10.2024 (EUREGHA report) - This annex document contains all the information on the session held with the External Stakeholders that participated in the session.
- Annex O: Document of Feedback of External Stakeholders User Requirements Session for Policy-Makers Tool DELI 06.11.2024.

## 2.3 User Requirements for Technical Partners to Develop the ONCODIR Tools

Gathering user requirements is a critical component in the development of ONCODIR tools. These requirements are derived directly from interactions with users during workshops and feedback sessions, and they are essential for guiding technical partners in creating effective and user-aligned tools.

### Types of User Requirements

User requirements can be categorized into several key types:



- **Functional Requirements:** Specific descriptions of the functions that the tools must provide. For example, the ability to track user health or generate personalized reports.
  - Example: The tool must allow users to input data about their symptoms and receive personalized recommendations.
- **Usability Requirements:** Standards that define how easy it is for users to interact with the tools, including accessibility, interface clarity, and system responsiveness.
  - Example: The user interface must be intuitive, allowing users to complete tasks with minimal steps.
- **Integration Requirements:** Needs related to the tools' ability to integrate with existing systems or workflows, ensuring easy adoption in various environments.
  - Example: The tool should be able to export data to existing patient management systems in clinical settings.

### **Process for Gathering Requirements**

The process for collecting and defining user requirements was carried out through:

- **Feedback Analysis:** Insights gathered during workshops were analyzed to identify common patterns and recurring requirements.
- **Prototype Reviews:** Users reviewed tool prototypes, allowing for direct feedback on proposed functionalities.

### **Validation of Requirements**

Once gathered, the requirements were validated by the technical partners following the next steps:

- **Revision and merging:** Consolidate the user requirements by reviewing and merging similar or redundant entries into a unified requirement.
- **Feedback Revisions:** Technical partners engaged with end-users to seek further details or clarification regarding their requirements as needed.
- **Continuous Iteration:** Requirements were revised and adjusted based on ongoing feedback and changes in user needs.
- **Consistent Review and Feedback Cycle:** End-users were consulted on the integration and incorporation of their requirements to ensure alignment with the initial specifications, allowing for necessary adjustments to be made.

### **Documentation of Requirements**

All user requirements were documented in a clear and accessible format, providing technical partners with a guide during tool development. Documents that describe each requirement with examples and acceptance criteria, including the ability to integrate the requirement, the difficulty of development, and the importance to be included in the tool.

### **Impact on Tool Development**

The thorough collection and definition of user requirements not only ensure that ONCODIR tools are relevant and useful but also facilitate effective collaboration between technical partners and users. By having a clear framework of requirements, ambiguities are minimized, and the likelihood that the tools meet user expectations is increased.



## 2.4 Next Steps

As the project progresses, it is essential to outline the next steps to ensure the continued alignment of the ONCODIR tools with user needs and project objectives. The following actions will guide the next phases of development and implementation.

### 1. Continued User Engagement through Task 2.2

Further workshops with end-users will be scheduled to validate ongoing developments and gather insights on new features or modifications. These sessions will ensure that user perspectives remain central to the development process. Regular check-ins with end-users through surveys and interviews to monitor satisfaction and capture evolving needs will be implemented.

### 2. Iterative Prototyping and Testing

Create and refine prototypes of the ONCODIR tools as they reach a greater maturity stage. These prototypes will undergo usability testing with end-users to gather actionable insights. Dedicated user testing sessions will be organized to observe how end-users interact with the tools, identifying any usability challenges or areas for improvement.

### 3. Integration of Feedback

Establish a structured process for integrating user feedback into the development cycle, ensuring that tool enhancements are directly informed by user experiences. In order to achieve it, regular meetings among technical partners and stakeholders to review feedback and assess the impact on development priorities will be held.

These next steps are crucial for maintaining a user-centered approach in the development of ONCODIR tools. By fostering continuous engagement with end-users, iteratively refining the tools, and documenting progress, the project will ensure that the final outcomes are aligned with user expectations and effectively address their needs.

### 3 Cancer Incidence Risk Factors Analysis considering heterogeneity within and between EU countries/regions

#### 3.1 Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide, with incidence steadily rising across many regions. According to the Global Cancer Observatory, CRC ranks as the third most common cancer globally, with 1,926,425 new cases reported in 2022 (accounting for 9.6% of all cancers) and is the second deadliest, with 904,019 deaths (1). The incidence of CRC has notably increased among individuals born after the early 1950s in almost every region, suggesting birth cohort effects likely tied to environmental and lifestyle factors that influence cancer initiation and progression over a lifetime (2). Substantial improvements in patient outcomes can be achieved by identifying and addressing modifiable risk factors, coupled with implementing personalized screening strategies for those at elevated CRC risk (3).

Identifying CRC risk factors is crucial, yet complex. A comprehensive risk assessment requires a systematic approach that includes a broad range of potential risk factors, especially environmental and lifestyle variables that are modifiable. Establishing a robust scoring system that incorporates these variables could allow for a more precise evaluation of an individual's CRC risk. Such a tool would be instrumental in guiding personalized prevention strategies and refining screening protocols, ultimately reducing CRC incidence and mortality.

The literature includes studies that systematically review CRC risk factors via meta-analyses, underscoring the need for broad, integrated analyses. In 2016, He et al. conducted a meta-analysis of nine case-control and nine cohort studies, finding evidence that procyanidins and isoflavones may reduce CRC risk (4). Hidayat's team in 2018 synthesized data from 15 studies, formulating a linear scale showing a 13% increased CRC risk per 5 kg/m<sup>2</sup> increase in BMI (5). In 2019, Oh's group reviewed 10 prospective studies and found that for every 10 g/day increase in cereal fiber intake, CRC risk was reduced by a factor of 0.91, suggesting a protective effect (6). A team (6) conducted a meta-analysis of ten prospective studies, finding an association in which for every 10 g/d of cereal fiber the risk was multiplied by 0.91, thus being a protective factor. In 2022, More recently, O'Sullivan's 2022 meta-analysis included 20 studies and found strong associations with several CRC risk factors: family history (RR 4.21), high alcohol intake (RR 1.71), dyslipidemia (RR 1.62), tobacco use (RR 1.35), and obesity (RR 1.54). However, significant heterogeneity across studies was noted, and some associations were not statistically significant (7). Hua et al. also conducted a comprehensive meta-analysis of 36 studies, identifying significant CRC risk increases associated with family history (OR 5.90), inflammatory bowel disease (OR 4.43), obesity (OR 1.52), smoking (OR 1.44), male gender (OR 1.44), alcohol consumption (OR 1.41), and Caucasian ethnicity (OR 1.20). This study additionally evaluated dietary patterns, including sugary drink intake (OR 1.55), processed meat (OR 1.53), and red meat consumption (OR 1.10) (8). With a similar meta-analysis that included 36 studies and found significant differences in terms of risk of family history (OR 5.90), inflammatory bowel disease (OR 4.43), obesity (OR 1.52), smoking (1.44), being male (OR 1.44), consuming alcohol (1.41), or being Caucasian (OR 1.20). This study also has the advantage of including dietary patterns such as consumption of sugary drinks (OR 1.55), processed meat (OR 1.53) or red meat (OR 1.10). Additional studies underscore the role of other factors. Jiang's team (8) found two studies linking CRC to docosapentaenoic acid and three studies

linking CRC to docosahexaenoic acid. Both elements were found to be a protective factor with relative risks of 0.76 and 0.80 respectively. Jin et al (9) performed a meta-analysis with 29 studies to evaluate the effects of nut and legume consumption, finding that the highest consumption group had a relative risk of 0.84 for nuts and 0.90 for legumes, both statistically significant. Zhang's team (10) included 44 studies in their 2023 meta-analysis. Finding ORs of 5.81 for family history, 2.58 for sugary drink consumption, 2.34 for tobacco, 1.51 for metabolic syndrome, 1.49 for alcohol, 1.37 for obesity in adolescence, 1.12 for red meat consumption. Khoa's team in 2023 (11) analyzed 12 studies in their meta-analysis focusing specifically on the risk factor diabetes mellitus, finding an OR of 1.43. Finally, in 2022 a meta-analysis by Alegria (12) focused on dietary factors, including fourteen cohort studies and seven case-control studies. Not all studies linked all types of foods, but they were able to find data on dairy products, fish, white meat and eggs.

These studies illustrate the challenge of conducting holistic CRC research that extends beyond a narrow set of risk factors. Moreover, the limited number of studies within each meta-analysis highlights the literature gap in understanding CRC risk comprehensively. We see a critical opportunity to perform a broader investigation, synthesizing data on a wide range of risk factors in an extensive meta-analysis. This will enable the development of a scoring system that reflects an individual's overall CRC risk, providing a precise tool for risk assessment and aiding in targeted prevention.

Aleksandrova's team previously addressed this need with the LiFeCRC score, which uses ten variables (including age, smoking, alcohol intake, physical activity, and diet) to estimate a 10-year CRC risk. Unlike a meta-analysis, they based their work on data from 255,482 participants in the EPIC study, adjusting risk factors for those who developed CRC (13).

Despite their value, meta-analyses face limitations. Quality variations among included studies can skew conclusions, as demonstrated by Du's critique of O'Sullivan's study (7), which noted exclusions and high heterogeneity in variables like obesity ( $I^2 = 99\%$ ), alongside diverse dietary patterns and inconsistent coding of terms (e.g., hyperlipidemia, hypercholesterolemia, and dyslipidemia). Additionally, data synthesis methods, such as statistical models or inclusion criteria, can introduce biases, while interpreting results amidst study heterogeneity remains challenging.

Our objective is to determine the relative weight of CRC risk factors through a consensus-driven systematic review and meta-analysis. This will allow us to develop a methodology for calculating CRC risk. While our work initially provides a narrative overview based on the literature, we aim to align this methodology with established prevention strategies, such as population-based secondary prevention, to enhance clinical practice and public health impact.

## 3.2 Literature Review

### Scope and Sources

Given that the review was going to be large and complex, a preliminary systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines before performing a definitive search. A systematic search was initially conducted primarily in PubMed and EMBASE and studies were defined as eligible for inclusion if their data were reported by observational studies published in English in the last 10 years, focusing on colorectal cancer, risk factors, and primary and secondary prevention strategies in adult population groups.

Prospective and retrospective cohort studies, case-control studies, and cross-sectional studies were included for the review.

### Methodology for Risk Factor Identification

Eligible risk factors included both modifiable and non-modifiable factors. No exclusions based on sex or clinical conditions were applied. Only studies in the human population were eligible. The search strategy using MeSH terms and Boolean operators was

- **STEP 1. Search:** ("colorectal cancer"[Title/Abstract] OR "colorectal cancers"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "colorectal neoplasms"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "colorectal carcinomas"[Title/Abstract])
- **STEP 2. Search:** ("risk factor"[Title/Abstract] OR "risk\*"[Title/Abstract] OR ("factor\*"[Title/Abstract] OR "relat\*"[Title/Abstract]))
- **STEP 3. Search,** adding the thesaurus corresponding to each group of risk factors (**Table 2**)
- **STEP 4. Search:** ("primary prevention"[Title/Abstract] OR "secondary prevention"[Title/Abstract] OR "prevention"[Title/Abstract] OR "preventi\*"[Title/Abstract])
- **STEP 5. Filter:** Studies and intervention programs: “controlled before-after studies”; “cost-benefit analysis”; “economic analysis”.
- **STEP 6. Combined search:** ("colorectal cancer"[Title/Abstract] OR "colorectal cancers"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "colorectal neoplasms"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "colorectal carcinomas"[Title/Abstract]) AND ("risk factor"[Title/Abstract] OR "risk\*"[Title/Abstract] OR ("factor\*"[Title/Abstract] OR "relat\*"[Title/Abstract]))
- **STEP 7. Combined search:** (("Age Factors" OR "Age Distribution") OR ("Gender" OR "Gender Distribution") OR ("Ethnicity" OR "Ethnic distribution") OR ("Genetic" OR "Genetics" OR "Heredity" OR "Anticipation Genetic" OR "Genetic Load") OR ("Inflammatory Bowel Diseases" OR "Crohn Disease" OR "Colitis, Ulcerative") OR ("Metabolic" OR "Metabolic Syndrome" OR "Metabolism", "Nutrition\*" OR "Nutritional Status" OR "Food" OR "Dietary Fiber" OR "Processed meat" OR "Red Meat" OR "Dietary Fats" OR "Diet\*") OR ("Socioeconomic Factors" OR "Social Class" OR "Socioeconomic Survey" OR "Low Socioeconomic Status" OR "Urban Population" OR "Rural Population") OR ("Educational Status" OR "Literacy" OR "Formative") OR ("Lifestyle" OR "Healthy Lifestyle" OR "Behaviour" OR "Sedentary Behaviour")) AND ("primary prevention"[Title/Abstract] OR "secondary prevention"[Title/Abstract] OR "prevention"[Title/Abstract] OR "preventi\*"[Title/Abstract])
- **STEP 8. Combined search:** ("colorectal cancer"[Title/Abstract] OR "colorectal cancers"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "colorectal neoplasms"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "colorectal carcinomas"[Title/Abstract]) AND ("risk factor"[Title/Abstract] OR "risk\*"[Title/Abstract] OR "factor\*"[Title/Abstract] OR "relat\*"[Title/Abstract]) AND (("Age Factors" OR "Age Distribution") OR ("Gender" OR "Gender Distribution") OR ("Ethnicity" OR "Ethnic distribution") OR ("Genetic" OR "Genetics" OR "Heredity" OR "Anticipation Genetic" OR "Genetic Load") OR ("Inflammatory Bowel Diseases" OR "Crohn Disease" OR "Colitis,

Ulcerative”) OR (“Metabolic” OR “Metabolic Syndrome” OR “Metabolism”, “Nutrition\*” OR “Nutritional Status” OR “Food” OR “Dietary Fiber” OR “Processed meat” OR “Red Meat” OR “Dietary Fats” OR “Diet\*”) OR (“Socioeconomic Factors” OR “Social Class” OR “Socioeconomic Survey” OR “Low Socioeconomic Status” OR “Urban Population” OR “Rural Population”) OR (“Educational Status” OR “Literacy” OR “Formative”) OR (“Lifestyle” OR “Healthy Lifestyle” OR “Behaviour” OR “Sedentary Behaviour”)) AND ("primary prevention"[Title/Abstract] OR "secondary prevention"[Title/Abstract] OR "prevention"[Title/Abstract] OR "preventi\*"[Title/Abstract])

- **STEP 9.** Filter added to the previous search strategy: Age >19 years old
- **STEP 10.** Filter added to the previous search strategy: Humans, not animals
- **STEP 11.** Remove duplicates

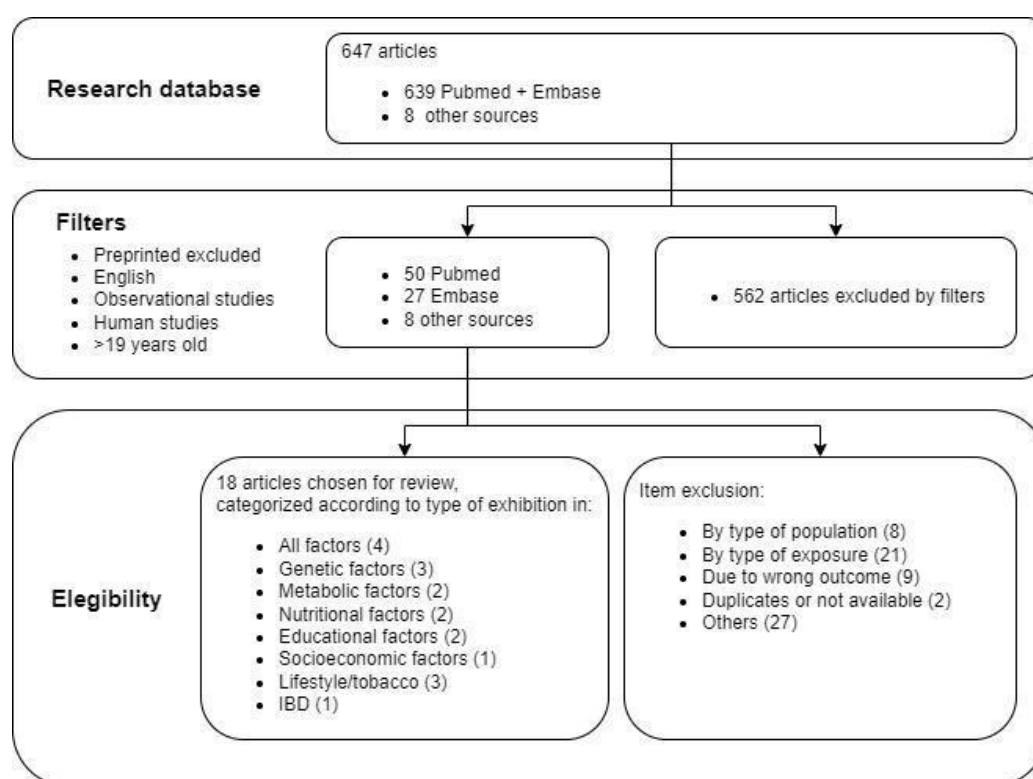
Table 2. Search Terms for each working group

Risk factor category	Thesaurus: third descriptor of the search strategy
Non-modifiable risk factors:	
Age, gender, ethnicity	“Age Factors”, “Age Distribution”, “Ag*”; “Gender”, “Gender Distribution”; “Ethnicity”, “Ethnic distribution”.
Genetic factors	“Genetic”, “Genetics”, “Heredity”, “Anticipation Genetic”, “Genetic Load”
Inflammatory Bowel Disease	“Inflammatory Bowel Diseases”, “Crohn Disease”, “Colitis, Ulcerative”
Modifiable risk factors:	
Metabolic and nutritional factors	“Metabolic”, “Metabolic Syndrome”, “Metabolism”, “Nutrition*”, “Nutritional Status”, “Food”, “Dietary Fiber”, “Processed meat”, “Red Meat”, “Dietary Fats”, “Fat*”, “Diet*”.
Socioeconomic factors	“Socioeconomic Factors”, “Social Class”, “Socioeconomic Survey”, “Low Socioeconomic Status”, “Urban Population”, Rural Population”
Educational factors	“Educational Status”, “Literacy”, “Formative”.
Lifestyle	“Lifestyle”, “Healthy Lifestyle”, “Behaviour*”, “Sedentary Behaviour”

\* used as wildcard to broaden the search

The narrative review conducted in this text identifies a set of risk factors that are consistently mentioned in the available literature. Grouping these risk factors into categories allows for the use of a unified search strategy, with modification of the thesauri or MeSH terms corresponding to each added factor. By organizing risk factors into categories, a researcher can streamline the search process and ensure comprehensive coverage of the relevant literature. This approach allows for the identification of studies that specifically investigate each category of risk factors, facilitating a thorough analysis and synthesis of the existing evidence. To implement this strategy, the researcher selects appropriate MeSH terms or thesauri related to each category of risk factors and incorporates them into the search scheme. This ensures that relevant articles addressing specific risk factors within each category are included in the search results. For each specific group of risk factors, the researcher will

identify and select the relevant thesauri or MeSH terms associated with that particular category. These terms will be integrated into the search strategy to ensure a focused and targeted retrieval of articles related to the specific group of risk factors. In each working group, the third step of the search scheme will be replaced by the respective thesauri or MeSH terms corresponding to the pre-established groups of risk factors. In our study, we will place special emphasis on modifiable risk factors, since they constitute the main objectives of primary prevention strategies, but we will not fail to classify risk markers such as age or sex, since they will condition the individual's risk profile and the degree of intensity of the intervention required on the modifiable factors. Articles were assessed using a checklist based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) initiative, which includes the following criteria: 1) study design; 2) size of the study population; 3) duration of follow-up; 4) characterization of exposure and outcome measures (we assessed the risk of bias in exposure measurement as well as the risk of bias in outcome measurement, categorizing this risk as high, moderate, or low); 4) level of control for potential confounders.



**Figure 7. PRISMA diagram of initial search**

For the final search, improvements were made to the search strategy:

- Correction of typographical errors that eliminated some of the articles, such as Ag\* (which the search interpreted as the element Silver), Fat\* which did not offer all the results.
- We did not use studies with pre-calculated risk; instead, we included only those with raw data.
- The period was extended from 2010 to 2024. We activated alerts in the databases to receive new articles while we were processing the work.
- For the initial set of baseline variables, we established that if a variable—particularly those related to food consumption— appeared in three or more distinct papers and demonstrated potential utility, it would be incorporated into our meta-analysis.



- If an existing meta-analysis is identified during the search, we would utilize its list of included papers to retrieve any relevant studies that may have been missed in our initial search
- Given that many variables may appear in either quantitative or qualitative form (for example, BMI, which can be reported as a mean with standard deviation or as weight categories), we organized the data into two main tables: one for quantitative data and another for dichotomous data."

The final strategy was made in Pubmed and Embase:

**Table 3.** Final search with improved strategy

#	Term	Records
1	("colorectal cancer"[Title/Abstract] OR "colorectal cancers"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "colorectal neoplasms"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "colorectal carcinomas"[Title/Abstract])	154.257
2	("risk factor"[Title/Abstract] OR "risk*"[Title/Abstract] OR "factor*"[Title/Abstract] OR "relat*"[Title/Abstract])	10.806.399
3	<b>risks (separated)</b> ("Age Factors" OR "Age Distribution" OR "Ag*") ("Gender" OR "Gender Distribution") ("Ethnicity" OR "Ethnic distribution") ("Genetic" OR "Genetics" OR "Heredity" OR "Anticipation Genetic" OR "Genetic Load") ("Inflammatory Bowel Diseases" OR "Crohn Disease" OR "Colitis, Ulcerative") ("Metabolic" OR "Metabolic Syndrome" OR "Metabolism", "Nutrition*" OR "Nutritional Status" OR "Food" OR "Dietary Fiber" OR "Processed meat" OR "Red Meat" OR "Dietary Fats" OR "Fat*" OR "Diet*") ("Socioeconomic Factors" OR "Social Class" OR "Socioeconomic Survey" OR "Low Socioeconomic Status" OR "Urban Population" OR "Rural Population") ("Educational Status" OR "Literacy" OR "Formative") ("Lifestyle" OR "Healthy Lifestyle" OR "Behaviour*" OR "Sedentary Behaviour")	8.113.157
	<b>as a single route (Search performed with this)</b> (("Age Factors" OR "Age Distribution") OR ("Gender" OR "Gender Distribution") OR ("Ethnicity" OR "Ethnic distribution") OR ("Genetic" OR "Genetics" OR "Heredity" OR "Anticipation Genetic" OR "Genetic Load") OR ("Inflammatory Bowel Diseases" OR "Crohn Disease" OR "Colitis, Ulcerative") OR ("Metabolic" OR "Metabolic Syndrome" OR "Metabolism", "Nutrition*" OR "Nutritional Status" OR "Food" OR "Dietary Fiber" OR "Processed meat" OR "Red Meat" OR "Dietary Fats" OR "Diet*") OR ("Socioeconomic Factors" OR "Social Class" OR "Socioeconomic Survey" OR "Low Socioeconomic Status" OR "Urban Population" OR "Rural Population") OR ("Educational Status" OR "Literacy" OR "Formative") OR ("Lifestyle" OR "Healthy Lifestyle" OR "Behaviour" OR "Sedentary Behaviour"))	
4	("primary prevention"[Title/Abstract] OR "secondary prevention"[Title/Abstract] OR "prevention"[Title/Abstract] OR "preventi*"[Title/Abstract])	1.074.036
5	"controlled before-after studies"; "cost-benefit analysis"; "economic analysis".	exclude

6	1 AND 2 AND 3 AND 4	3.806
	("colorectal cancer"[Title/Abstract] OR "colorectal cancers"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "colorectal neoplasms"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "colorectal carcinomas"[Title/Abstract]) AND ("risk factor"[Title/Abstract] OR "risk*"[Title/Abstract] OR "factor*"[Title/Abstract] OR "relat*"[Title/Abstract]) AND (("Age Factors" OR "Age Distribution") OR ("Gender" OR "Gender Distribution") OR ("Ethnicity" OR "Ethnic distribution") OR ("Genetic" OR "Genetics" OR "Heredity" OR "Anticipation Genetic" OR "Genetic Load") OR ("Inflammatory Bowel Diseases" OR "Crohn Disease" OR "Colitis, Ulcerative") OR ("Metabolic" OR "Metabolic Syndrome" OR "Metabolism", "Nutrition*" OR "Nutritional Status" OR "Food" OR "Dietary Fiber" OR "Processed meat" OR "Red Meat" OR "Dietary Fats" OR "Diet*") OR ("Socioeconomic Factors" OR "Social Class" OR "Socioeconomic Survey" OR "Low Socioeconomic Status" OR "Urban Population" OR "Rural Population") OR ("Educational Status" OR "Literacy" OR "Formative") OR ("Lifestyle" OR "Healthy Lifestyle" OR "Behaviour" OR "Sedentary Behaviour")) AND ("primary prevention"[Title/Abstract] OR "secondary prevention"[Title/Abstract] OR "preventi*"[Title/Abstract])	
7	Age >19y	1.413
8	Humans NOT Animals	1.413
9	2022-2024	685
10	9 AND ("Epidemiologic Studies"[Mesh] OR "Epidemiologic Studies" OR "Epidemiologic Study" OR "Cohort Studies"[Mesh] OR "Cohort Studies" OR "Cohort Study" OR "Historical Cohort Studies" OR "Historical Cohort Study" OR "Cohort Analyses" OR "Cohort Analysis" OR "Closed Cohort Studies" OR "Closed Cohort Study" OR "Incidence Studies" OR "Incidence Study" OR "Longitudinal Studies"[Mesh] OR "Longitudinal Studies" OR "Longitudinal Study" OR "Longitudinal Survey" OR "Longitudinal Surveys" OR "Follow-Up Studies"[Mesh] OR "Follow-Up Studies" OR "Follow-Up Study" OR "Followup Studies" OR "Followup Study" OR "Prospective Studies"[Mesh] OR "Prospective Studies" OR "Prospective Study" OR "Case-Control Studies"[Mesh] OR "Case-Control Studies" OR "Case-Control Study" OR "Case-Comparison Studies" OR "Case-Comparison Study" OR "Case-Compeer Studies" OR "Case-Compeer Study" OR "Matched Case-Control Studies" OR "Matched Case-Control Study" OR "Nested Case-Control Studies" OR "Nested Case-Control Study")	

### Key Findings from Scientific Literature

A total of 3,758 files were initially collected and uploaded to the bibliographic manager, Zotero, for review by our team of four. After an initial screening to remove duplicates, posters, conference abstracts, review articles, case reports, economic studies, IARCs, and genetic predictive models, 2,083 files remained. Following a title review, this number was further narrowed to 328 files for full-text analysis. Some studies, such as Guo et al. (15), were excluded due to language constraints, as they were not available in English (e.g., Chinese).



During the results writing process, database alerts notified us of newly published related papers, allowing us to include additional studies in the analysis after the final search, such as Gong (2024) (16) and Malyutina (2024) (17).

### 3.3 Development of the Risk Stratification Matrix

The data for each variable were collected in two main tables. The first was the quantitative table, with six columns for each paper and variable: number of participants, mean, and standard deviation, for both cases and controls. The second table was the dichotomous table, also with six columns for each paper: cases with exposure, cases without exposure, non-cases with exposure, non-cases without exposure, and the total number of exposed and non-exposed. The studies were ordered by year from 2024 to 2014, and within each year alphabetically.

The detailed procedure for each ordinal variable is explained on each corresponding moment. Only articles that provided raw data and published the corresponding tables were included; therefore, some otherwise relevant articles had to be excluded due to the lack of this information (For example, publishing the mean without the standard deviation such Erben 2019 (18) in alcohol, or not publishing the total population for each category like Jones 2017(19) that shows 174 cases of cancer in the low vegetable consumption group without mentioning the total number of people in this group, or publishing the OR without the raw data such Tayyem 2023 (20)). When a study (for example the physical activity in Warren 2019 (21)) indicated the data of a variable in the total cohort and in the CRC cases, it was not possible to calculate the data in the controls, and that variable was therefore discarded. Some prospective studies (for example Yang 2016 (22), Kyro 2013 (23) or Roswall 2010 (24)) reported cases and total person-years in the cohort, being impossible with these data to calculate non-cancer participants.

During data entry we also noticed that some studies used controls who also had cancer other than CRC, such Lam (25) or Lewandowska (26). In these cases, we decided to exclude them to avoid confounding factors. Jin 2022 (27) was a nationwide population that in many variables absorbed even 83.5% of the weight. We discarded it because it displaced many of the findings.

Some studies had to be discarded because the outcome was not exactly CRC, but polyps or adenomatosis that could alter our results despite adequate study planning. This is the case of the studies such Gibbs 2023 (28), Anthony 2022 (29), Song 2021 (30), Budhathoki 2020 (31), Ho 2014 (32), Lee 2018 (33), Passarelli 2021 (34), Stein 2010 (35), or Santiago 2021 (36). In the study from Barry 2020 (37), the outcome was not CRC, but one or more advanced adenomas or three or more adenomas of any type at the third year of colonoscopy. This study was discarded. Palacios 2010 (38) was also discarded because under the outcome “colorectal neoplasia” mixed colorectal adenocarcinomas with colorectal adenomas and tubulovillous adenomas

Some studies focused on risk factors for CRC mortality, not CRC incidence, and could not be used, such as Zell 2010 (39)

During the search we found many meta-analyses like those by Alegria 2022 (12), Jiang 2022 (8), Hidayat 2018 (5) or He 2016 (4). In their list of papers we found some that could be used. That is the explanation for there being some older papers from 2014 in our search.

On several occasions the data to be analyzed were not in the main article, but were in the supplementary material, as in the case of Gong 2024 (16), Knuppel 2020 (40), Kunzmann 2016 (41) or Mejbourn 2020 (42)

Some of the data had 0 participants, which made it impossible to accurately calculate the OR. In such cases, we added 0.5 to all four cells of the OR following Weber's method (43). This adjustment affected the studies by Giacomazzi 2023 in alcohol (44), Mahfouz 2014 in exercise (45), Taha 2022 in underweight (46), Puzzono 2022 in sweets and desserts (47) or Wismayer 2022 in family history (48).

Some variables were collected by some studies as a whole, and sometimes separated into groups. An obvious example was the treatment of meat, as some studies group red meat and processed meat as a whole, others collected them separately. The same happened with fruits and vegetables, as some studies collected the data together and sometimes separately. Sometimes even vegetables are separated according to their cooking method. Fish and cheese can also be found in subcategories. Finally, it was decided to collect the following tables: studies in which fruits, vegetables, red meat, and processed meat were collected separately; collect fish as a whole, collect cheese as a whole, and finally make two tables in which we collect the studies that use fruits and vegetables together, and the studies that use red and processed meat together. Andersen (49) included meat in their study but did not specify whether it was red or processed so that data was discarded.

When the variable is dichotomous it is easy to collect: consumption vs. non-consumption. As a general rule, if the information appeared in tertile, quartile or quantile format, which was typical of food consumption or exercise, the smallest segment was classified as non-consumption or sedentary, and compared to the rest of the groups added together, compare the lowest segment vs. the sum of the others.

Quantitative variables appear in the studies using two scenarios. Either they used the mean and standard deviation; or they used the median and interquartile range. In this second scenario we used tools to estimate the mean and standard deviation and thus unify all the works. These methods are described by Luo (50) and Wan (51).

For all food groups, in the quantitative analysis all amounts reported by the studies were transformed into grams per day. The original amount could be in servings per day or per week, grams per week or monthly consumption. If reflected in servings, the food consumption questionnaire used by the original study was analyzed to transform these servings into grams. Reflected quantities were used using mean and standard deviation. In case these variables did not appear, the median and quartiles 1 and 3 were used for their estimated calculation, using for the estimated mean the formula of by Luo (50) and for the calculation of the estimated standard deviation the formula of Wan (51).

Some studies could not be used in their entirety because they used quantities that were difficult to compare with other studies. This is the case of Jeon (52), whose dietary variables (such as red meat, processed meat, calcium, etc.) were standardized using sex- and study-specific quartiles, and using them as quantitative variables. Baroudi's team (53) recorded daily caloric intake in kilojoules, with 748 Kj (or 178 Kcal) in healthy subjects and 1452 Kj (or 347 Kcal) in cases with CRC. These data must be wrong and we could not find a logical way to correct them, so they have been discarded. Another example is Kunzmann (54) which uses Food Patterns Equivalents Database standardizing them for 1000 Kcal, which makes it impossible to compare it with the other studies as continuous variables. However, it has been used for the dichotomous variables of fruits and vegetables. Le Marchand 2020 (55) uses a

quantitative food frequency questionnaire from the year 2000, so when it indicates servings per day of red meat it actually indicates 135g per day. However, the grams per day of dietary fiber cannot be calculated because it does not indicate the calculation method. Rennert 2020 (56) indicates “servings per day” using the Molecular Epidemiology of Colorectal Cancer scale, so it can be calculated that a serving of fruit is 140g and of vegetables 150g. Alegria 2020a (57) indicates the data in ml but we can convert it to grams per day with the conversion of 100 ml = 3.78g.

Some studies appeared to be quite similar, leading us to believe they may have been conducted on the same population. However, we treated them as separate studies because the final data differed, such as the case of Deoula (58) and El Kinany (59). The two studies by Bahrami 2020 (60) and Bahrami 2022 (61) have the same data on numerous variables, such as BMI, family history and education. However, Bahrami 2022 includes the new variable “daily calorie intake”, so we added this new variable.

Some studies have the quantitative data separated into different groups or cohorts. For example, Genua (62) separates between an Irish cohort and a Czech cohort. Schulpen (63) separates between men and women. Win (64) separates between a group with mutation and a group without mutation. Gibbs (65) has three cohorts from three different databases, etc. These data cannot be summed up together, so each group or cohort has been analyzed separately.

After filling in the tables, a total of 165 studies could be used for at least one of the variables. The summary of this data is in table 4. With this data, the meta-analysis was ready to be performed.

**Table 4.** Papers that were been used in meta-analysis and variables in which they contributed

<b>Paper</b>	<b>Ref.</b>	<b>Dichotomous variables</b>	<b>Continuous variables</b>
<b>Abd Rashid 2023</b>	(66)	4, 7, 23, 25, 29, 30, 31, 33, 37, 38	1, 2
<b>Aglago 2020</b>	(67)	4, 26, 27, 29, 30, 31, 36, 37, 38	1, 2, 3, 7, 11, 12, 14
<b>Aglago 2023</b>	(68)	9, 22, 29, 30, 37, 38	2, 5, 6, 7, 8, 9, 10, 12, 14
<b>Alegria 2019</b>	(69)	23, 26, 29	-
<b>Alegria 2020a</b>	(57)	12, 16, 18, 18, 21, 23, 25, 26, 29, 30, 34, 37, 38	2, 3, 4, 5, 6, 7, 8, 9, 10, 11
<b>Alegria 2020b</b>	(70)	17, 22	-
<b>Aleksandrova 2016</b>	(71)	26, 29, 38	-
<b>Aleksandrova 2017</b>	(72)	26, 29, 38	5, 6, 7, 10, 11, 12, 14, 15, 16
<b>Andersen 2017</b>	(49)	7, 29, 37, 38	2, 10, 14, 15
<b>Angelo 2016</b>	(73)	4, 5, 29, 30, 31	5, 8, 9, 10, 11, 13
<b>Archambault 2020</b>	(74)	3, 4, 7	-
<b>Bahrami 2020</b>	(60)	7, 29, 36, 37	3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15
<b>Bahrami 2022</b>	(61)	29	2
<b>Bakken 2018</b>	(75)	12, 26, 37, 38	-
<b>Baroudi 2013</b>	(53)	12, 13, 14, 17, 18, 18, 26, 27, 29, 36	12, 13,
<b>Barrubes 2018</b>	(76)	12, 13	-
<b>Beaugerie 2013</b>	(77)	8	-
<b>Biancone 2016</b>	(78)	4, 29	-
<b>Boyle 2011</b>	(79)	9, 23, 24, 26, 27, 28, 35	-
<b>Brenne 2024</b>	(80)	4, 9, 12, 15, 17, 18, 18, 27, 28	1, 14, 15

<b>Budhathoki 2011</b>	(81)	4, 7, 27, 29, 30	1, 2, 12, 14, 15
<b>Burton 2010</b>	(82)	29	-
<b>Butler 2017</b>	(83)	9, 22, 23, 24, 25, 26, 27, 29, 37	-
<b>Byrne 2021</b>	(84)	3, 4, 38	-
<b>Campbell 2010</b>	(85)	2, 3, 5, 9, 14, 22, 23, 24, 25, 26, 29, 30, 31, 37, 38	-
<b>Carr 2018</b>	(86)	7, 22, 29, 30, 37, 38	-
<b>Carr 2020</b>	(87)	7, 22, 29, 30, 37, 38	-
<b>Carrat 2017</b>	(88)	29	14
<b>Castello 2019</b>	(89)	7, 26, 29, 30, 31, 37, 38	2, 14, 16
<b>Catalano 2020</b>	(90)	4	-
<b>Cavalcante 2017</b>	(91)	4	1
<b>Cea 2017</b>	(92)	22	-
<b>Chang 2021</b>	(93)	2, 7, 9, 14, 15, 17, 18, 19, 21, 22, 23, 24, 26, 27, 28, 29, 30, 32, 34, 35, 38	-
<b>Chen 2015</b>	(94)	7, 8, 9, 22, 23, 24, 25, 26, 27, 29, 33, 37, 38	2
<b>Chen 2022</b>	(95)	7, 9, 16, 22, 23, 24, 29, 30, 31, 37, 38	-
<b>Cheng 2015</b>	(96)	7	1, 14, 16
<b>Cheng 2022</b>	(97)	4, 7	-
<b>Cho 2016</b>	(98)	7, 23, 26, 27, 28, 29, 30, 31, 33, 37, 38	2
<b>Cho 2020</b>	(99)	3, 4, 5, 6	-
<b>Cho 2021</b>	(100)	4	-
<b>Choi 2021</b>	(101)	3, 4, 32	-
<b>Collatuzzo 2022</b>	(102)	29	3, 4, 7, 12, 14
<b>Cottet 2013</b>	(103)	7	2, 15, 16
<b>Da Silva 2018</b>	(104)	23, 24, 25	-
<b>Deding 2020</b>	(105)	4, 22, 23, 25, 27, 28, 29, 30, 31	-
<b>Deoula 2020</b>	(58)	7, 22, 32, 33, 36, 37, 38	-
<b>Dore 2016</b>	(106)	7, 29	-
<b>Doubeni 2012a</b>	(107)	23, 24, 25, 26, 29, 30, 31	-
<b>Doubeni 2012b</b>	(108)	37, 38	-
<b>El Kinany 2020</b>	(59)	7, 23, 24, 25, 26, 27, 29, 30, 31, 32, 33, 36, 37, 38	2, 3, 4, 7, 12
<b>Erben 2019</b>	(18)	4, 7, 22, 29, 37, 38	1, 15
<b>Erben 2021</b>	(109)	7	1, 15
<b>Feng 2021</b>	(110)	4, 5, 6, 7, 15, 17, 18, 18, 21, 22, 26, 27, 28, 29, 30, 31, 38	-
<b>Ferreira 2021</b>	(111)	9, 14, 15, 17, 18, 23, 24, 25, 27, 28, 29, 30, 31	-
<b>Florensa 2023</b>	(112)	22	-
<b>Franchi 2022</b>	(113)	3, 4, 7, 18, 23, 24, 37, 38	-
<b>Friis 2015</b>	(114)	9, 22	-
<b>Galas 2013</b>	(115)	4, 29, 30, 31, 37, 38	1, 2, 8, 9, 11, 12, 14, 15, 16
<b>Gao 2020</b>	(116)	4, 27, 29	1
<b>Garcia 2017</b>	(117)	8, 9, 11, 22, 23, 24, 25, 27, 28, 29, 30, 31	-
<b>Gavrilas 2018</b>	(118)	4, 12, 13, 14, 16, 18, 23, 24, 32, 37, 38	-
<b>Genua 2021</b>	(62)	4, 27	1
<b>Gharbi 2020</b>	(119)	4, 7, 14, 16, 32, 33, 37	14

<b>Giacomazzi 2023</b>	(44)	7, 23, 24, 26, 27, 28, 29	-
<b>Gibbs 2020</b>	(65)	29, 30, 31, 37, 38	2, 7, 8, 9, 10, 14, 16
<b>Gong 2017</b>	(120)	3, 4, 7, 12, 14, 17, 18, 18, 21, 23, 24, 25	1, 14
<b>Gong 2024</b>	(16)	24	-
<b>Guertin 2017</b>	(121)	7, 22, 26, 33, 38	2, 14, 16
<b>Halfter 2021</b>	(122)	4	-
<b>Hassanpour 2023</b>	(123)	4, 26, 27, 28, 29, 30	13, 14
<b>Hastert 2016</b>	(124)	4, 5, 6, 7, 22, 29, 30, 31, 38	-
<b>Hatime 2021</b>	(125)	7, 12, 16, 19, 21, 26, 29, 30, 31, 32, 33, 36, 37, 38	-
<b>Hernandez 2021</b>	(126)	4, 7, 11, 22, 29, 30, 31, 38	2, 3, 8, 9, 10, 11, 12, 14, 16
<b>Hodge 2015</b>	(127)	4, 7, 27, 29, 30, 31, 37, 38	1
<b>Hoffmeister 2014</b>	(128)	7, 23, 24, 29, 30, 31, 37, 38	-
<b>Hori 2023</b>	(129)	17, 18, 29, 30	-
<b>Hsu 2022</b>	(130)	3, 4, 9, 10, 11, 23, 24, 26, 27, 28, 29, 30, 36, 37, 38	-
<b>Hughes 2015</b>	(131)	26, 29, 30, 31, 37, 38	-
<b>Innes 2014</b>	(132)	4, 11, 23, 24, 26, 29, 30, 31, 33, 34, 38	1, 14
<b>Jeon 2018</b>	(52)	4, 7, 22, 26, 27, 28, 29, 30, 37, 38	1, 2, 14
<b>Jimba 2021</b>	(133)	4, 10	-
<b>Jin 2023</b>	(134)	10	-
<b>Jones 2018</b>	(135)	7, 29, 30, 31, 38	-
<b>Jung 2019</b>	(136)	11, 33, 38	-
<b>Kantor 2014</b>	(137)	4, 18, 21, 22, 23, 24, 29, 30, 31	-
<b>Kantor 2016</b>	(138)	23, 24, 25	-
<b>Kasai 2016</b>	(139)	4, 27, 29	1, 14
<b>Katsidzira 2019</b>	(140)	32, 37, 38	-
<b>Khankari 2020</b>	(141)	22, 23, 24, 25, 29, 30	-
<b>Khatatbeh 2018</b>	(142)	3, 4, 7, 8, 9, 11, 29, 23, 24, 25, 26	-
<b>Kim 2013</b>	(143)	27, 28, 29, 30, 31, 37, 38	2, 14
<b>Kim 2017</b>	(144)	14	-
<b>Kim 2020</b>	(145)	7, 23, 25, 26, 27, 29, 30, 31, 37, 38	2, 14, 15, 16
<b>Kim 2024</b>	(146)	7, 23, 25, 26, 27, 28, 29, 30, 31, 33, 37, 38	2, 14
<b>Knudsen 2016</b>	(147)	4, 16, 19, 18, 23, 26, 29, 34, 37, 38	-
<b>Knuppel 2020</b>	(40)	14, 15, 16	-
<b>Kunzmann 2015</b>	(54)	17, 18, 21	-
<b>Kunzmann 2016</b>	(41)	17, 18, 19	-
<b>Kvaerner 2023</b>	(148)	4, 7, 29, 33, 34, 37, 38	1, 5, 6, 7, 10, 12, 14, 16
<b>Lawler 2023</b>	(149)	4, 5, 7, 9, 24, 29, 30, 37, 38	15
<b>Le Marchand 2020</b>	(55)	7, 29, 30	2, 5, 12, 14, 16
<b>Lee 2020</b>	(150)	3, 4, 10	-
<b>Levi 2017</b>	(151)	4, 23, 24, 25	-
<b>Lin 2015</b>	(152)	22	-
<b>Linseisen 2021</b>	(153)	26, 29, 30, 31, 37, 38	14
<b>Liu 2022</b>	(154)	10	-
<b>Liu 2023</b>	(155)	4, 7, 10, 16, 17, 18, 22, 26, 27, 28, 29, 30, 31, 38	-

<b>Ma 2023</b>	(156)	7, 27, 28, 29, 30, 32, 33, 34, 35, 37, 38	2, 14, 15
<b>Malyutina 2024</b>	(17)	9, 11, 27, 28, 29, 30, 31, 33, 37, 38	14
<b>Mahfouz 2014</b>	(45)	14, 15, 19, 18, 23, 24, 25, 26, 27, 28, 29, 32, 33, 34, 35, 36, 37, 38	5, 6, 7
<b>Marques 2017</b>	(157)	3, 4, 27, 28, 29, 30, 31	-
<b>McCullough 2021</b>	(158)	22, 26, 27, 29, 30, 31, 37, 38	2, 5, 6, 12, 14
<b>Mejborn 2020</b>	(42)	14, 15	-
<b>Moon 2022</b>	(159)	10	-
<b>Murphy 2018</b>	(160)	9, 26, 37	2, 5, 6, 7, 8, 9, 10, 12, 14, 16
<b>Nakagawa 2017</b>	(161)	7, 9, 14, 23, 25, 26, 27, 28, 29, 30	-
<b>Okada 2020</b>	(162)	4, 7, 9, 11, 16, 17, 21, 22, 23, 24, 25, 26, 27	-
<b>Oxentenko 2010</b>	(163)	23, 24, 25	-
<b>Oyeyemi 2018</b>	(164)	26	-
<b>Pan 2017</b>	(165)	-	1, 14
<b>Papadimitriou 2022</b>	(166)	3, 4, 7, 9, 23, 24, 25, 26, 29, 30, 31, 37, 38	-
<b>Papantoniou 2017</b>	(167)	7, 22, 23, 24, 26, 29, 30, 37, 38	2, 5, 16
<b>Parent 2010</b>	(168)	26	-
<b>Peng 2015</b>	(169)	8	-
<b>Puzzono 2022</b>	(47)	7, 18, 26, 27, 29, 30, 31	14
<b>Ren 2023</b>	(170)	4, 7, 22, 27, 29, 30	-
<b>Reghan 2012</b>	(171)	23, 24, 25	-
<b>Rennert 2020</b>	(56)	7, 17, 18, 22, 23, 24, 26	-
<b>Romaguera 2017</b>	(172)	16, 26	-
<b>Ruiz-Saavedra 2022</b>	(173)	7, 29	1, 2, 12, 14, 16
<b>Schulpen 2020</b>	(63)	7, 38	1, 2, 14, 16
<b>Schumacher 2021</b>	(174)	5, 6, 7, 9, 11, 23, 24, 25, 29, 30, 31	-
<b>Sehdev 2015</b>	(175)	8, 22, 24	-
<b>Shafiee 2023</b>	(176)	4, 29, 30	-
<b>Shiao 2018</b>	(177)	4, 5, 6, 24, 27, 29	1, 2
<b>Shin 2015</b>	(178)	7, 23, 26, 27, 28, 29, 30, 31, 33, 37, 38	-
<b>Shin 2017</b>	(179)	9, 11, 23	-
<b>Simonian 2018</b>	(180)	4, 22, 26, 29	14
<b>Speciani 2023</b>	(181)	37, 38	-
<b>Taha 2022</b>	(46)	3, 4, 7, 8, 9, 23, 24, 25, 26, 29, 30	-
<b>Theodoratou 2014</b>	(182)	7, 22	2, 9, 11, 12, 13, 16
<b>Tran 2023</b>	(183)	7, 26, 27, 28, 29, 30, 31, 33, 37, 38	14
<b>Turati 2017</b>	(184)	3, 4, 7, 16, 26, 37, 38	-
<b>Ulaganathan 2018</b>	(185)	10, 11, 24, 27, 28, 29, 30, 36, 37, 38	2, 14, 15
<b>Vulcan 2015</b>	(186)	22, 26, 37	1, 5, 8, 9, 12, 13, 14, 16
<b>Vulcan 2017</b>	(187)	3, 4, 23, 26, 27, 29, 30, 31, 37	1, 14
<b>Vulcan 2019</b>	(188)	4, 22, 26, 27, 29, 30, 31, 37	1, 3, 6, 8, 12, 14
<b>Wang 2022a</b>	(189)	7, 26, 27, 28	-



<b>Wang 2022b</b>	(190) 7, 22, 29, 30, 31	2, 5, 6, 7, 11, 14, 15, 16
<b>Ward 2010</b>	(191) -	2, 12, 16
<b>Warren 2019</b>	(21) 3, 4, 5, 7, 24, 29, 30, 31, 37, 38	-
<b>Warren 2022</b>	(192) 4, 5, 23, 24, 25, 26, 29, 30, 31, 37, 38	-
<b>Weigl 2019</b>	(193) 7	-
<b>Wells 2014</b>	(194) 4, 5, 6, 7, 9, 22	1, 5, 14, 16
<b>Wieszczy 2020</b>	(195) 4, 7	-
<b>Win 2011</b>	(64) 4, 23, 24, 25, 27, 28, 29, 30	1, 14
<b>Wismayer 2022</b>	(48) 1, 3, 4, 7, 23, 24, 27, 28, 29, 30, 31, 32	1
<b>Xu 2015</b>	(196) 7, 23, 25, 26, 27, 28, 29, 32, 33, 37, 38	1, 14
<b>Yarmand 2024</b>	(197) 4, 7, 22, 29, 30, 31, 37, 38	1, 2, 12, 14, 15
<b>Yee 2024</b>	(198) 7, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34, 36, 37, 38	-
<b>Yu 2022</b>	(199) 4, 7, 9, 26, 29, 30, 37	1, 2, 7, 12, 14
<b>Zamora-Ros 2013</b>	(200) 7, 22, 23, 24, 25, 26, 29, 30, 31	2, 5, 6, 8, 9, 12, 14, 16
<b>Zargar 2021</b>	(201) 12, 14, 17, 18, 27, 32, 33	-
<b>Zhang 2020</b>	(202) 7, 27, 28, 29, 32, 33, 34, 35, 37, 38	2, 3, 5, 8, 9, 11, 12, 14
<b>Zhou 2020</b>	(203) 4, 7, 27, 29	1, 14

Coding for the dichotomous variables: 1 = Age (dichotomous on 25-year-old); 2 = Age (dichotomous on 30-year-old); 3 = Age (dichotomous on 50-year-old); 4 = Sex; 5 = Ethnicity (African American); 6 = Ethnicity (Asian); 7 = Family history; 8 = Inflammatory bowel disease; 9 = Diabetes; 10 = Metabolic syndrome; 11 = Hypertension; 12 = Milk and dairy products; 13 = Cheese; 14 = Red meat; 15 = Processed meat; 16 = Processed and red meat together; 17 = Vegetables; 18 = Fruits; 19 = Fruits and vegetables together; 20 = Fish; 21 = Grains and fiber; 22 = NSAIDs; 23 = BMI (dichotomous on 25 kg/m<sup>2</sup>); 24 = BMI (dichotomous on 30 kg/m<sup>2</sup>); 25 = BMI: underweight vs normoweight; 26 = Exercise; 27 = Alcohol consumption; 28 = Alcohol (restrictive version); 29 = Smoking; 30 = Smoking (restrictive version); 31 = Former Smoking; 32 = Urban housing; 33 = Currently married; 34 = Unemployment; 35 = Sedentary work; 36 = Illiterate; 37 = Primary education; 38 = Secondary education.

Coding for the continuous variables: 1 = Age (years); 2 = Daily calorie intake (Kcal/day); 3 = Milk and dairy products (g/day); 4 = Cheese (g/day); 5 = Red meat (g/day); 6 = Processed meat (g/day); 7 = Processed and red meat together (g/day); 8 = Vegetables (g/day); 9 = Fruits (g/day); 10 = Fruits and vegetables together (g/day); 11 = Fish (g/day); 12 = Fiber (g/day); 13 = Whole grains (g/day); 14 = BMI (kg/m<sup>2</sup>); 15 = Exercise (MET-h/week); 16 = Alcohol (g/day);

### 3.4 Meta-Analysis

The meta-analysis was performed using the software SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). For the dichotomous variables we used the log odds ratio with random effects, using the Mantel-Haenszel method to estimate the OR. For continuous outcomes, both mean difference (MD) and standardized mean differences (SMD) were calculated using Cohen's D method with random effects. Confidence intervals for the random effects estimates were calculated using the Hartung and Knapp method (204). Heterogeneity in the correlation throughout papers was valued by Cochran's Q test (205) and quantified by I<sup>2</sup>. For the Q statistic, a p-value of less than 0.1 was considered statistically significant. The I<sup>2</sup> statistic had the following cut-off points: less than 25% (low heterogeneity), 25–50% (moderate heterogeneity), and

greater than 75% (high heterogeneity). Egger's regression test (206) was conducted to assess the possibility of publication bias, illustrating this visually using a funnel plot when the variable included 10 or more studies. The outliers were checked again, and if the text explained the result, we included it in the description. To compare the OR of the dichotomous variables with the Cohen's D of the quantitative variables, all Cohen's D are transformed to OR using the logit method thanks to the effect size calculator by Campbell Collaboration (207). All p-values were calculated as two-tailed, with a significance threshold  $\alpha$  set at less than 0.05.

### Initial results and scoring methodology

The summary of the variables and their OR are found in the tables 4 for quantitative variables and 5 for dichotomous variables.

**Table 5. Summary of Quantitative variables**

#	RISK FACTOR	NO. OF STUDIES	COHEN'S D	STANDARD ERROR	P VALUE <0.05	OR (95%CI)
1	Age (years)	36	0.35	0.06	Yes	1.89
2	Daily calory intake (Kcal/day)	42	0.07	0.03	Yes	1.14
3	Milk and dairy products (g/day)	8	-0.11	0.07	No	0.82
4	Cheese (g/day)	4	-0.02	0.05	No	0.96
5	Red meat (g/day)	17	0.48	0.32	No	2.39
6	Processed meat (g/day)	11	0.27	0.22	No	1.63
7	Processed and red meat together (g/day)	16	0.16	0.12	No	1.34
8	Vegetables (g/day)	14	-0.19	0.08	Yes	0.71
9	Fruits (g/day)	14	-0.29	0.15	Yes	0.59
10	Fruits and vegetables together (g/day)	12	-0.20	0.15	No	0.70
11	Fish (g/day)	11	-0.04	0.06	No	0.93
12	Fiber (g/day)	23	-0.09	0.04	Yes	0.85
13	Whole grains (g/day)	3	-1.43	1.39	No	0.07
14	BMI (kg/m2)	58	0.06	0.02	Yes	1.10
15	Exercise (MET-h/week)	16	-0.09	0.03	Yes	0.85
16	Alcohol (g/day)	19	0.08	0.02	Yes	1.16

**Table 6. Summary of Quantitative variables**

#	RISK FACTOR	NO. OF STUDIES	OR	P VALUE <0.05
1	Age (dichotomous on 25-year-old)	2	0.94	No
2	Age (dichotomous on 30-year-old)	2	0.38	No
3	Age (dichotomous on 50-year-old)	17	0.42	Yes
4	Sex	65	1.33	Yes
5	Ethnicity: African American	11	1.15	No
6	Ethnicity: Asian	6	0.98	No
7	Family history	72	1.80	Yes
8	IBD without specifying	6	2.25	Yes
9	Diabetes	26	1.31	Yes
10	Metabolic syndrome	8	1.90	Yes



<b>11</b>	Hypertension	10	1.55	Yes
<b>12</b>	Milk and dairy products	9	0.80	No
<b>13</b>	Cheese	3	1.70	No
<b>14</b>	Red meat	14	1.88	Yes
<b>15</b>	Processed meat	7	1.94	Yes
<b>16</b>	Processed and red meat together	11	1.41	Yes
<b>17</b>	Vegetables	14	0.73	No
<b>18</b>	Fruits	13	0.78	No
<b>19</b>	Fruits and vegetables together	5	0.43	No
<b>20</b>	Fish	11	0.99	No
<b>21</b>	Fiber	8	0.80	Yes
<b>22</b>	NSAIDs	42	0.83	Yes
<b>23</b>	BMI (dichotomous on 25 kg/m <sup>2</sup> )	52	0.87	Yes
<b>24</b>	BMI (dichotomous on 30 kg/m <sup>2</sup> )	43	0.82	Yes
<b>25</b>	BMI: underweight vs normoweight	33	1.08	No
<b>26</b>	Exercise	60	0.81	Yes
<b>27</b>	Alcohol consumption	49	1.06	No
<b>28</b>	Alcohol (restrictive version)	29	1.08	No
<b>29</b>	Smoking	101	1.22	Yes
<b>30</b>	Smoking (restrictive version)	72	1.19	Yes
<b>31</b>	Former Smoking	49	1.19	Yes
<b>32</b>	Urban housing	14	0.78	Yes
<b>33</b>	Currently married	20	0.97	No
<b>34</b>	Unemployment	9	0.85	No
<b>35</b>	Sedentary work	5	0.82	No
<b>36</b>	Illiterate	10	1.47	Yes
<b>37</b>	Primary education	61	1.40	Yes
<b>38</b>	College education	66	1.36	Yes

### Age

First we studied age as a continuous variable. Studies with age matching between cases and controls were discarded. In the case of Hastert 2016 (124): mean and SD were not published. They have been calculated using the midpoint of each interval. In the case of Kvaerner 2023 (148) and Ruiz-Saavedra 2022 (173): mean and SD were not published. but median. P25 and P75. They have been calculated using the method by Luo (50) and Wan (51). In the case of Cavalcante (91), the standard deviation of the age seem to be the standard error by mistake, therefore transformed into 15.2 and 19.8. Many outliers were found, some of them were not explained in the text such Ruiz-Saavedra 2022 (173), but others have and explanation: Abd Rashid 2023(66): estates that cases were significantly older than controls (61.0 years  $\pm$  11.8 vs. 50.8 years  $\pm$  15.4) ( $p < 0.001$ ). Yu 2022 (199) explained that with  $p > 0.05$  participants who developed CRC were older, similar to Innes 2014 (132) that obtained significant, positive association with age ( $p < 0.00001$ ). On the other hand, Cavalcante 2017 (91) found that mean age in CRC was lower than in controls, but not significant ( $p=0.294$ )

Regarding age as a dichotomous variable, several studies reported age in five- or ten-year groups. The sum of these groups allowed the participants to be dichotomized into groups below or above the cut-off age. We created three tables, based on cut-offs of 25, 30, and 50 years. For the 25-year group, we only found the study by Choi 2021 (101), to which we also added the study by Wismayer 2022 (48), despite its cut-off point being 20 years. For the 30-year group, Chang 2021 (93) and Campbell 2010 (85) were the only participants. Dore 2016 (106) has a group under 30 years old, but with 0 cases of

cancer, so it was not considered for the analysis. For the 50-year-old group, there were many useful studies, although we had to include some studies that did not cut exactly at 50 years but at 59 like Wieszchy 2020 (195), 55 like Khatatbeh 2018 (142), 54 like Hsu 2022 (130), 52.4 like Vulcan 2017 (187), 45 like Marques 2017 (157) or 40 like Choi 2021 (101). Some outliers like Hsu 2022 (130) do explain their finding (the group  $\geq 55$  years was at a 5.53-fold risk of CRC compared with age  $\leq 45$ ”, although others do not explain it like Archambault 2020 (74) or Marques 2017 (157).

### **Sex**

Studies with sex matching between cases and controls were discarded. Ruiz-Saavedra 2022 (173) was discarded because all 7 cases of CRC happened in men, which can cause a bias. The two Archambault 2020(74) cohorts (Discovery and Replication) were treated as two different cohorts and cases were not summed.

### **Ethnicity**

Studies with race matching between cases and controls were discarded, such Le Marchand 2020 (55). Ethnicity was reported in very different ways in the different studies, sometimes in a very detailed manner and sometimes more generally, making comparison difficult. Eleven studies studied the black or African-American population, and six studies referred to the Asian race. They were the ones that we include in the study. We had to discard the study by Knudsen (2016) (147) which only separated between Norwegians and non-Norwegians, Rennert (2020) (56) which separated between Arabs and Jews, Abd Rashid 2023(66) which separated between Malay, Chinese and Indian or Chang 2021 (93) which separated between White, Southeast Asian, South Asian and Other.

### **Family history**

Most studies only collected yes/no as a response to Family History. Some include first degree or second degree in the same category, such as Abd Rashid 2023 (66), Giacomazzi 2023 (44), or Weigl 2019(193). Others specify that they are first-degree relatives, such as Puzzono 2022 (47), Ruiz-Saavedra 2022 (173), Carr 2020 (87), Kim 2020 (145), Turati 2017 (184), or Hastert 2016(124).

Some outliers are not explained in the text, such as El Kinany 2020 (59) or Ruiz-Saavedra 2022 (173), where there is 1 case and 9 controls with a family history. Other outliers are explained, such as Hatime 2021(125), which explains that cases were more likely to have a family history of CRC (5.5% vs. 0.8%). Deoula 2020 (58) also comments that cases have more chances to have a family history of CRC compared to controls. Theodoratou 2014 (182) obtains an OR of 20.20 with a p-value of  $1.6 \times 10^{-49}$ . Puzzono 2022(47) indicates that even after excluding hereditary CRCs, they found a p-value of 0.004 for the association of family history with CRC. Wismayer 2022 (48) indicates that in his study the risk of having colon cancer was higher when there was a family history of CRC.

### **Inflammatory bowel disease (IBD)**

The main difficulty with this variable is that in some cases it specifies whether the disease is ulcerative colitis or Crohn’s disease, as in Sehdev 2015 (175) or Beaugerie 2013 (77). However, most studies (Taha 2022 (46), Khatatbeh 2018 (142), Garcia 2017 (208), Chen 2015 (94), Sehdev 2015 (175), Beaugerie 2013 (77)) only indicate IBD, without specifying or specifying that both diseases were considered the same, such Peng 2015 (169). Finally, we decided that there was not enough material to divide the two diseases, and we grouped everything as IBD. Some studies were discarded: Algaba 2013 (209) because it compared to different types of cancer, Dore 2016 because we could not identify the comorbidity of

the controls, Biancone 2016 (78) because it compared Crohn's Disease to Ulcerative Colitis, not to a control group and Carrat 2017 (88) because controls were individually matched to cases by intestinal bowel disease: Crohn's disease on one side. ulcerative colitis or IBD unclassified on the other. Some of the Outliers are Taha 2022 (46), which warns that IBD is underdiagnosed among Palestinians, which might cause type II errors. In the Peng 2015 (169) study, the HR was 0.99.

### **Diabetes, metabolic syndrome and hypertension**

Diabetes has been recorded in various ways in the studies. Most just said "diabetes yes/no" such as Chen 2022 (95), Okada 2020 (162) and many others. Some studies specified type 2 diabetes such as Aglago 2023 (68), Malyutina 2024 (17) or Taha 2022 (46). Only Dore 2016 (106) subdivided diabetes into type 1 and type 2, but as this study was the only one, for our analysis we added both together under the variable "diabetes". Boyle 2011 (79) includes diabetes and high blood sugar together, finally we added the variable as diabetes. The two cohorts of the Papadimitriou 2022 (166) (EPIC and NLCS) and Wells 2014 (194) (Multiethnic and Women CRC Outcome) studies were studied separately. Lee 2018 (33) seems to have a mistake in table 3, since a total of 819 participants have diabetes and 3514 of them are adenoma-negative; so we discarded this data. As an outlier, Murphy 2018 (160) highlights, which found that there was more diabetes in controls than in CRC cases.

Only 8 studies reported metabolic syndrome, most of them were specific studies on this topic. Moon 2022 (159) and Ulaganathan 2018 (185) are outliers, although it is not explained in the text.

Hypertension has Innes 2014 (132) as the only outlier, We can attribute this to the fact that table 1 included "On anti-hypertensive medication", a condition that we have equated to hypertension.

### **Milk and dairy products (not cheese)**

On the dichotomous aspect, studies picked up the data in different but comparable ways. Some were based on a yes vs. no answer, such Zargar 2021 (201) that indicates consumption of dairy products over the past year or Bakken 2018 (75). Other divided in ordinal steps the consumption, so we compared the lowest or no-consumption segment with the above segments, like in the case of Brenne 2024 (80) where the cut-off point was 1 glass per day, Barrubés 2018 (76) that cut on 117g per day, Hatime 2021 (125) that cut on 112.34 g/day, Gavrilas 2018 (118) that cut in <1 vs 1 or above servings per week of full fat milk, Gong 2017 (120) that cut on 0 times per week vs above, Baroudi 2014 (53) that cut on <3 a week vs over, or Alegria 2020a (57) that cut in three tertiles

On the quantitative aspect, seven studies were included in the quantitative analysis of milk and dairy products, except cheese. The amounts reported in these studies were in grams per day (Vulcan 2019, Alegria 2020a, Aglago 2020, Bahrami 2020, El Kinany 2020, Zhang 2020, Hernandez 2021, Collatuzzo 2022).

### **Cheese**

Cheese in its quantitative aspect has a particularity, since the SMD is negative (-0.021) but its MD is positive (0.016). This calculation is based on only four studies: Collatuzzo(102), Alegria (57), Bahrami (60) and El Kinany 2020 (59), the first two finding cheese as a risk factor and the last two as a protective factor. The final OR is 0.96. On the other hand, in its quantitative aspect there were only three studies: Barrubés (76), Gavrilas (118) and Baroudi(53), their signs being respectively: irrelevant, high risk and protective. The overall OR was 1.7, with a non-significant p value of 0.39. From a biological plausibility point of view, both alternatives are coherent (protective and risky at the same time) and we attribute

this to two reasons: It could be a protective effect because it has vitamin D, calcium and a fat of interest (butyric fatty acid with a modulating effect on the microbiota in general, but in particular short and medium chain saturated fatty acids seem to be of interest to the enterocyte), but it could have a risky effect due to its amount of salt and because it is a food that is easy to overeat.

El Kinany (59) and Bahrami (60) include semi-cured and cured cheeses, and above all more traditional ones (especially El Kikany) from the northern and eastern Mediterranean region (creamier, even used in desserts) and the cheeses used in their analysis by : Collatuzzo (102) and Alegria (57), are generally more cured, more European and with more salt in their composition (for example, a manchego or a blue cheese).

A systematic review on this topic (210) concludes with a lack of association with a lot of heterogeneity that derives from a low consumption, since in the studies there is only one serving per day, but that is surprising because due to its amount of calcium it should be protective.

In the dichotomous aspect, just three studies were found: Barrubés 2018 (76) that compared 11g/day of cheese consumption vs above; Gavrilas 2018 (118) that compared. <1 servings per week of fermented cheese vs above; and Baroudi 2014 (53) that compared <2 servings a week vs above

4 studies were included in the quantitative analysis of cheese. The amounts reported in these studies were in grams per day (Alegria 2020a, Bahrami 2020, El Kinany 2020, Collatuzzo 2022).

### **Red meat and processed meat**

On the dichotomous aspect of red meat, there were several ways of measure: Chang 2021: red meat. servings per week 2 years ago (One serving of red/processed meat defined as 2–3 oz or the size of the palm of hand): <2 vs ≥2 Ferreira 2021: do not consume vs less than once per month and over Zargar 2021: consumption of red meat over the past year. Yes vs no Gharbi 2020: red meat consumption, frequent vs rare/never Knuppel 2020: red meat, <1 grams per day vs above Mejbourn 2020, red meat < 65 g/day vs above Gavrilas 2018: red meat in servings per week. <1 vs 1-2 or above Gong 2017: pork. Rarely vs <250g per week and above Kim 2017: ≥43g day consumption vs <43g day consumption Nakagawa 2017: red meat intake > times per week. Yes vs no Nakagawa 2017: red meat intake > times per week. Yes vs no Mahfouz 2014: red meat. <500 g per week vs above Baroudi 2013. Yes vs no Campbell 2010: red meat, <2 servings per week vs above

In separate, fifteen studies were included in the quantitative analysis of red meat. The amounts reported in these studies were in grams per day (Zamora-Ros 2013, Mahfouz 2014, Vulcan 2015, Murphy 2017, Aleksandrova 2017, Papantoniou 2017, Murphy 2018, Budhathoki 2020, Alegria 2020a, Zhang 2020, Kværner 2023) or converted into grams per day from any consumption in oz/day (Wells 2014) or servings per day (Angelo 2016, Le Marchand 2020, McCullough 2021, Wang 2022b, Aglago 2023). On the other hand, ten studies were included in the quantitative analysis of processed meat. The amounts reported in these studies were in grams per day (Zamora-Ros 2013, Mahfouz 2014, Murphy 2017, Aleksandrova 2017, Murphy 2018, Vulcan 2019, Budhathoki 2020, Alegria 2020a, Kværner 2023) or servings per day (McCullough 2021, Wang 2022b, Aglago 2023).

About the processed meat, on the dichotomous aspect there were several ways of measuring: Brenne 2024. Daily intake vs less Chang 2021: processed meat. servings per week 2 years ago (One serving of red/processed meat defined as 2–3 oz or the size of the palm of hand): <1 vs ≥1 Feng 2021: processed meat. Never vs ≤1 time per week and ≥2 times per week Ferreira 2021: processed meat consumption,

present vs absent 0 grams per day vs above < 35 g/day vs above Mahfouz 2014: processed meat. <25g per week vs above

Many studies picked up red and processed meat together. On the dichotomous aspect we have: Liu 2023: red and processed meat. <2 times per week vs over Chen 2022: red and processed meat intake: ≤1 time per week vs multiple times per week. ≥1 time per day Alegria 2020a: Red and processed meat first tertile vs Second and third tertile Gharbi 2020: processed meat consumption, frequent vs rare/never Hatime 2021: red and processed meat in grams per day: <23.23 vs above Knuppel 2020: ≤1 grams per day vs above Okada 2020: meat or fried food: yes vs no Gavrilas 2018: processed meat in servings per week. <1 vs 1-2 or above Romaguera 2017: red and processed meat together. 0 and 0.5 WCRF/AICR score vs 1 [0 points means Red meat >500g per week or processed meat ≥100g per week (≥ 3 oz). 0.5 points means red meat ≤500 (18 oz) per week or processed meat 21–<100g (0.75 oz–<3 oz) per week]] Turati 2017: red and processed meat together. <0.5 WCRF/AICR score vs ≥0.5 [0.5 points means red meat ≤500 (18 oz) per week or processed meat 21–<100g (0.75 oz–<3 oz) per week] Knudsen 2016: red and processed meat (servings per week): >4 vs ≤4.

On the quantitative aspect, the amounts reported in these studies were in grams per day (Mahfouz 2014, Aleksandrova 2017, Murphy 2018, Alegria 2020a, Aglago 2020, El Kinany 2020, Collatuzzo 2022, Kvaerner 2023, Bahrami 2020) or converted into grams per day from any consumption, as a servings per day (Aglago 2023, Wang 2022b, Yu 2022, Gibbs 2020).

### **Vegetables and fruits**

About vegetables on the dichotomous aspect, there were several ways of picking up the data: Brenne 2024. Daily intake of vegetables vs no Hori 2023: total vegetables, lowest quartile vs over Liu 2023: vegetable consumption. <4 servings per day vs over Chang 2021: vegetables. servings per day 2 years ago (Examples for one serving of vegetables: 1 cup of raw leafy vegetables. 1/2 cup of other vegetables (cooked. canned. frozen. or chopped raw). 1/2 cup of vegetable juice): <1 vs ≥1 Feng 2021: fresh vegetable intake: <1 time per week vs 1 time per week or above Ferreira 2021: consuming at least one serving of vegetables 1 day in a week or less vs 2-3 days in a week or over Zargar 2021: consumption of green and non-green leafy vegetables over the past year. Yes vs no Alegria 2020a: vegetables: first tertile vs Second and third tertile Rennert 2020: vegetable consumption: >4 portions per day vs below Okada 2020: vegetables: yes vs no Gong 2017: vegetable. Less than 250 g per day vs above Kunzmann 2016: <1.06 FPED cup equivalents per 1,000 kcal/d vs over Kunzmann 2015: <3,6g/1000 kcal vegetable fiber vs above Baroudi 2013. <3 a week vs ≥3 a week.

A dozen studies were included in the quantitative analysis of vegetables. The amounts reported in these studies were in grams per day (Zamora-Ros 2013, Vulcan 2015, Murphy 2018, Vulcan 2019, Alegria 2020a, Bahrami 2020, Zhang 2020, Hernandez 2021) or converted into grams per day from any consumption, as a servings per day (Galas 2013, Angelo 2016, Gibbs 2020, Aglago 2023).

Respect of the fruits, on its dichotomous aspect several ways were applied to this variable: Brenne 2024. Fruit and berries, daily intake vs less Hori 2023: total fruit, lowest quartile vs over Liu 2023: fruit intake, <4 servings per day vs over Chang 2021: fruits. servings per day 2 years ago (Examples for one serving of fruit: 1 medium-sized fresh fruit. 1/2 cup chopped. cooked. or canned fruit. 1/4 cup of dried fruit. 1/2 cup of fruit juice): <1 vs ≥1 Feng 2021: fresh fruit intake: <1 time per week vs 1 time per week or above Ferreira 2021: consuming at least one serving of fruit rarely and 1-3 days per month vs once a week and over Zargar 2021: consumption of fruits over the past year. Yes vs no Alegria 2020a: fruits:



first tertile vs Second and third tertile Rennert 2020: vegetable consumption: >3 portions per day vs below Gong 2017: fruit. Rarely and 2 times per week vs above Kunzmann 2016: <0.79 FPED cup equivalents per 1,000 kcal/d vs over Kunzmann 2015: <1.5g/1000 kcal of fruit fiber vs above Baroudi 2013. <3 a week vs ≥3 a week.

The fruits on its quantitative aspect were reported in several ways, such grams per day (Zamora-Ros 2013, Theodoratou 2014, Vulcan 2015, Murphy 2018, Alegria 2020a, Bahrami 2020, Zhang 2020, Hernandez 2021) or converted into grams per day from any consumption, as a servings per day (Galas 2013, Angelo 2016, Gibbs 2020, Aglago 2023).

Many studies collected vegetables and fruits as a whole, specially in the dichotomous aspect, where we can find: Chang 2021: fruits and vegetables. servings per day 2 years ago: <3 vs ≥3 Hatime 2021: fruits and vegetables in grams per day: <280 vs ≥280 Knudsen 2016: Fruits and vegetables. servings per day < 3 vs ≥3 Kunzmann 2016: fruits and vegetables excluding juice <1.64 FPED cup equivalents per 1,000 kcal/d vs over Mahfouz 2014: fruits and vegetables. <5 servings per days vs above.

On the quantitative aspect, another dozen studies were included in the quantitative analysis of the two groups together. The amounts reported in these studies were in grams per day (Zamora-Ros 2013, Theodoratou 2014, Vulcan 2015, Alexandrova 2017, Murphy 2018, Alegria 2020a, Bahrami 2020, Zhang 2020, Hernandez 2021) or converted into grams per day from any consumption, as a servings per day (Galas 2013, Angelo 2016, Gibbs 2020, Aglago 2023) or grams in week ( ).

## **Fish**

On the dichotomous aspect Brenne 2024. Fish, daily intake vs less Franchi 2022: no fish consumption vs canned fish, non-canned fish and both Puzzono 2022: frequency of fish consumption. Never vs 2-3 times a month or above Feng 2021: oily fish intake: <1 time per week vs 1 time per week or above Alegria 2020a: Fish: first tertile vs Second and third tertile Gavrillas 2018: fish in servings per week. <1 vs 1-2 or above Gong 2017: braised fish. Less than one time per week vs above Knudsen 2016: Fatty fish. servings per week. < 1 vs ≥ 1 Kantor 2014: dark fish (salmon + tuna), 0 vs >0 servings per week Mahfouz 2014: fresh fish. Less than once per week vs above Baroudi 2013. <1/15 days vs ≥1 a week.

On the quantitative aspect, Ten studies were included in the quantitative analysis of fish. The amounts reported in these studies were in grams per day (Theodoratou 2014, Alexandrova 2017, Alegria 2020a, Aglago 2020, Bahrami 2020, Zhang 2020, Hernandez 2021) or converted into grams per day from any consumption, as a servings per day (Galas 2013, Angelo 2016, Wang 2022b).

## **Grains, fiber and legumes**

Several studies picked up the fiber as a dichotomous variable: Chang 2021: high fiber foods. servings per day 2 years ago (Foods high in fiber. such as whole grain bread (not white bread). wholegrain or high-fiber breakfast cereal/muesli/bran. brown rice. barley. oats. and legumes (beans. peas. lentils). Examples of one serving of high-fiber food: 1 slice of wholegrain bread. 1/2 cup of cooked or cold high-fiber cereals. 1/2 cup of brown rice or wholegrains): <1 vs ≥1 Feng 2021: cereal consumption: <1 time per week vs 1 time per week or above Alegria 2020a: fiber-containing food: first tertile vs Second and third tertile Hatime 2021: Relatively unprocessed cereals (grains) and/or pulses (legumes) (g/day). <202 vs above Okada 2020: food with cereals or fibers: yes vs no Gong 2017: Cereals. Less than 50 g per week vs above Kunzmann 2015: <3,0g/1000 kcal of grain cereal fiber vs above Kantor 2014: Dietary fiber intake: <12.4g/day to over

Soybeans are a legume with distinctive characteristics due to their high protein content and relatively low fiber levels. We did not find it useful to separate soybeans from other legumes, as their potential effects on CRC risk are likely related to fiber content. We suspect that soybeans may have been isolated in some studies due to their association with phytoestrogens, which, while statistically significant, are of limited clinical relevance. This distinction may also be explained by geographic factors, as in certain Asian regions, soy consumption is so prevalent that it warrants classification as a separate category. In this study, we classified legumes, including soybeans, under one variable and categorized nuts separately under another variable.

On the quantitative aspect, twenty-three studies were included in the quantitative analysis of fiber. The amounts reported about fiber in these studies were in grams per day (Ward 2010, Zamora-Ros 2013, Alexandrova 2017, Murphy 2018, Aglago 2020, Zhang 2020, Collatuzzo 2022, Yu 2022, Aglago 2023, Kværner 2023, Yarmand 2024, Ruiz-Saavedra 2022, Hernandez 2021, Bahrami 2020, El Kinany 2020, Le Marchand 2020, McCullough 2021, Vulcan 2019, Vulcan 2015, Theodoratou 2014, Baroudi 2013, Galas 2013, Budhathoki 2011).

We also evaluated the consumption of whole grains as a whole and not in the form of individual foods (e.g., whole wheat bread). In this case, this variable was only included on three occasions in grams per day (Theodoratou 2014, Vulcan 2015, Angelo 2016).

### **Body Mass Index (BMI)**

In its quantitative aspect, the BMI variable was extensively collected with 58 studies using mean and standard deviation, except Kvaerner 2023 (148) and Ruiz-Saavedra 2022(173) who published P25, P50 and P75 so they were calculated using the method by Luo (50) and Wan (51). Its main outliers were Hassanpour 2023 (123), in which the cases had a lower BMI than the controls ( $27.59 \pm 3.25$  vs  $28.76 \pm 3.97$  kg/m<sup>2</sup>,  $p=0.001$ ); Le Marchand 2020 (55) which indicates that BMI may have changed during follow-up, and two studies that are not explained in the text: Linseisen 2021 (153) and Zhou 2020 (203). The paper by Li 2013 (211) could not be used because it classified BMI into quintiles instead of WHO categories.

In its dichotomous aspect, we made three tables. In the first one we established the cut-off point at 25 kg/m<sup>2</sup> (limit between normal weight and overweight) with 52 studies providing data. The main outliers were Abd Rashid 2023 (66) who adds the following explanation: in the case group there was a lower BMI (62.0% underweight and 5.1 normal weight) compared to the controls. Giacomazzi 2023 (44) found BMI as a risk factor, since the <24 kg/m<sup>2</sup> group had an OR of 2.1 [95% CI, 1.0 to 4.3];  $P=0.04$  compared to the higher group. Another outlier is Chang 2021 (93) who admits that the inverse association they have found between BMI and CRC is contradictory with the results of the meta-analyses and the NHS cohort, but in line with a study carried out on veterans in the United States (212). On the other hand, the outliers Alegria 2019 (69) and Okada 2020 (162) do not explain their findings

For the second table we set the cut-off point at 30 kg/m<sup>2</sup> (limit between overweight and obesity). Again, outliers appear, some without explanation such as Taha 2022 (46) or Shiao 2018 (177), and others such as Giacomazzi 2023 (44) or Chang 2021 (93) that have already been explained in the previous paragraph

Additionally, we made a third table in which we compared the underweight group (below 18.5 kg/m<sup>2</sup>) with the normal weight group (18.5 to 25 kg/m<sup>2</sup>), information that we were able to extract from 33

studies. The outliers Taha 2022 (46), Warren 2022 (192) and Chen 2015 (94) do not explain their findings

### Exercise

For the quantitative version of the exercise, we had four measurements: Met-h/day (Yarmand 2024 (197), Lawler 2023 (149), Bahrami 2022 (61), Bahrami 2020 (60), Andersen 2017 (49)), Met-h/week (several studies), Met-min/week (Kim 2020 (145), Ulaganathan 2018 (185)) and daily minutes of activity (Kvaerner(148), Le Marchand (55), Ruiz (173), Nieuwenhuis (213) or Wells (194). We converted the first and third groups to Met-h/week to have comparable units, but we had to leave out studies that only indicated daily minutes since we could not calculate MET. Warren 2019 (21) was excluded because it showed the data of CRC and all cohorts instead of non-cases. Carr 2018 (86) and Carr 2020 (87) express the mean, but not standard deviation, so we had to exclude them.

For the dichotomous version of exercise, there were numerous ways to collect physical activity. The most basic was to confront the question of exercise yes vs. no, as in Yu 2022 (199), Okada 2020 (162) or Jeon 2018 (52). In some cases where several options appeared, we compared no-exercise versus the sum of the other options, as in Romaguera 2017 (172), Taha 2022 (46) or Chen 2015 (94). Some studies were very strict, confronting never exercise vs. have exercise such Hsu 2022 (130), or grading exercise in very specific steps as Turati 2017 (184) who used the WCRF/AICR scale, or Knudsen 2016 (147), who considered as no-exercise "< 7 times per week 30 minutes of physical activity" similarly to Chen 2015 (94). On the contrary, Doubeni 2012a (107) and Howard 2008 (214) consider physical activity if the person exercises >1 time per month.

About the outliers, Hassanpour 2023 (123) states that between cases and controls there was no significant difference in age, alcohol consumption and physical activity. Alegria 2019 (69) also states that contrary of what it could be expected, CRC could be related to modifications in the lifestyles, including exercise, in cases after diagnosis.

### Alcohol

On the quantitative aspect, Twenty-one studies were included in the quantitative analysis of alcohol. The amounts reported in all these studies were in grams per day (Kvaerner 2023, Ruiz-Saavedra 2022, Wang 2022b, Hernandez 2021, Gibbs 2020, Kim 2020, Le Marchand 2020, Schulpen 2020, Castello 2019, Guertin 2017, Aleksandrova 2017, Papantoniou 2017, Vulcan 2015, Theodoratou 2014, Cottet 2013, Galas 2013, Zamora-Ros 2013, Ward 2010) or in serving in day (Murphy 2018, Cheng 2015, Wells 2014), turned into grams per day using standard drink defined by WHO.

As a dichotomous variable, alcohol was collected in very heterogeneous ways. Some were simple versions of alcohol yes vs no, such as Giacomazzi 2023 (44), Zargar 2021 (201), Shiao 2018 (177) and many others. Others specified whether consumption was regular, such as Ma 2023 (156). Very few studies indicate ex-drinkers, such as Tran 2023 (183), Wismayer 2022 (48), Feng 2021 (110) or Kim 2020 (145). Others established cut-off points such as Puzzono 2022 (47) (Never vs 2-3 times a month or above), Chang 2021 (93) (in the last two years less than once per month vs 1-3 times per month or above), or cut-off points based on grams per day such Linseisen 2021 (153)  $\leq 7.9\text{g/day}$  or Hatime 2021 (125)  $< 10\text{g/day}$ . The article by Chen 2022 (95) was not included because the cut-off point is "above recommended levels". The cut-off points could be different for men than for women, such as Romaguera 2017 (172) who considered consumption  $> 28\text{g/day}$  in males and  $> 14\text{g/day}$  in females; or



Knudsen 2016 (147) who considered consumption >14 glasses per week in males or >7 glasses per week in females, or Vulcan 2017 who considered consumption >20 g/day in males and >15 g/day in females; or Lawler 2023 (149) who considered consumption >3 daily drinks in males and <1 daily drink in females. As can be seen, in the non-drinker group there were studies that included 0 drinks, 1 drink and even up to 2 daily drinks like the cases of Lawler 2023 (149) or Andersen 2022 (192). Also, some studies made a sudden jump, going from non-drinkers to heavy drinkers such as Yu 2022 (199), or to moderate alcohol consumption such as Warren 2022 (192) and Nakagawa 2017 (161), or a jump from non-drinkers to >20g/d for men like the case of Vulcan 2017 (187). This bias led us to propose an additional table, which we titled “alcohol (restricted version)”, in which we included only those articles in which zero alcohol consumption was specified in order to compare people with zero alcohol consumption with those who consumed some alcohol, a strategy that we will also replicate in smoking.

### Smoking

Tobacco use was recorded in a variety of ways, and it was decided to make two tables: one comparing zero smoking versus active and former smoking, and one comparing zero smoking versus former smoking. Many articles recorded all three categories, such as Abd Rashid 2023 (66), Lawler 2023 (149), Tran 2023 (183), and many others. Some articles only recorded two categories (ever smoker yes vs no), such as Ma 2023 (156), Aglago 2023 (68), Budhathoki 2020 (31), Jeon 2018 (52), and many others. Some only indicated smoking yes vs no, such as Hassanpour 2023 (123), Giacomazzi 2023 (44), Bahrami 2020 (60), and many others. Some established ordinal cut-off points such as Puzzono 2022 (47) and Nakagawa 2017 (161) ( $\leq 10$  cigarettes per day), Jung 2019 (136) (1 pack per day) or Boyle 2011 (79) (<1 pack per year). Weinstein 2011 (215) recorded the number of cigarettes per day. Santiago 2021 (36) was the only to distinguish forms of consumption: cigar. pipe. hookah or marijuana smoker. Brenne 2024 (80) was not included because it was the only study that included smoking in pack-years, so it could not be compared. In a similar way to alcohol, we made a smaller table, called “tobacco, restrictive version” in which we collected only those studies that specified zero tobacco consumption

### Education

The variable "education" was collected in numerous ways. Finally, we divided education into four ordinal blocks, one after the other: the first would be the illiterate or uneducated. The second would be primary education “Elementary school, read and write, primary school, middle school”. The third block would be secondary education “Junior Middle school, Senior High school, Technical school, Professional school, High school GED, GCSE A-levels or equivalent, Certificates/STPM”. Finally, the fourth would be tertiary education “College, University, Post-graduate degree, Degree/Diploma, Bachelor-of-arts-or-of-sciences, Tertiary, Vocational school”.

Some studies had the education collected in the number of years of education, not in a quantitative way, but in an ordinal way. For example, Speciani (181) cuts on <7 years of education. 7-11 years of education and >11 years of education. We could not use these studies for our analysis. These studies are: Speciani 2023 (181), Chen 2022 (95), Franchi 2022 (113), Taha 2022 (46), Carr 2020 (87), Erben 2019 (18), Bakken 2018 (75), Carr 2018 (86), Vulcan 2019 (188), Turati 2017 (184), Vulcan 2015 (186), Hoffmeister 2014 (128), Innes 2014 (132) and Cottet 2013 (103). Other special cases than we could not use were Le Marchand 2020 (55) and Wells 2014 (194) that show the average years of education in cases and controls

### Propensity score matrix

Propensity score methods have gained widespread popularity as a bridging tool between observational studies and randomized controlled trials, largely due to their adaptability and distinct design features (217). In analyses utilizing propensity scores, particularly when the outcomes are binary, various metrics such as risk differences, number needed to treat (NNT), and relative risks are often reported (218). Multiple methodologies are available for calculating these metrics, with notable contributions from McCaffrey, Imbens, Spreeuwenberg, and Rassen (219). Recent advancements have introduced more sophisticated approaches, including the Doubly Robust method, which is particularly advantageous in scenarios where there is misspecification in the outcome or propensity score model. Additionally, the Bayesian method has become increasingly relevant in situations where there is considerable uncertainty in the parameter estimates (220). These newer techniques offer more flexibility and robustness, ensuring more accurate and reliable results in complex analyses. A very similar approach to our objectives is found in chapter 3 of the study by Davies (221), in which they create a Score system for the risk of diabetes.

To estimate the combined total risk of several variables, we created a calculator in Microsoft Excel that would allow us to attribute a total risk to a person using a number of variables. To do this, we assigned the variables that best fit the model, prioritizing the quantitative variables over the dichotomous ones (especially noticeable in the case of food consumption and exercise), and prioritizing those that had been statistically significant. Transforming the quantitative variables into a measure that allows us to know how much the risk changes for each unit of increase in the variable took some calculations. First, knowing the mean difference and the standardized mean difference, we could calculate the Pooled SD, which is the absolute value of the MD/SMD division. Next, we proceed to calculate the OR for each unit of change, using the formula  $OR = \exp(\log(ORSD)/SD_{pooled})$ . If we wanted to know the OR for ten units of change, the formula would be  $OR = \exp(10 * \log(ORSD)/SD_{pooled})$ .

Once the OR per unit of change of the quantitative variables is known, a composite score was calculated as a linear predictor (LP) combining all ORs (both binary and continuous variables). For dichotomous variables, it is simply the natural logarithm of the OR in case the patient meets this variable. For quantitative variables, we multiply the value given by the patient by the natural logarithm of the OR for one unit of change. The sum of each of the linear scores would give us a final score, whose value 0 would be indifferent, negative values would be protective and positive values would be at risk. To assess the distribution of this score, a large-scale simulation was conducted, generating data for up to 16.8 million hypothetical patients, each with a unique combination of the variables. From the simulated scores, a histogram and boxplot were created to visualize the distribution. Key statistics such as minimum, maximum, and decile values were computed. Additionally, an alternative method for calculating deciles was proposed. This method assumes a uniform distribution and calculates deciles by dividing the range (difference between max and min scores) by 10.

**Figure 8** shows an example of a smoker woman that consumes 200 daily grams of vegetables, fruits and grains, some alcohol and sedentary lifestyle

**Figure 8.** Example of the score matrix

Factor	Example of a patient	OR from Meta-analysis	SMD	MD	SD Pooled	OR for change of 1 unit	OR for change of 10 unit	Linear Score (LS) log(OR) 1 unit
Male	0	1.33				1.330		0.00
Black	0	1.15				1.150		0.00
Family History	0	1.79				1.790		0.00
IBD	0	2.25				2.250		0.00
DM2	0	1.3				1.300		0.00
Metabolic Syndrome	0	2.25				2.250		0.00
Ever Smoker	1	1.19				1.190		0.17
Former Smoker	0	1.1				1.100		0.00
Illiterate/no studies group	0	1.47				1.470		0.00
Primary education only	0	1.4				1.400		0.00
University education	1	0.73				0.730		-0.31
Age	50	1.89	0.348	3.864	11,101	1,059	1,774	2.87
Diary products or plant-based derivatives	250	0.82	-0.114	-14.943	131,005	0.998	0.986	-0.38
Cheese intake	0	0.96	-0.021	0.016	0.751	0.947	0.581	0.00
Red Meat intake	0	2.39	0.483	9.027	18,689	1.048	1.594	0.00
Processed meat intake	0	1.63	0.268	5.998	22,394	1.022	1.244	0.00
Raw vegetable intake	200	0.71	-0.204	-24.972	122,287	0.997	0.972	-0.56
Cooked vegetable intake	0	0.71	-0.186	-13.316	71,737	0.995	0.953	0.00
Fruit intake	200	0.59	-0.292	-27.312	93,542	0.994	0.945	-1.13
Fish intake	0	0.93	-0.040	-1.816	44,910	0.998	0.984	0.00
Whole grains intake	200	0.88	-1.425	-3.886	2,727	0.954	0.626	-9.38
Alcohol consumption	20	1.16	0.076	1.382	18,305	1.008	1.084	0.16
Body Mass Index	23	1.1	0.061	0.274	4,465	1.022	1.238	0.49
METs	0	0.85	-0.087	-3.050	35,244	0.995	0.955	0.00

\*Significant features according to MA

min-max	Deciles	p2.5-p97.2	Deciles	Simulated*	Deciles
-9.92	1	-9.92	1	-9.92	1
-7.12	2	-3.91	2	-2.91	2
-4.33	3	-1.91	3	-1.12	3
-1.53	4	0.08	4	0.98	4
1.26	5	2.07	5	2.35	5
4.06	6	4.07	6	4.06	6
6.86	7	6.06	7	5.78	7
9.65	8	8.06	8	7.15	8
12.45	9	10.05	9	9.25	9
15.24	10	12.04	10	11.04	10

CALCULATOR (deciles)	SCORE (sum LS)	min-max	p2.5-p97.2	Simulated*
-9.06	1	1	1	1

\* Simulations where calculated using 37.7M of patients with unique combinations of the 24 variables included in the model. More information in 'Deciles distribution' sheet

min-max	5 ranks	p2.5-p97.2	5 ranks	Simulated*	5 ranks
-9.92	1	-9.92	1	-9.92	1
-4.33	2	-1.91	2	-1.12	2
1.26	3	2.07	3	2.35	3
6.86	4	6.06	4	5.78	4
12.45	5	10.05	5	9.25	5

CALCULATOR (5 ranks)	SCORE (sum LS)	min-max	p2.5-p97.2	Simulated*
-9.06	1	1	1	1

\* Simulations where calculated using 37.7M of patients with unique combinations of the 24 variables included in the model. More information in 'Quintile distribution' sheet

## 3.5 Next steps

### Other variables that we can include in the future expansion of the meta-analysis

Some foods, nutrients and biomarkers appeared only once or twice so they could not be compared. For example chocolate in Brenne 2024 (80), ultra-processed food in Theodoratou 2014 (182) and Chang 2021 (93), garlic in Speciani 2023 (181), McCullough 2012 (222) and Hu 2014 (223), carrots in Deding 2020 (105), tomato in Jiang 2023 (224), sugar in Debras 2020 (225) and Alegria 2020a (57), butter in Baroudi 2014 (53), total fat in Dahm 2010 (226) or Arafa 2011 (227), olive oil in Baroudi 2013 (53) or Arafa 2011 (227), flavonoids in Nimptsch 2016 (228), proanthocyanidins in Rossi 2010 (229), inflammatory biomarkers in Kim 2020 (145), serum p53 autoantibodies in Teras 2018 (230), ghrelin in Murphy 2018 (160), serum albumin in Ho 2014 (32), nonstarch polysaccharide in Yu 2022 (199), or exposure to pesticides, solvents and glue in Giacomazzi 2023 (44). Some drugs such as salicylates, thiopurines and methotrexate were studied by Carrat 2017 (88), Beaugerie 2013 (77) and Biancone 2016 (78). The studies by Bahrami 2022 (61) and Safari 2013 (231) distinguished between different cooking methods, such as fried, boiled, grilled, or steam cook.

Many studies collected dyslipidemia, and we can use it for the future: Hsu 2022 (130), Jin 2022 (27), Shin 2017, (179), Borgquist 2016 (232), Chen 2015 (94), Kasai 2016 (139), Ho 2014 (32) and Passarelli 2021 (34)

Other variables in which we can expand the meta-analysis are those related to vitamins and folate: B1 (Baroudi 2013; Bahrami 2020, Hassanpour 2023), Vitamin C (Baroudi 2013, Galas 2013, Theodoratou 2014, Alegria 2020b, Bahrami 2020, Hassanpour 2023), Vitamin D (Vulcan 2015, Papantoniou 2017, Vulcan 2019, Alegria 2020b, Bahrami 2020, Gibbs 2020, Zhang 2020, McCullough 2021, Hassanpour 2023), Vitamin E (Bahrami 2020, Hassanpour 2023), Folate (Baroudi 2013, Zamora-Ros 2013, Vulcan 2015, Guertin 2017, Andersen 2017, Vulcan 2019, Alegria 2020b, Bahrami 2020, Le Marchand 2020, McCullough 2021, Aglago 2023, Hassanpour 2023), Calcium (Baroudi 2013, Galas 2013, Kim 2013, Zamora-Ros 2013, Vulcan 2015, Papantoniou 2017, Vulcan 2019, Alegria 2020b, Bahrami 2020, Gibbs 2020, Le Marchand 2020, Zhang 2020, McCullough 2021, Aglago 2023, Hassanpour 2023), etc.

### Limitations

There are potential concerns regarding heterogeneity both within and across countries and regions. However, the studies selected for this analysis were rigorously vetted based on strict quality and methodological standards. This ensures that the analysis not only maintains a high degree of accuracy but is also relevant to diverse populations. By including a broad spectrum of high-quality research, we have captured the complex realities of cancer risk factors across different settings. This robust and comprehensive approach strengthens the relevance of our findings, providing a reliable evidence base for designing targeted public health interventions, guiding research priorities, and improving healthcare strategies. The insights derived from this analysis are particularly suited to addressing the diverse public health needs within Europe, with potential for broader global applicability.

The Score represents a composite measure derived from the univariate effects of individual risk factors within a multivariate model. While this approach allows for the simultaneous consideration of multiple risk factors, there is a possibility of either overestimating or underestimating the contribution of certain factors. In multivariate models, interactions between variables and potential confounders can obscure the true effect size of specific risk factors, leading to biases in the final score. This underscores the need for careful interpretation and validation of the Score to ensure it accurately reflects the combined impact of the risk factors considered. Further adjustments and sensitivity analyses may be required to mitigate any potential distortions in the estimation of these effects.

In this study, only those studies that provided raw data were included, while studies reporting pre-calculated effect estimates were excluded. As a result, there is a possibility that some valuable data generated by the scientific community may have been overlooked. This limitation could lead to a narrower scope of the analysis, potentially missing out on relevant findings that could have further enriched the overall interpretation. However, prioritizing raw data ensures greater control over the analytical process and reduces the risk of introducing biases from varying methodologies used in pre-calculated estimates.

It is important to acknowledge that risk factors interact in a non-linear manner, meaning that the sum of their relative weights may not necessarily correspond to the aggregate relative weight for each individual patient. The variable 'exercise' presents a particular challenge in this context, as it requires careful differentiation between the co-occurrence of factors that contribute additively to the overall score and those that exhibit effective interaction. In cases of interaction, the simultaneous presence of certain factors does not merely lead to an additive increase in risk scores, but rather introduces multiplicative effects that must be considered. This distinction is critical, as overlooking these interactions may result in an oversimplification of complex relationships between risk factors and their cumulative impact on health outcomes.

## 4 Behavioral barriers identification, preferences assessment, and equitable target population impact groups

### 4.1 Introduction

The increasing incidence of colorectal cancer (CRC) highlights the urgent need for effective primary prevention strategies. As public health initiatives aim to mitigate this preventable disease, understanding the barriers and facilitators that influence participation in these interventions becomes imperative. Various demographic factors, including socioeconomic status, cultural beliefs, and educational levels, significantly impact individuals' willingness and ability to engage in preventive measures. In addition, the diverse characteristics of the different population groups affected by this incidence increase requires a nuanced approach to intervention design, ensuring that strategies are tailored to address specific needs and obstacles faced by each community.

It becomes apparent that exploring these dimensions systematically will illuminate the complex interplay between individual agency and systemic influences, ultimately contributing to more effective and inclusive public health policies. Through a deeper understanding of these dynamics, stakeholders can develop targeted initiatives that not only enhance participation rates but also promote health equity among at-risk populations.

To this end, in 2023, the ONCODIR project, aimed in providing a comprehensive set of internally integrated, novel, easy-to-use tools to enable the effective primary prevention of colorectal cancer as part of its holistic support decision-making system. With one of the project's main objectives being to analyze and address the main barriers that prevent the uptake of dedicated prevention programs while ensuring equal and affordable access for all to cancer prevention strategies between and within EU countries, delving into the relevant social, cultural, economic and technological determining factors of individuals' participation in such interventions was deemed necessary.

Through a population survey across the consortium countries and a series of focus groups with healthcare experts from across Europe, multiple barriers were mapped, facilitators identified, as well as relevant inequalities linked with populational vulnerabilities recognized. This chapter focuses on the results of the study conducted within T2.4 of ONCODIR that mapped barriers and facilitators that was acknowledged as such by citizens, clinicians, and policy makers from all consortium countries, while enriched and validated by cancer survivors and healthcare experts from across Europe. The quantitative survey findings and the qualitative insights from the focus group sessions are presented below. An integrated analysis and comparative discussion of the findings conclude this chapter in a way of better reflecting on the key results of the study.

### Background

Colorectal cancer (CRC) presents a considerable public health challenge, being the third leading cause of cancer-related deaths in the United States (Commonwealth Fund, 2022) and the second in Europe (European Commission, 2020). Primary prevention strategies are crucial in reducing CRC risks, as studies emphasize the importance of education on lifestyle modifications. Barriers, such as limited healthcare access and inadequate provider-patient communication, complicate efforts to improve CRC outcomes (Sanger et al., 2020). By systematically understanding patient needs and preferences, as demonstrated in evidence-based interventions (A O'Cathain et al., 2019), healthcare providers can

address these barriers. Furthermore, targeted educational strategies can raise awareness and encourage participation among diverse population groups, particularly those facing health disparities. A comprehensive grasp of these barriers and facilitators to CRC prevention can guide tailored interventions that ultimately reduce incidence rates and improve public health.

Participation in colorectal cancer prevention interventions is often impeded by numerous barriers that disproportionately affect various population groups. One significant factor is the absence of relevant provider recommendations, leaving many unaware of their risk factors and the necessity of preventive measures. Financial concerns and inadequate insurance coverage further limit access to these life-saving interventions, especially among marginalized groups, perpetuating health inequities (Foster et al., 2014). Fear and misconceptions about colorectal cancer also deter participation in prevention efforts, underscoring the need for culturally relevant health education initiatives that address both psychological and logistical barriers (Foster et al., 2014). These challenges highlight the importance of tailored interventions to promote greater engagement in colorectal cancer prevention.

Participation rates in colorectal cancer prevention programs reveal significant disparities influenced by socioeconomic and cultural factors. Individuals from lower socioeconomic backgrounds often face barriers such as limited access to health education and healthcare resources, leading to a lower understanding of colorectal cancer risks and the importance of prevention. This lack of awareness is further exacerbated in culturally diverse communities, where language barriers and inadequate translation of materials hinder effective communication (Javanparast et al., 2011). Marginalized groups often encounter minimal health provider recommendations and culturally relevant outreach efforts, deterring their participation. Addressing these disparities requires targeted interventions that enhance awareness and accessibility across diverse population segments (Kim et al., 2017).

Enhancing engagement in CRC primary prevention interventions requires an understanding of the facilitators that resonate with different population groups. Accessibility, tailored communication, and social support are crucial in encouraging participation. Providing accessible resources, such as transportation options and flexible scheduling, can reduce logistical barriers that often deter individuals from seeking preventive care. Additionally, culturally sensitive communication strategies that resonate with specific demographics can foster a sense of belonging and urgency, motivating individuals to participate (Kim et al., 2017).

Moreover, fostering social support networks—such as peer groups or community organizations—can instill confidence and accountability among participants. When individuals feel supported by their community, they are more likely to engage actively in preventive measures (O’Cathain et al., 2019). Addressing these facilitators effectively not only improves participation rates but also enhances the overall effectiveness of CRC prevention efforts (Kim et al., 2017).

A comprehensive understanding of effective communication strategies and community engagement initiatives is essential for addressing the barriers to CRC primary prevention interventions. Recent studies emphasize the need for tailored messaging that resonates with specific populations, particularly marginalized groups who may encounter unique obstacles in accessing healthcare resources. For instance, the integration of community coalitions in the Educational Program to Increase Colorectal Cancer Screening (EPICS) demonstrates how community-specific modifications to research protocols can enhance the interventions' relevance and accessibility, ultimately bridging gaps between evidence-based practices and community needs (Ansa et al., 2019).



Qualitative insights reveal the critical role of trusted community leaders, such as church pastors, in disseminating CRC prevention messages. These leaders can amplify awareness and knowledge, fostering engagement among congregation members who may otherwise lack information about risk factors and preventive measures (Coffey et al., 2013). Establishing these dynamic channels of communication is vital to improving participation rates across diverse population groups.

Methods

To comprehensively identify barriers, facilitators, and vulnerabilities in CRC primary prevention a study utilizing both quantitative and qualitative approaches was conducted. This mixed-methods study began with a large-scale survey targeting a diverse group of participants. The survey assessed their awareness, attitudes, and behaviors related to CRC prevention shedding light on common obstacles, key facilitators, and effectively established mitigation strategies.

To this end, a dedicated, structured, closed-ended questionnaire was developed. Despite the preliminary questionnaire version being developed by ECPC before their departure from ONCODIR, its final version was the product of iterative rounds of feedback from key contributing partners; MoHGR, EUREGHA, INCLIVA and POLA. The final version of the questionnaire, which comprised 96 items—46 addressing citizens’ views, 29 targeting clinicians, and 21 focusing on policy-makers—was made available in all consortium languages: Dutch, English, French, German, Greek, Italian, Lithuanian, Romanian, and Spanish. Each participant was assigned to the section corresponding to the capacity they identified with the most and responded only to the questions within that section.

It was administered digitally from May to July 2024 through an online platform certified for ensuring data protection rights (SurveySparrow) with participation being voluntary and completely anonymous. All ONCODIR consortium partners were asked to actively promote the dissemination of the questionnaire across all consortium countries while the questionnaire was circulated among the partners of the sister-project PREVENT given a dissemination opportunity presented during their 2nd plenary meeting. Convenience sampling was selected due to time constraints.

Before circulating the questionnaire, a sample size formula was applied to determine the required number of citizens needed to obtain reliable and concrete results from the survey. For a 95% confidence interval, a 50% population proportion for maximum variability, and 5% margin of error, our sample required at least 384 participants given the estimated general population of the consortium countries combined.

With over 4000 people reached, 922 citizens took part in the survey. Citizens’ demographics are summarized in Table 6 below.

Table 7. Demographic Statistics of Citizens

Characteristic	%	n
Gender		
Male	25	231
Female	68.5	632
Non-binary /Prefer not to disclose/ Not specified	6.5	59

<b>Age Range</b>		
<24	4.5	40
24-50	16	151
50+	64	588
Prefer not to disclose	15.5	143
<b>Speaking Language</b>		
Dutch	0.3	1
English	1.4	13
French		
German	0.65	6
Greek	15.6	144
Italian	3.3	31
Lithuanian	75.9	700
Romanian	2.1	20
Spanish	0.75	7
<b>Highest level of education completed</b>		
Primary/Secondary Education	6.9	64
College/Associate Degree	21.3	196
Bachelor's degree	27.9	257
Master's degree	35.6	328
Doctoral degree	5.5	51
Prefer not to say	2.8	26

Prior to recruiting General Practitioners and Gastroenterologists from diverse settings (primary, secondary, tertiary), a comparative analysis of corresponding studies was conducted to estimate the required clinicians' sample size. As predominantly studies investigating barriers and facilitators of primary prevention interventions involving clinicians adopted qualitative approaches with semi structured interviews and focus groups conducted in small experts' groups (Rubio-Valera et al., 2014), a small convenience sample of 30-50 clinicians was selected to whom the dedicated section of the structured questionnaire was administered. All in all, 66 clinicians from different regions and work settings (primary, secondary, tertiary) across all consortium countries participated in the survey. Particularly, 4 Dutch, 16 English, 8 French, 1 German, 5 Greek, 20 Italian, 6 Lithuanian, 3 Romanian, and 3 Spanish speaking healthcare professionals enrolled in the study.

An analogous process was undertaken prior to recruiting policy makers from the consortium countries to have an estimate of the adequate sample size. With the scarce corresponding studies adopting qualitative or mixed methods approaches, we opted again for a small convenience sample of 30-50 policy makers, as in the literature the sample sizes are either not reported or extremely small (Alberti



et al., 2007; Lee et al., 2014). 28 policy makers were enrolled in the survey; in particular, 2 Dutch, 6 English, 1 French, 2 German, 7 Greek, 1 Italian, 6 Lithuanian, 2 Romanian, and 1 Spanish speaking.

1016 adults took part in the study from all consortium countries. Interestingly, 69% of them were previously affected by cancer, and approximately 11% of this percentage has been affected by colorectal cancer. In addition, 57% of survey participants reported having at least one family member affected by cancer in general, and 17% affected by CRC specifically.

Following the survey, a series of focus groups were designed and conducted to provide deeper insights into the context of these barriers and facilitators, through the validation of the already identified ones via the survey and the addition of new ones that were not recognized during the previous process. Given that the citizens participating in the survey primarily came from Lithuania, it was deemed preferable to have the focus group sessions organized with partners from the remaining consortium countries, and if possible, from out of -the consortium as well, to gain as diversified insights as possible.

During September and October 2024 a series of 6 focus groups was conducted by the EUREGHA, EFPC, ESDO, and MOHGR partners. Particularly, EUREGHA organized two, while EFPC and ESDO each organized one. Additionally, MoHGR facilitated 2 focus groups- one for Greek policy makers and another with representatives from INCLIVA and UNIRIOJA- and developed all supporting material the activities. Given the findings of the comparative analysis, invited in the focus groups were experts-clinicians and policy makers that during their discussions unveiled cultural beliefs, misconceptions, and personal stories that quantitative data alone couldn't capture.

The results corresponded to those of a workshop conducted during an international event organized by YCE in Romania in early August where more than 40 cancer survivors from all over Europe addressed from another point of view the challenges of CRC primary prevention. The details and results of each session are presented later.

By integrating these two approaches, the study painted a holistic picture of the multifaceted challenges and enablers, guiding the creation of tailored interventions to boost participation and reduce health disparities.

## 4.2 Quantitative Data Overview & Qualitative Insights

### Quantitative Data Overview

#### Citizen Feedback Analysis - Understanding public opinion

The citizens participating in our survey were asked to list the influencing factors for making choices about a healthy lifestyle and what motivates them to make positive changes regarding their health-related behaviors. Considering the influencing factors, they identified some financial/economic constraints they face as the most potent ones (53.66%). Accessibility/lack of facilitation to healthy options (32.51%) and limited access to healthcare services (26.32%) appeared as rather impactful, while social influences (17.21%) and lack of knowledge about healthy choices (15.41%) seemed as well having a significant effect. Regarding motivation, personal health goals (74.36%), awareness of health risks (58.86%) and the probability to improve one's life quality (51.17%) emerged as the most important ones. Advice from healthcare professionals and support from family and friends were

acknowledged by 1 out of 3 participants though community programs and initiatives as well as rewards and incentives found to have very limited impact.

The individuals in the study appeared well-informed about preventive health measures, such as screenings, vaccinations, and lifestyle modifications in general, not specifically to CRC ( $M=3.35$ ,  $SD=1.03$ ). They recognized as highly significant receiving advice tailored to their specific needs ( $M=3.8$ ,  $SD=.94$ ) as well as they were very interested in the development of genetic screening tools to identify a higher individual risk of cancer for appropriately personalized preventive interventions for cancer, including CRC ( $M=3.84$ ,  $SD=1.06$ ). While over 60% of participants indicated that their preferred method of receiving such information was through one-on-one consultations, 1 out of 2 reported using digital information sources for acquiring health information, with over 30% attending webinars and podcasts. Both social media and the traditionally printed materials such as brochures, pamphlets etc., deployed for primary prevention, were not favorably viewed by the participants.

In relation to receiving information, regular check-ins with healthcare providers and the provision of resources by them were identified by citizens as the most supportive system for better managing their health (65.14%). Family emerged as the second most important factor (54.86%), whilst the positive influence of online health forums/ platforms (27.92%) and wellness workshops or events (26.93%) were highlighted. Almost 1 out of 5 survey participants conveyed receiving support from printed educational materials while even less from mobile applications for health tracking (17.21%), yet considering both of them supportive.

This perceived support takes different forms and impacts the subjects' health and well-being. Over 60% attributed a positive influence to receiving emotional support during difficult times, 45% to the encouragement and motivation to adopt healthy behaviors, and 33% to the sense of belonging and reduced feelings of isolation. The practical assistance available within such nurturing relationships (26%) as well as the opportunity to participate with other people in health-related activities (21.18%) were highlighted. This viewing is rather interesting as solely 11.84% of the citizens participating in the study acknowledged as such support groups and communities while 1 out of 5 participants did not recognize any impact of social support on his/her health and wellbeing.

Despite social support facilitating individuals' uptaking and maintaining positive health behaviors, several barriers were identified hindering it, with lack of time and/or conflicting schedules (29.775%) as well as lack of awareness on available support resources (29.663%) being the most prominent ones. Difficulty in expressing one's health concerns and needs (15.62%), geographical distance from one's family and friends (11.69%), the potential stigma or fear of judgment (8.2%), and the limited availability of the existing support resources (7.1%) were among the barriers challenging the study participants.

In this light, it was heavily supported that to promote health and well-being across the members of different communities the encouragement of regular health check-ups and preventive screenings should be a priority (69.5%). Some other means of promotion involve creating safe spaces for physical activity and recreation (45.48%), collaborating with local healthcare providers for outreach (42.57%), promoting healthy eating options within the community (41.29%), providing accessible community health programs and workshops (38%) and fostering a sense of belonging and support (30.4%). Such an ecosystem could address a barrier identified solely by a small percentage of the sample; the cultural differences that impede effective communication (2.8%) while positively influencing health decisions

through jointly sharing cultural practices (10%). Additionally, addressing mental health stigma could involve not only offering primary prevention for CRC but also providing mental health support (33.4%).

Cultural influences were found to be impactful by 8.1% of the sample, whereas cultural sensitivity in delivering healthcare services and information was characterized as moderately important by the participants ( $M=3.06$ ,  $SD=1.17$ ). Despite 47% of the citizens not considering their cultural background influential on their health behaviors, the remaining participants have demonstrated a noteworthy impact by traditional health practices and remedies (54.53%), cultural dietary preferences (45.67%), views on exercise and physical activity (46.64%), and attitudes towards preventive care (44.02%), especially with respect to CRC primary prevention.

Financial limitations appeared hindering participant's decision regarding healthcare ( $M=3.08$ ,  $SD=.95$ ). As the citizens enrolled in the study reside in EU member states their health insurance coverage impacted positively (41%) or not significantly (45%) their health-related decisions. However, 1 out of 2 reported that financial constraints prevent them from seeking preventive services, while job-stability and pertinent benefits encourage them towards preventive care ( $M=3.47$ ,  $SD=.9$ ). It is important to note though that among the survey participants 25% acknowledged that the wellness programs offered by their employers cast a positive effect on their decision-making whilst 52% reported discrepancies between the objectives of the offered programs and their actual impacts.

This last finding is critical, particularly as it is combined with the fact that the corresponding free-of-charge or low-cost programs offered at community levels were considered poorly accessible ( $M=2.62$ ,  $SD=1.13$ ). Despite being adequately aware ( $M=3.24$ ,  $SD=1.13$ ), participants appear to be limitedly familiar with them ( $M=2.97$ ,  $SD=1.19$ ), as either they had participated in them occasionally (30%) or not at all (46%) due to different barriers. Eligibility criteria (11.7%) and the complexity of the application process (8%) deterred solely a limited fraction of the sample. Nonetheless, the lack of proper awareness campaigns (44.6%) and the additional challenges that each one faced (38.6%) impeded them from participating. Language barriers, stigmatization, and the fear of being judged were acknowledged by few participants.

In this light, citizens were in favor of increasing public awareness campaigns about the availability of prevention programs (27%) as well as enhancing accessibility to health-information via digital platforms as well (14%). They also supported the improvement of communication channels between healthcare providers and communities (17%) while strengthening the collaboration between healthcare providers and community leaders to increase program visibility. Yet, significant improvements to these programs are required as the eligibility criteria for participation should be expanded (8%), the application processes facilitated (10%), and multilingual resources available (1%).

### **Detection of Statistically Significant Inequalities**

Given the diversity in languages and the imbalanced number of responses across different linguistic groups, it was essential to explore whether socioeconomic barriers varied significantly between respondents based on the language in which they filled out the questionnaire. Although, there were circulated questionnaires specifically designed for citizens, clinicians, and policymakers, the analysis focuses solely on the citizens' responses, as this group provided a sufficiently large sample size to yield representative data.

To assess these potential inequalities, the Chi-square ( $\chi^2$ ) test of independence was employed. This test is designed to examine whether there are statistically significant differences between categorical variables. By comparing responses from one language or a set of languages against others, the analysis aims to reveal any disparities in how different groups experience or perceive barriers to CRC primary prevention.

As stated above, one of the challenges faced in this analysis was the imbalanced number of responses per language. This uneven distribution means that certain language groups may be overrepresented or underrepresented, which could introduce bias into the results. However, the Chi-square test remains robust for large sample sizes, like the one analyzed in this study and offers insight into whether the detected inequalities are statistically significant, despite these imbalances.

The results below include the Chi-square statistic ( $\chi^2$ ) and p-values for the inequalities, as they provide the basis for confirming them across the different language groups. A p-value less than the chosen significance level (i.e. typically .05) reassures us that the observed disparities are unlikely to have occurred by chance.

For questions that utilized a 5-item Likert Scale the analysis also includes the mean value and standard deviation of the scaling per linguistic group. Moreover, for questions with categorical answers like "Yes," "No," and "Not sure," numerical weights are assigned to these responses: 1 for "Yes," -1 for "No," and 0 for "Not sure." This allows us to draw the mean value and standard deviation from the data, offering a way to quantify and compare the responses across different groups. These metrics offer additional insight into the central tendency and variability of responses, helping to further quantify differences between language groups in terms of perceived barriers.

The significance level is set at .05. The specific details of the inequalities revealed through the analysis are outlined below:

❖ **How well-informed do you feel about preventive health measures, such as screenings, vaccinations, and lifestyle modifications?**

Potential answers: Importance scale (1 = Not at all informed, 5 = Extremely well-informed)

Language Groups Compared: Lithuanian vs Others

Distribution for Lithuanian: 43 (1), 142 (2), 200 (3), 282 (4), 32 (5)

(M=3.169, SD=1.004)

Distribution for Others: 1 (1), 13 (2), 43 (3), 96 (4), 59 (5) (M=3.939, SD=.0875)

Chi-square Statistic ( $\chi^2$ ): 123.3278, p-value: < .00001

The results imply a significant difference in how well-informed respondents feel about preventive health measures between Lithuanian respondents and those from other language groups. The mean value for Lithuanians (3.169) indicates they generally feel less informed compared to respondents from other language groups (3.939). The Chi-square statistic of 123.3278 and the p-value of less than .00001 confirm that this difference is highly statistically significant, meaning it is unlikely to be due to chance. Additionally, the higher standard deviation among Lithuanian respondents (1.004) suggests greater variability in their sense of being informed, compared to the lower standard deviation (.875) in other language groups. This disparity underscores a potential inequality in the level of awareness or

understanding of preventive health measures across different populations, warranting targeted strategies to address these gaps.

❖ **How does your health insurance coverage influence your healthcare decisions?**

Potential answers: Positively, Negatively, No significant impact

Language Groups Compared: South vs North

Distribution for South (i.e. Greek, Spanish, Italian): 66 (Positively), 63 (Negatively), 44 (No significant impact) (M=.017, SD=.863)

Distribution for North (i.e. English, German, French, Dutch, Romanian, Lithuanian): 307 (Positively), 56 (Negatively), 365 (No significant impact) (M=.345, SD=.616)

Chi-square Statistic ( $\chi^2$ ): 106.6587, p-value: < .00001

The results imply a significant difference between Southern and Northern respondents regarding the impact of health insurance on healthcare decisions. In the North, 307 respondents viewed their insurance positively against only 56 that presented a negative insight, while responses in the South were more evenly spread. The high Chi-square statistic and p-value confirm that this difference is highly statistically significant reflecting the differences in social security given the distinct administrative characteristics of the countries in the analysis.

❖ **Have financial constraints ever prevented you from seeking preventive healthcare services?**

Potential answers: Yes, No, Not sure

Language Groups Compared: Greek vs Others

Distribution for Greek: 91 (Yes), 37 (No), 8 (Not sure) (M=.397, SD=.885)

Distribution for Others: 300 (Yes), 359 (No), 115 (Not sure) (M=-.076, SD=.92)

Chi-square Statistic ( $\chi^2$ ): 38.0061, p-value: < .00001

The results imply a statistically significant difference between Greek respondents and others regarding whether financial constraints have restricted their seeking preventive healthcare. Greeks were more likely to answer "Yes" (91), whereas responses from other groups leaned more toward "No" (359). The Chi-square statistic and very low p-value indicate this difference is highly significant, pointing to potential financial barriers specific to the Greek population as they come from a more than 10-year recession that was followed by the pandemic and the inflation crisis.

❖ **How do employment-related factors, such as job stability and benefits, influence your preventive healthcare decisions?**

Potential answers: Importance scale (1 = Not at all influenced, 5 = Extremely influenced)

Language Groups Compared: Greek vs Others

Distribution for Greek: 6 (1), 7 (2), 28 (3), 39 (4), 54 (5) (M=3.955, SD=1.105)

Distribution for Others: 12(1), 39 (2), 447 (3), 173 (4), 91 (5) (M=3.383, SD=.82)

Chi-square Statistic ( $\chi^2$ ): 94.038, p-value: < .00001

The results imply a statistically significant difference between Greek respondents and others regarding how employment-related factors influence their preventive healthcare decisions. Greeks reported being more strongly influenced, with a higher mean value (3.955), compared to other language groups (3.383). The Chi-square statistic and p-value confirm that this difference is statistically significant, suggesting employment factors may play a more pronounced role in healthcare decisions for Greek population.

❖ **How accessible are low-cost or free community health resources in your area?**

Potential answers: Importance scale (1 = Not at all accessible, 5 = Highly accessible)

Language Groups Compared: South vs North

Distribution for South (i.e. Greek, Spanish, Italian): 35 (1), 47 (2), 49 (3), 26 (4), 17 (5) (M=2.672, SD=1.228)

Distribution for North (i.e. English, German, French, Dutch, Romanian, Lithuanian): 130 (1), 242 (2), 226 (3), 167 (4), 21 (5) (M=2.627, SD=1.072)

Chi-square Statistic ( $\chi^2$ ): 22.7031, p-value: .000145

The results imply a statistically significant difference in the perceived accessibility of low-cost or free community health resources between Southern and Northern language groups. While both regions reported similar mean values (2.672 for the South, 2.627 for the North), the Chi-square statistic of 22.7031 and p-value of .000145 indicate that the distribution in responses between the two groups is significant. The Northern respondents generally reported higher frequencies of "Not at all accessible" (130 for 1) compared to their Southern counterparts. This suggests that perceptions of accessibility in low-cost health resources may vary meaningfully between these regions, warranting attention for targeted strategies.

### Clinician Insights - Evaluating the perspective of healthcare providers

The clinicians participating in the survey acknowledged several barriers from their point of view holding patients back from adopting and maintaining healthy behaviors to a moderate extent (M=3.17, SD=.85). Mainly, their lack of knowledge about healthy choices (30.1%), their poor health literacy levels (24.1%) and their limited awareness on the impact of health recommendations (24.1%) were regarded as such barriers. Socio-cultural influences (22.9%) and motivational challenges (20.5%) considered as having analogous impacts, as their patients tend to rely on their social support networks for encouragement and assistance in their health journeys (M=3.56, SD=.99) while often let them influence their decisions regarding treatment (M=3.37, SD=.99).

In addition, healthy options being less accessible to individuals than the less healthy ones were as well recognized as a relevant barrier (20.5%). Social determinants including income, educational level, and living conditions were documented as influencing also individuals' health behaviors and choices (M=4.04, SD=.84). Corresponding were the effects of financial parameters as insurance coverage and affordability frequently hindered individuals' from seeking and maintaining healthcare services (M=3.65, SD=1.07).

Clinicians admitted discussing rather frequently the impact of potential barriers on the recommended lifestyle changes during consultations (M=3.38, SD=1.03); an approach their patients favor (M=3.3,



SD=1.04). From such discussions, individuals' lack of knowledge on healthy choices (37.7%) in conjunction with their low health literacy levels (36.4%), sociocultural influences (36.07%) and the motivational challenges they face (28.6%) emerged as the most prominent behavioral barriers they experience. Their joint effect might be grave, as according to the clinicians on the sample healthcare providers have restricted capacity to address and/or improve the health literacy levels of their patients given their relevant competencies ( $M=2.99$ ,  $SD=0.93$ ) along with cultural competencies to address properly their cultural backgrounds ( $M=2.93$ ,  $SD=0.82$ ).

Additionally, the lack of incentives towards healthier choices (44.3%), accessibility to healthy choices (37.18%), the limited infrastructure & programs to facilitate making activity choices more feasible (37.18%), and financial constraints (31.6%) appeared as the most potent structural obstacles. Among the barriers, the lack of technical developments to facilitate easy intake of healthier options (17.7%) and the lack of access to genetic testing for high risk of CRC groups (20.3%) were agreed upon as well. This finding is important considering half of the clinicians in the survey was in favor of prioritizing the development of such tools (20%) and pilot them to test their effectiveness (30%), while others appeared hesitant considering their efficacy (24%) and the maturity of circumstances to implement such interventions (20%).

#### Policy Makers' Perspectives - Considering the views of those shaping regulations

The policymakers taking part in the survey regarded the lack of knowledge about healthy choices (63.9%), social influences (61.1%) and poor health literacy levels (55.6%) as the primary behavioral barriers that affect individuals' health-related quality of life, especially in populations with CRC. Motivational challenges (38.9%) and accessibility of healthy options (38.9%) cast a significant effect, whilst cultural influences affect to a slightly lesser extent (36.1%). As they reported, the relevant standing policies currently address behavioral barriers, with their impact being evaluated through feedback from citizens (50%) and experts (53.1%). Particularly, they predominantly address the lack of knowledge on healthy choices (48.5%) and aim to improve citizens' health literacy levels (42.4%). They also target social influences (36.4%), strive to enhance the accessibility of healthy options (33.3%) and respond adequately to cultural influences (24.2%).

Regarding structural barriers, impediments to healthy choices are reported as the most significant issue (48.5%), while policy-makers also noted financial constraints (45.5%), accessibility of healthy options (45.5%), and lack of infrastructures and programs to facilitate active choices (45.5%) cast analogous impacts. Structural reforms target mainly the accessibility of healthy choices (35.5%), supporting decision-making towards them (29.03%) and providing infrastructures & programs for physical activity (29.03%). Financial constraints are addressed through relevant current policies at a lower level according to 1 out of 3 survey participants. However, it's important to note that the efficacy of these policies is assessed through collaborations with research institutions (59.4%), data analysis and evaluation (46.9%).

These results hold significant importance as the study participants admitted that evidence-based research (69.7%), health outcomes (60.6%), and accessibility (54.55%) are the criteria that guide their health-policy decisions. Cost effectiveness (51.52%) and patient satisfaction (51.52%) impact their decision-making process as collaborating with stakeholders (42.42%) and innovation & technology aspects (36.36%) are being influential to a lesser extent. Public opinion, legal & ethical considerations, and cultural sensitivity appear to affect them the least (21.2%).

Among the barriers they identified, the lack of technical developments to facilitate easy intake of healthier options (30.3%) and the lack of access to genetic testing for high risk of CRC groups (42.42%) were highlighted as well. This finding is important considering that despite being mostly open to innovative healthcare delivery models ( $M=3.91$ ,  $SD=.92$ ), 1 out of 3 policymakers in the study admitted that the standing policies address the lack of technical developments to facilitate the intake of healthier options as well as the reduced accessibility to genetic testing for risk groups. When asked about the usefulness of personalized interventions for CRC in the population more than half of the policymakers in the sample were in favor of it once its usefulness is validated through pilot studies (36%) and/or the required resources are available (28%). Yet, those willing to foster research and development (11%) or introduce such interventions via pilot programs (17%) represented smaller fractions of the sample.

The existing disease prevention and health promotion programs are utilized to a low to moderate extent with room for further significant improvement (72.7%) as their success is depended on their accessibility of the targeted populations (45.5%) and the health literacy levels of the specific groups (33.3%) according to the policymakers enrolled in the survey. A fraction of the sample doubts programs' effectiveness due to the barriers previously identified (21.2%), while others highlighted the necessities for adequate resources allocation (27.27%), active communication strategies (24.24%), intersectoral collaboration (21.21%) and educational awareness campaigns (18.18%).

Moving forward, it is imperative to have policies enhancing and raising public awareness about prevention, especially for CRC (78.8%), as well as investing in improving population's health literacy competencies (63.6%). Additionally, it's important to facilitate the access to health information through the proper digital platforms (51.5%), support the widespread mobile apps deployment (48.5%), and enhance the communication channels between healthcare providers and communities (48.5%), while providing resources in multiple languages to address relevant barriers (39.4%). Having better dietary profiles fostered through guidelines (39.4%) and promoting genetic testing (39.4%) need to be considered as well. Also, streamlining and simplifying the application processes for healthcare programs (33.3%), expanding the eligibility criteria (33.3%), creating judgment-free environments & reducing stigmatization (33.3%), and collaborating with community leaders to increase program visibility (27.3%) should be emphasized.

In this scope, policies promoting early detection (64.7%), ensuring equitable access to CRC preventive measures (52.9%), and enhancing health literacy competencies (50%) is critical to be prioritized. In addition, fostering patient-centered care (47.06%), involving community reach & educational programs (47.06%), and addressing environmental factors influencing CRC (44.1%) should be assessed as well. The policies incorporating holistic approaches to health & well-being (41.18%), as well as those integrating technological advancements for prevention (41.18%), and all that encourage research and innovation for prevention (35.3%) need also to take precedence. Finally, cultural competency training for healthcare professionals (26.47%) and accelerating collaboration between the public and private sector (23.5%) need also to take precedence should be taken into consideration.

Financial barriers should be addressed through Public-Private Partnerships (PPP) in the form of collaborative projects, synergies (41.18%), and joint funding opportunities (38.24%). However, developing supportive regulatory frameworks that encourage private investment in prevention (32.6%), improving communication & transparency between public /private stakeholders (32.6%), providing incentives for innovative approaches in healthcare economics models (32.6%), and



facilitating joint research efforts to identify cost-effective preventive option (29.4%) ought to be well-thought-out. Promoting awareness and education to both public and private sectors on the benefits of collaboration (26.47%), providing dietary guidelines in schools (35.3%) and occupational setting (26.47%), as well as aligning public policies to the economic goals of private entities could alleviate significant economic burden from citizens.

Key Takeaways

It becomes apparent that there are multiple factors influencing one’s healthy choices posing both behavioral and structural barriers to the adoption of positive and preventive health behaviors.

All three groups in our survey agreed on the potent effect of financial barriers that were recognized as the most significant structural barrier due to its numerous manifestations. Health insurance coverage, affordability of healthier choices, job stability, as well as work were identified as parameters hindering individuals’ from seeking preventive care. Additional structural barriers acknowledged involve the lack of incentives towards healthier choices and the scarcity of infrastructure and programs to facilitate making activity choices more feasible.

Especially for the citizens’ subgroup of the sample, further analysis of the data revealed statistically significant differences among the survey participants. Regarding health insurance, respondents from Northern Europe appeared more positively affected by their health insurance coverage. Particularly, Greek respondents were more likely to report financial constraints preventing them from seeking preventive healthcare while as well being more influenced by employment-related factors in their preventive healthcare decisions.

Table 8. Common Behavioral Barriers Validated by the Citizens (KPI-1.1a)

Behavioural Barriers	
Financial/Economic Constraints	Geographical Distance from Support Network
Accessibility to Healthy Options	Potential Stigma or Fear of Judgment
Limited Access to Healthcare Services	Limited Availability of Support Resources
Social Influences	Cultural Differences Impeding Communication
Lack of Knowledge about Healthy Choices	Financial Constraints Preventing Preventive Services
Lack of Time/Conflicting Schedules	Eligibility Criteria for Programs
Lack of Awareness of Support Resources	Complexity of Application Processes
Difficulty Expressing Health Concerns	Language Barriers
Geographical Distance from Support Network	Stigmatization

Accessibility was deemed as a critical factor for the adoption of preventive behaviors as identified barriers impair not only one’s ability to approach and make use of healthcare services, but also his/hers ability to make healthy choices, as they are frequently out-of-the-way when compared to the less healthy ones. A statistically significant difference in the perceived accessibility of low-cost or free community health resources was identified between Southern and Northern groups, with Northern respondents reporting higher frequencies of non-accessibility.

Knowledge and health literacy barriers emerged as prominent ones given how they impact individuals’ decision-making capacity. Individuals with poor health literacy levels present with limited awareness for preventive care and the impact of health recommendations. Their knowledge gap makes them more susceptible to social influences, cultural obstacles and motivational challenges. The repercussions caused in this case can be severe considering how persons rely on their social support networks, including their families, for encouragement & assistance, schedule regular check-ins with healthcare providers, and make decisions regarding treatment. As highlighted in the survey, the influence of online health forums and platforms is also critical in today’s context.

Table 9. Statistically Significant Inequalities (KPI- 1.3a)

Population	Inequality
Lithuanian Citizens	Level of awareness or understanding of preventive health measures
Southern Vs Northern	Impact of health insurance on healthcare decisions
Southern Vs Northern	Accessibility of free/low-cost community health resources
Greek Citizens	Preventive care influenced by financial constraints
Greek Citizens	Preventive care influences by work-related factors

Technological barriers also emerged as significant, with all study groups agreeing on the significance of the lack of technical developments that facilitate the easy intake of healthier options and access to genetic testing for high-risk CRC groups. However, clinicians appeared merely supportive of prioritizing the development of such tools and piloting them whereas policymakers appeared more concerned with resources availability and circumstances’ maturity for such endeavors.

As it was noted, the policies currently at place addressing barriers improve knowledge on healthy choices, while enhancing individuals’ health literacy levels. They also address socio-cultural influences, accessibility issues, and financial constraints to a lesser extent, indicating great room for improvements. The policies and programs, especially those targeting CRC prevention, is important to promote regular health check-ups and preventive screenings through the collaboration of health authorities, healthcare providers, and community leaders. This way, apart from increasing public awareness about prevention programs via making health information truly available and accessible, they could be able to tackle cultural influences and stigma. Nevertheless, if the participation criteria for preventive programs are not expanded and the application processes are not facilitated, individuals may be deterred again from participating.

Table 10. Behavioral Shift Strategies for CRC Prevention Programs (KPI- 1.1b)

Improve population health literacy		
Public awareness campaigns about the availability of prevention programs		
Partnerships between healthcare providers and community leaders to increase program visibility and accessibility		
Create judgment-free environments & reduce stigmatization		
Facilitate access to health information via digital platforms	and	facilitate the widespread use of mobile apps for health management

Develop dedicated community outreach & educational programs
Provide resources tailored to the characteristics of the targeted populations
Foster patient-centred care

## Qualitative Insights

### Focus Group Sessions

Within T2.4 we sought to have barriers, facilitators, and strategies for CRC primary prevention not only investigated but validated through rounds for discussions with experts as well. To this end, 6 focus groups as well as one workshop were organized and carried out by the task contributing partners. Details of all events are presented below in alphabetical order along with their results; common emerging themes, patterns, and trends are presented later in the chapter.

### EFPC



**Figure 9.** Instance of EFPC's Event on Sep. 17th, 2024

The European Forum for Primary Care organized a focus group session on September 17<sup>th</sup>, 2024, during their annual conference in Slovenia. The group joined 7 healthcare experts from Slovenia, Slovakia, and the Netherlands, who validated our previous acknowledged behavioral and structural barriers, adding cognitive biases as well as adherence challenges to them. Regarding the structural barriers, they addressed additional manifestations of the validated ones and in particular income inequality, employment stability, healthcare affordability, housing conditions, food insecurity, and transportation barriers. Additional barriers they identified were low education and health literacy levels, poor digital health literacy competencies, financial stresses relevant to the cost of healthy options, the sense of priority & importance one appoints to CRC prevention, the contemporary lifestyle, and the lack of time for properly mitigating those issues within patient-provider communication. Concerning patient-provider communication, they characterized it as inadequate and linked it to an extent to the lack of trust towards healthcare professionals.

Considering how critical patient-provider communication is, it was discussed that moving forward great focus should be given on individuals' preferences through the implementation of preference assessment tools to facilitate patient-centered care and support decision-making preferences. In addition, co-creation of health decisions and participation should be fostered, health education should be supported, and health literacy should be enhanced. It is crucial doctors undergo dedicated trainings

to be able to provide individual care to their patients in a way of engaging them in their care from the early intervention stages. Especially for lower socio-economic citizens, it's important to provide them healthy meal suggestions, reduce their preventive behaviors knowledge gap, and keep supporting them through follow-up consultations.

Supplementary ways to address the identified barriers would be through public awareness campaigns, communication campaigns endorsed by the governments, and social dialogues supported by different stakeholders. Health education in schools and sustainable programs that run through the course of one's lifetime could as well pose significant impacts. However, as individual care is very important house visits to individuals that require them, and stress relief initiatives ought to be established as well.

When the participants discussed to whom those policies should target mostly, they agreed upon undocumented migrants and those of the lower socio-economic levels, i.e., citizens with no employment stability or/and poor housing conditions, residing in communities with scarce resources, and poor/ no health insurance as they have limited or no access to screening. Besides, citizens with low educational level are identified as target populations for CRC preventions along with vulnerable and marginalized populations including the disabled, those living in care homes, prisoners, refugees & migrants and individuals without social support networks. Finally, participants labelled "ONCODIR", and "ONCOSCREEN" an EU funded project focusing on enhancing CRC screening through novel technologies, as two programs that address both behavioral and structural barriers for participating in CRC prevention interventions.

## ESDO

The European Society of Digestive Oncology organized a focus group session on October 14<sup>th</sup>, 2024, composed of 7 healthcare experts from their members. During their discussion, the barriers previously identified were validated while additional ones were voiced. Concerning behavioral barriers to CRC primary prevention, they recognized lack of interest & awareness, ones' asymptomatic status, fear of cancer, and embarrassment, while attributed culinary cultural influences as important as well. Regarding the structural barriers, they addressed additional manifestations of the validated ones and in particular taboos due to living in multicultural societies as well as lack of time to dedicate to preventive behaviors due to professional and/ or family obligations. In addition, they recognized geographic disparities and the low acceptance of colonoscopy to be deterring for individuals to uptake preventive behaviors. Also, they commented on the insufficient face-to-face communication with healthcare professionals, as well as the lack of cultural competence among healthcare professionals.

Having agreed on the patient-provider communication aspects requiring improvement, that were raised at the beginning of the EFPC focus group, participants studied additional ways of addressing the barriers mapped. Media and social media campaigns need to provide tailored information to the necessities of the different populations, not solely linguistically, but also with regards to the potential communication barriers generally and the equality promotion, while dedicated apps is important to be deployed. They also addressed how invitation schemes for prevention programs could be ameliorated to target more cultural barriers whilst facilitating participation.

In addition, co-creation of health decisions and participation should be promoted, health education should be endorsed, and health literacy should be upgraded. Doctors are indicated to attend special training programs for personalized health provision to their patients in a way of integrating them to

the preventive care from the early intervention stages. Especially for lower socio-economic citizens it's important to recommend them healthy meal suggestions, mitigate their preventive behaviors knowledge gap, and encourage them to follow-up consultations.

The focus group participants argued also regarding whom those policies should primarily target, highlighting the need to focus on individuals from lower socio-economic backgrounds and those facing significant language and cultural barriers, such as cultural minorities. At some stage in the discussion, two effective strategies for addressing CRC prevention barriers were brought into perspective; the sugar-tax policy in the United Kingdom and the dissemination of health information via comic strips in the Netherlands. Despite being no CRC-specific measures, these examples are promising ones. Eventually, the participants' final comment emphasizes that breaking down cultural, behavioral and socioeconomic barriers constitutes a major way forward in improving the uptake of preventive measures with established efficacy.



**Figure 10.** Illustrative picture from the ESDO session on Oct. 14th, 2024

## **EUREGHA**

The European Regional And Local Health Authorities organized two focus group sessions on September 18<sup>th</sup>, and October 4<sup>th</sup>, 2024, with five and six experts from their network of collaborators correspondingly. During those meetings, the behavioral barriers previously identified were validated while additional ones were identified. Particularly, it was argued that communication and cancer prevention campaigns are harder to implement due to the high level of stigma and fatalism towards cancer. In addition, youngsters' aversion to engage in preventive behaviors (especially males), low cancer awareness levels by those not affected by cancer before, and resistance to change were also highlighted.

Although cognitive biases were not validated as a barrier, predispositions such as the mentality of "not approaching prevention if healthy" and the tendency to succumb to alcohol consumption due to social norms were credited as contributing factors to negative health behaviors that hinder prevention.



Valuable points were raised regarding the influence of the perception that CRC is less of a severe threat when compared to other types of cancer, as well as the impact of prior experiences with the healthcare system; doctors significantly influence the willingness to engage in prevention.

Considering the structural barriers, it was pointed out that all the pre-identified ones were intertwined making prevention a long-term decision requiring long term vision at all levels, i.e., policy, individuals, etc. However, it was highlighted that potent barriers emerge from the GPs as it is depending on them to cast a positive effect on CRC prevention and testing to the individuals they interact with. An interesting point raised concerning structural barriers was how the disabled are deterred from participating in prevention programs, not only due to their physical limitations but also because health decisions are often made by third persons on their behalf.

Possible barriers, related to GPs' age and background, can be linked with the avoidance of digital solutions that could improve people's engagement in prevention. Moreover, most GPs are primarily involved in CRC treatment rather than prevention, indicating a radical change in their function within the health systems. Last but not least, structural barriers are posed by the distrust of citizens towards healthcare systems and providers, which is cultivated through social mass media, and individuals' inadequate follow-up behaviors, even in cases of free screening, due to lack of time, additional costs, etc.

To address those barriers, multi-level solutions are required. Prevention is important to be embedded in the daily life of people, to increase 'convenience' throughout the day incorporating preventive behaviors in activities people enjoy. Sports areas could be set up within office spaces and buildings while sport club memberships & welfare programs could be included in employment contracts or remuneration packages across all levels in both the public and private sectors, allowing employees free access.

As discussed prevention goes beyond the 'health service', therefore a shifting of focus towards a societal systemic issue is needed. Governmental policies can have a great impact on improving the general eco-system in which individuals make their choices, i.e., improving the basic quality of food, lowering sugars, fats, etc., through multidisciplinary collaboration. Living labs or other participatory approaches should be featured to better understand community needs and thus work on a better bottom-up co-created model to support preventive behaviors with significant community reach while GPs enjoy a redefined and incentivized role.

Ambassador programs can be very effective, but they should be tailored to the target population. Engaging with popular CRC 'champions' could increase outreach, while younger individuals should be included in prevention initiatives, as CRC cases among the 30-40 age groups are rising. According to the sessions' participants, it is important for future interventions to target the workforce and encourage them to invest in prevention while forming synergies with teachers, employers' associations, and key community leaders to enhance interventions' potential. Carers could also be a targeted group to ensure support prevention and access to screening for people with disabilities.

During both focus groups, participants presented different effective strategies for addressing those barriers from across Europe. In Spain, a labelling system for healthy "Mediterranean" restaurants is established while in Flanders' Ambassador programs for people with disabilities are at place. In Belgium, there are policies for providing additional remuneration to employees moving by bike with a corresponding city program in Forlì (Italy), where economic incentives are offered to employees

depending on the kms made by bike as tracked by a dedicated app. In addition, the yearly financial support offered by the government of Wales for buying healthy food options and milk, a levy on soft drink's industry to reduce the amount of added sugar in beverages, and the "Healthy Weight, Healthy Wales" initiative are highlighted. It is also stated that "4PCan" Project employs social sciences to support and promote primary cancer prevention.

Moreover, in terms of CRC specific strategies within the COPAC project in Bucharest, a partnership with military hospital was established and 340 events were created with community's support during the 3-year implementation of the project to enhance awareness and prevention. Finally, in Catalonia, diet & physical activity recommendations for CRC primary prevention were incorporated in the screening guidelines for individuals aged 50-69, while in Wales, the recommended age for initiating screening was lowered to 51 years.

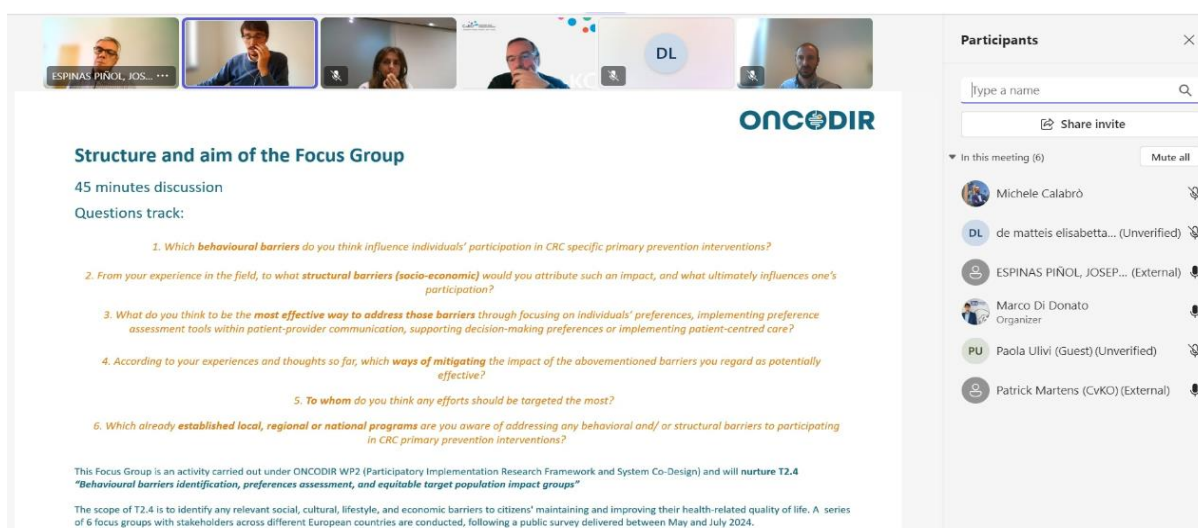


Figure 11. EUREGHA's workshop on Sept. 18th, 2024

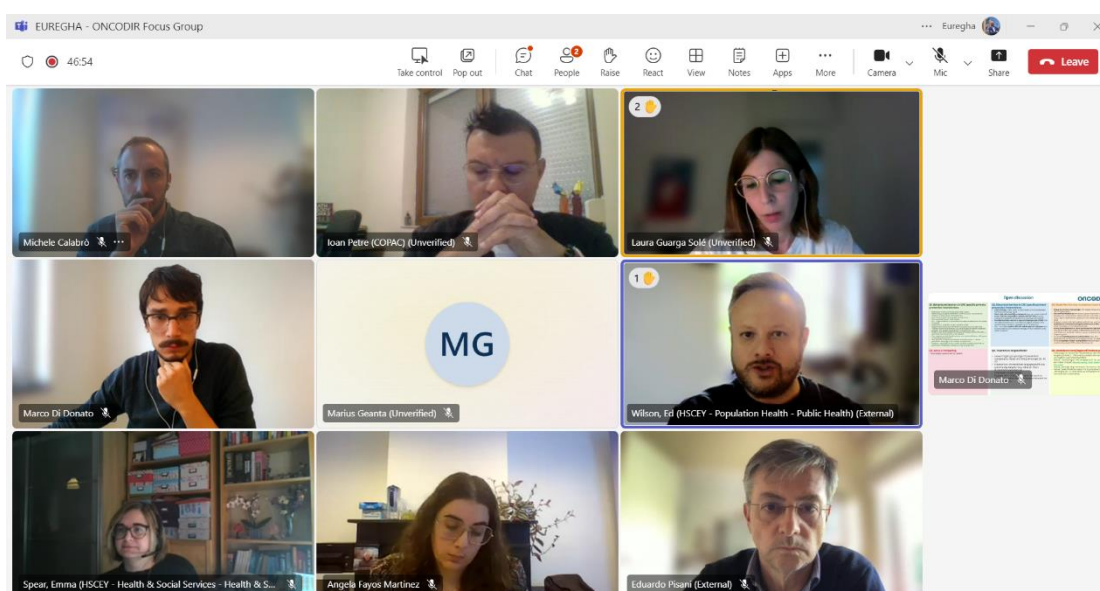


Figure 12. EUREGHA's workshop on Oct. 4th, 2024

## INCLIVA & URIOJA

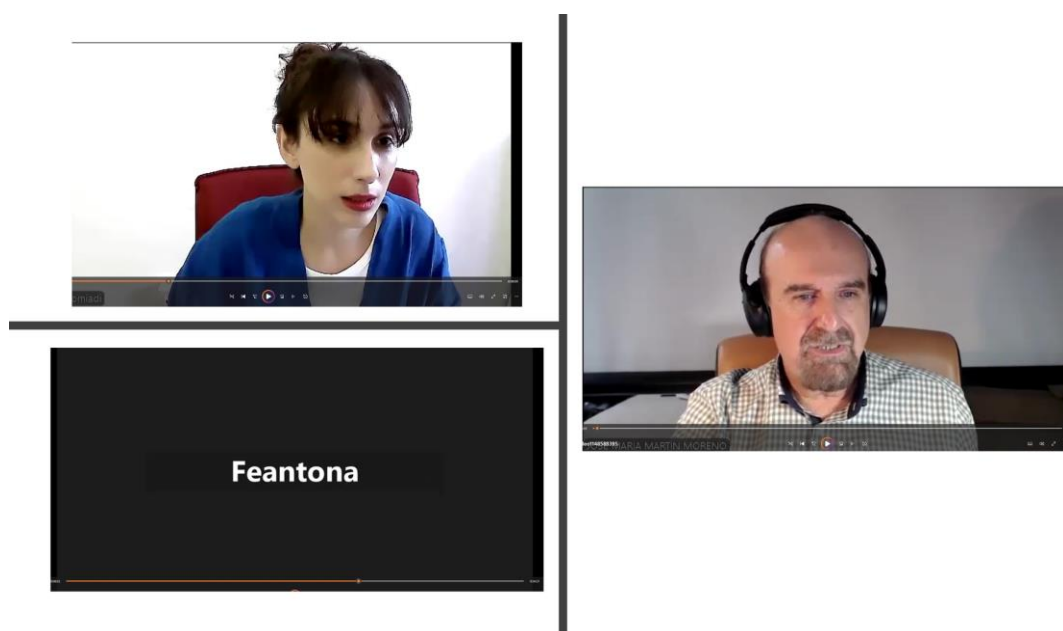
On October 15<sup>th</sup>, 2024, an online meeting with experts from the University of Rioja and Instituto de Investigación Sanitaria de Valencia was organized. The focus group was attended by 4 experts and was moderated by a MoHGR team member. Concerning behavioral barriers, they approached the ones identified previously (e.g. poor engagement to prevention, avoidance of casual testing, etc.) from a different perspective highlighting how the individuals' information behaviors, in conjunction with their health literacy levels, significantly impair how their ability to address the challenges they face in adopting and maintaining preventive behaviors, particularly given the influence of structural barriers.

Regarding the structural barriers, they addressed additional manifestations of the validated ones, particularly pointing to the geographic disparities, the accessibility of healthy options and their respective costs, as they also require mental resources apart from money and time. Additional structural barriers they identified were the lack of organizational health literacy, the poor mechanisms for collecting data relevant to primary prevention policies in order to provide evidence-based decisions, as well as the policy gaps related to how the prevention healthcare sub-system operates within and across countries along with the deficiency of specific standards. One point raised, however, underlined that prevention is not solely a responsibility of healthcare systems; it involves multiple stakeholders at a collective level across all levels of administration.

Considering facilitators, the ones discussed can be divided into three separate groups based on their level of implementation: local, regional, and national. At the local level, it's essential to be performed needs assessments to better understand the requirements of the targeted populations while attempting to incorporate prevention in the different aspects of their daily lives, i.e., schools, businesses, community centers, etc., and surpass any posed challenges such as lack of physical activity infrastructure, poor resources, low digital health information literacy skills, etc. At the regional level, all interventions are important to encompass educational aspects not only to appropriately enhance health education and CRC prevention awareness but also to fulfill sustainability potential. At the national level, the relevant policy gaps should be mapped and bridged in a way that facilitates synergies & partnerships among different public & private entities, enhances organizational health literacy, enables genetic testing, while ensuring the standards of preventive care.

It also became apparent during the discussion that prevention interventions ought to be offered to all society's members at the settings where they live, work, and interact in the most convenient way possible. Prevention is important to be more of an integral part of our lives than the whole of society partakes in it rather than a healthcare service. However, when dedicated interventions target specific population groups, they should be tailored to their needs. For example, in rural areas they have to address the lack of infrastructure apart from educating individuals or deploy apps to offer health-related services, making them truly accessible. In the end of the discussion, the NHS Preventive Program was presented as a promising strategy despite not being CRC specific as well as elements of the National Cancer Plans of different EU countries that could be regarded as insightful best practices. Nevertheless, data on implemented strategies are scarce due to the lack of monitoring & evaluation mechanisms.





**Figure 13.** Instance of the joined session (MoHGR moderation, INCLIVA and URIOJA) on Oct. 15th, 2024

### MoHGR

On October 17<sup>th</sup>, 2024, 6 executives of the Greek Ministry of Health with an average of 15 years working service for the Ministry, were invited to discuss from their perspective the barriers impeding individuals from engaging in CRC primary prevention interventions. They identified 3 critical behavioral parameters; cultural beliefs and predispositions that influence citizens' perception on CRC as reflected in the engagement & participation rates of previously implemented primary and secondary prevention interventions, lack of CRC prevention awareness as Greeks tend to link CRC prevention with cancer anxiety & fear, and poor health literacy levels that are echoed in individuals' unhealthy lifestyle choices including inadequate diet and lack of physical activity.

With respect to structural barriers, they agreed upon the lack of standing preventive policies, in conjunction with insufficient resources allocated to preventive care that hinder their outreach and effectiveness. Currently, geographic disparities and inaccessibility of preventive services are exacerbated due to the poor organizational health literacy levels and ineffective coordination of involved entities & stakeholders. Despite universal health coverage being granted for almost 10 years, accessibility of preventive services is significantly limited because of the out-of-pocket costs individuals are asked to pay for because of systemic inadequacies, i.e., transportation fees. In addition, the stigma associated with cancer prevention and screening is rather high, discouraging individuals from seeking preventive care.

Concerning facilitators, they identified different ones that should be employed separately depending on how they address the different barriers. It is crucial policymakers embrace and endorse CRC prevention as a priority linking it with a fully functional electronic health record that enables tracking persons with risk factors and facilitating the provision of individual preventive care. Financial incentives should be assigned to both individuals and healthcare providers to increase participation rates. Active involvement of doctors, nurses, and healthcare professionals in promoting CRC prevention is imperative to foster a supportive stigma-free environment that enables people to feel comfortable initiating, discussing, and maintaining positive health behaviors. In this scope, both community

outreach and patient education programs are required to raise awareness, instruct, and sustain any interventions offered.

Given the sociodemographic and epidemiological profiles of Greek residents, the focus group participants identified three population groups that ought to be prioritized for interventions' implementation. In the first group, they included those with a higher CRC risk, i.e. individuals over 50, those with a family history of CRC, adenomatous polyposis or hereditary nonpolyposis colorectal cancer, as well as those with inflammatory bowel disease or adenomatous polyps previously removed. In the second group, they placed the communities of migrants and refugees, both documented and undocumented, residing in Greece, while in the third group contains adults with lifestyle risk factors such as obesity, smoking, excessive alcohol consumption, and poor dietary habits.



**Figure 14.** Instance from the MoHGR session on Oct. 15th, 2024

## YCE

Youth Cancer Europe held a dedicated workshop within their 5-day long meeting in Cluj-Napoca, Romania, on August 9<sup>th</sup>, 2024. During this event, 42 cancer survivors from across Europe, and namely, from Austria, Belgium, Germany, Ireland, Lithuania, Macedonia, Moldova, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, and the UK, reflected on the structural & behaviors barriers and facilitators related to CRC primary prevention assisting us shed light on the issues at hand from their unique and invaluable perspective.

Concerning behavioral barriers, they predominantly recognized the effects of emotional & affective parameters ( $M=4.59$ ) as well as social norms ( $M=4.32$ ), attributing less impact on behavioral ( $M=3.51$ ) and health behavior obstacles ( $M=3.49$ ), habits & routines ( $M=3.35$ ), cognitive biases ( $M=2.89$ ), and adherence challenges ( $M=2.65$ ). During their discussion on behavioral barriers, many of the

aforementioned were revalidated, however, they addressed some new barriers. First of all, it is mentioned the lack of dedicated excellence centers, where individuals are treated with dignity, as this will make them feel more accepted, bending their innate resistance to change. The second barrier concerns those with a previous unresolved trauma related to cancer that deter them from engaging in preventive behaviors.

Regarding the structural barriers, there was a consensus about the socio-economical ones and the ones pertaining to the patient-provider relation. Yet, additional issues emerged from the open dialogue, including a lack of organizational health literacy, as practitioners often misdiagnose blood in feces as hemorrhoids in young adults. Other concerns included healthcare discrimination-linked to recession and various political-economic factors-and gender bias, as males more frequently constitute the primary target population for CRC prevention interventions.

Effective patient-provider communication was deemed the most potent facilitator for engagement to CRC primary prevention. The workshop participants were in favor of patient-centered care (M=2.82) where preferences assessment tools are implemented (M=2.62) to not only investigate individuals' preferences but also to support them appropriately in their decision-making processes, enhancing patient-professional collaboration. To this end, health education from a young age, integrated awareness campaigns, and sustainable relationships with one trusted healthcare professional are required. Schools should also cultivate preventive health behaviors through coordinated interventions including but not limited to healthy school lunches. The participants agreed that once a holistic approach to cancer is adopted, survivors need to be actively integrated in order to collaborate with doctors to support & promote prevention.

The workshop participants argued that as all lives matter, CRC primary prevention interventions should be targeted to all individuals as it can affect everyone. Conversely, with prioritization of said interventions in mind, they identified several groups that ought to receive support earlier than others. These groups involve vulnerable & marginalized populations, including rural populations, homeless and migrants, emphasizing those belonging to multiple minorities and those at higher risk due to known risk factors or CRC family history. Moreover, children, teenagers, young adults, people with learning disabilities and the neurodivergent should be prioritized. The traveling community and people consuming fast food rather frequently also need to be educated on how important mindful nutrition is. In the end of the session, the participants shared a few effective strategies for primary prevention including the Polish campaign "I plan the long life" and POLA's initiative of communicating survivors' stories through social media. With respect to CRC, facilitated screening strategies in Romania and Flanders were presented.



Figure 15. Instances from the YCE's workshop

### Patterns & Insights

During all group sessions various behavioral and structural barriers to CRC primary prevention, such as stigma, accessibility, income inequality, employment stability, healthcare affordability, housing conditions, food insecurity, and transportation were addressed. Among the commonly agreed identified challenges were cognitive biases, adherence issues, low health literacy levels, poor digital health literacy competencies, and inadequate patient-provider communication. Concerning behavioral barriers cultural beliefs, predispositions & biases, lack of CRC prevention awareness linked with cancer anxiety and fear, and poor health literacy levels leading to unhealthy lifestyle choices emerged as the most potent.

The highlighted structural barriers encompass geographic disparities, accessibility and cost of healthy options, lack of organizational health literacy, ineffective coordination among stakeholders, healthcare discrimination, and poor data collection mechanisms. Besides, the necessity for a societal systemic approach to prevention was emphasized, focusing on embedding preventive behaviors into daily activities. Structural barriers also concern the lack of dedicated excellence centers, inadequate patient-provider communication, and GPs' current role contributing predominantly to treatment rather than prevention. Inadequate preventive policies, insufficient resources, and inaccessibility of preventive services due to systemic inadequacies and out-of-pocket costs were widely recognized as well.

Table 11. Structural Barriers Validated During Focus Groups (KPI- 1.2a)

Barriers	
Political	Fragmented healthcare policies, bureaucratic obstacles, lack of political engagement, public health prioritization.
Economic	Insurance gaps, healthcare system funding, economic inequality, employment stability, unemployment, costly healthy lifestyle options.
Societal	Social isolation, community engagement, public perception, intergenerational attitudes, peer pressure.

Technological	Accessibility, healthcare IT systems, digital health literacy, telehealth adoption, cybersecurity concerns.
Legal	Legislative gaps, regulatory delays, employment laws, data privacy regulations, legal liability.

Proposals for addressing those barriers included setting up sports areas within office spaces, incorporating sport club memberships in employment contracts, and integrating welfare programs to work benefits & remuneration. Financial incentives as well as the active involvement of the school community were suggested as governmental policies apart from improving food quality, and making healthy options more accessible, need to foster multidisciplinary collaboration to enhance the overall impact. Living labs and participatory approaches to understand community needs and support preventive behaviors were proposed, alongside redefining GPs' roles and incentivizing their involvement in prevention.

With patient-provider communication being consistently identified as inadequate, the lack of effective communication is linked to a lack of trust towards healthcare professionals. Emphasis was also placed on improving communication by implementing preference assessment tools, fostering co-creation of health decisions, and supporting patient-centered care through dedicated training for doctors. This would help reduce the preventive behaviors knowledge gap, especially in lower socio-economic groups, and ensure ongoing support through follow-up consultations. In addition, financial incentives for healthcare providers are required to ensure the active involvement of healthcare professionals in promoting CRC prevention.

The discussions underscored the significant role that cultural and social factors impose on CRC prevention behaviors, such as cultural influences, generational taboos, and low levels of acceptance among more heavily influenced groups. The needs for culturally tailored information, leveraging media and social media campaigns, and improving invitation schemes for prevention programs in order to overcome cultural barriers were emphasized. Ambassador programs, customized to target populations and initiatives engaging younger age groups, were recommended.

Healthcare system challenges emerged, as well as the need for dedicated training for healthcare providers to enhance their ability to deliver individual care and engage patients from the early stages of intervention was validated. All groups agreed on the importance of collaborative health decision-making, while supporting health education and literacy. They also recognized the necessity of sustainable programs that extend throughout an individual's life and address specific needs, such as financial difficulties.

The identification of priority groups for CRC primary prevention interventions is challenging for all stakeholders, as their backgrounds and characteristics directly influence their perception to the needs of each population subgroup. The subgroups that have been assigned higher priority involve individuals with higher CRC risk profiles, such as migrants & refugees of all statuses, individuals with high lifestyle risk factors, vulnerable & marginalized populations including rural populations, homeless, minorities, prisoners, children, teenagers, young adults, people with learning disabilities, the disabled, the neurodivergent, and people without social support networks.

Table 12. Facilitators for enhancing the uptake of CRC prevention programs (KPI- 1.2b)

Facilitators
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Political	Strengthen collaboration between healthcare providers & community leaders, engagement of different stakeholders across societies, public health reforms, Public-Private-Partnerships, leverage of health data that are not currently available to policy makers, adaptation of evidence-based policy making, prioritize health outcomes & accessibility in decision-making processes, order cost-effectiveness & patient satisfaction in healthcare strategies, streamlining of bureaucratic processes, enhancement of organizational health literacy, introduction of supportive regulatory frameworks for private investments in prevention, implement policies addressing CRC environmental factors, promote policies enhancing public awareness on CRC prevention.
Economic	Insurance reforms, changes in healthcare system budgeting to ensure public health is prioritized adequately, financing/providing remuneration for healthy eating options, creation of safe spaces for physical activity at low/no cost, offering health programs at community level at low/ no costs, incentives for innovative approaches in healthcare economics models, financial incentives to healthcare professionals for more 1-to-1 primary prevention interventions, financial incentives to employers & business owners to incorporate prevention into their remuneration packages.
Societal	Introduce regular check-ins with healthcare providers through community programs, establish & ameliorate the impact of community outreach & outreach programs, address mental health alongside CRC prevention to reduce stigma & encourage participations, ensure cultural sensitivity in delivering healthcare services & information, provide cultural competency trainings to healthcare professionals, foster opportunities to cultivate family support, enhance communication between communities & healthcare providers, improve health literacy, deploy multilingual resources, offer early detection opportunities at low/no costs & ensure equitable access to preventive measures.
Technological	Expand the use of telemedicine, provide telehealth tools & support for healthcare providers to improve patient-provider communication, develop & implement comprehensive digital health platforms, deploy user-friendly mobile health applications, encourage the use of wearable health devices that support healthy behaviors, utilize EHR systems to inform decision-making (at societal level) & provide individual care, make use of digital information sources & improve individuals' digital health literacy competencies, create online health information portals/support the adoption of webinars, podcasts, online health forums for such purposes, offer educational programs for VR environments for maximum impact, develop accessible genetic testing to identify individuals at high risk on CRC and offer tailored preventive interventions at low/no costs.
Legal	Simplification of consent processes for prevention programs participation, ameliorate data privacy regulations, institute anti-discrimination health policies, establish regulatory reforms required for PPPs, expedite the processes of regulatory approvals, develop mandates for preventive healthcare benefits within employment laws, support & facilitate health policies implementation, introduce legal protections to reduce liability fear, raise awareness & offer incentives for partnerships between the public and private sector.

Key Insights

- o Addressing barriers is crucial for improving the uptake of preventive measures as implementing interventions designed to promote equality and provide targeted support for high-risk groups can lead to better health outcomes.
- o Effective communication campaigns, endorsed by governments and supported by various stakeholders, are necessary to raise public awareness about CRC prevention. These campaigns should provide tailored information to different populations, considering linguistic and cultural barriers.
- o Establishing community support groups, peer networks, and training community health workers can provide essential social support, particularly for lower socio-economic citizens. Stress relief initiatives and house visits for those in need can further enhance individual care.
- o Supporting health education in schools and promoting lifelong learning programs can have a significant impact on improving health literacy and preventive behaviors.
- o Prevention should be embedded in daily life activities to increase convenience and adherence. Sports areas in workplaces and sport club memberships in employment packages can facilitate this integration.
- o Tailored communication and prevention programs considering cultural and social norms are essential. Engaging community leaders and using culturally relevant materials can improve outreach and participation, especially among marginalized groups.
- o Addressing barriers requires collaboration across local, regional, and national levels. Needs assessments at the local level, educational interventions at the regional level, and policy adjustments at the national level can create a supportive ecosystem for CRC prevention through addressing structural barriers, including organizational health literacy and stakeholders’ coordination.
- o Emphasizing patient preferences and engaging them in decision-making through preference assessment tools can significantly enhance patient-centered care. This approach is crucial for building trust and improving adherence to preventive measures.
- o Improving communication and trust between patients and healthcare providers is critical for enhancing engagement in CRC preventive behaviors. This includes training healthcare providers in effective communication and empathy and establishing patient advisory councils.
- o Targeted interventions, addressing geographic and economic disparities and ensuring accessibility of healthy options, are crucial for effective prevention. Special attention should be given to vulnerable and marginalized populations to ensure equitable access to CRC preventive measures. This includes targeted interventions and support for individuals with higher CRC risk due to genetic or lifestyle factors.
- o Best practices of strategies implemented across Europe that could be, if not already applied to CRC primary prevention include Spain’s healthy restaurant labelling system, Belgium’s remuneration policies for cycling employees, Wales’s financial support for healthy food, the sugar-tax policy in the UK, and the use of comic strips for health information in the Netherlands.

Table 13. Strategies for Inequalities Removal (KPI- 1.3b)

Field of Identified Inequality	Strategy
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Awareness	Dissemination of health information as comic strips in the Netherlands, the COPAC project in Bucharest for enhancing awareness & prevention, the labelling system for healthy restaurants in Spain, the ambassadors' program for people with disabilities in Flanders, the Polish campaign "I plan the long life".
Accessibility of community health resources	The "Healthy Weight, Healthy Wales" initiative, the NHS Preventive Program.
Financial Barriers	Remuneration policies for employees moving by bike in Belgium & Forlì (Italy), annual financial support offered by the government of Wales for buying healthy food options and milk.

### 4.3 Integrated Analysis & Comparative Discussion

Through the international survey and the focus group/ workshop sessions involving healthcare experts, policymakers, and citizens the detailed analysis conducted identified common barriers, effective facilitators, population groups in need for interventions, and efficient strategies already implemented. One valid conclusion drawn is that the complexity of CRC primary prevention requires a holistic approach with integrated and comprehensive policies to overcome the various barriers. The obtained insights provide a robust foundation for developing actionable strategies aimed at enhancing CRC primary prevention efforts, whilst easily being able to accommodate needs pertaining to secondary prevention as well. This section summarizes the results of cross-group comparisons, while presenting emerging patterns & contradictions, and discusses implications and recommendations for properly addressing the identified barriers.

#### Cross-Group Comparisons

Concerning the perspectives of healthcare experts, policymakers, and citizens, including cancer survivors, several common behavioral and structural barriers to CRC primary prevention emerged. These barriers entail stigma & fear associated with cancer, low health literacy, and inadequate patient-provider communication. Although some groups stressed the importance of cognitive biases in shaping health behaviors, others did not view them as a significant barrier.

Financial constraints, accessibility issues, and cultural influences were consistently highlighted as the most prominent structural barriers. Across all groups, tailored communication, financial incentives, expansion/development of community outreach programs, and extensive development of digital health solutions were recognized as key facilitators moving forward. Genetic testing came across as a controversial field despite the consensus on its usability and benefits due to resistance to change. Analogous were the attitudes towards innovative financial schemes and healthcare budgeting, though it was not discussed to the same extent.

Differences were noted in the prioritization of target population group. Besides, various stakeholders emphasizing high-risk individuals, marginalized populations, and those with low socio-economic status, as those in need of being highly prioritized, it was agreed that "a whole-of-society" approach is imperative for effective prevention programs that target all settings in which individuals live and work. The perceptions on the role of healthcare providers, especially GPs, varied across groups. Some emphasized the need for enhanced training, whereas others focused primarily on integrating digital solutions to individualize and facilitate preventive care.

Policy priorities also diverged, reflecting the need to organizational health literacy improvements, requirements for making healthy options accessible to citizens, and public-private partnerships promotion. Community programs received mixed reviews, having some stakeholders advocating for their effectiveness and others questioning their impact.

### Emerging Patterns and Contradictions

Common patterns included the universal recognition of barriers such as stigma, financial constraints, and accessibility issues, the imperative need for improving patient-provider communication, enhancing cultural sensitivity, as well as cultivating health literacy and cultural competencies. The role of financial incentives emerged as a common facilitator, but there were differentiated views on their effectiveness. Some stakeholders expected that financial incentives could significantly increase participation in preventive measures, while others were skeptical about their long-term impact.

The importance of social support networks and family involvement in encouraging positive health behaviors was universally acknowledged. Nevertheless, the extent to which these factors can be addressed and should be prioritized varied significantly among groups, given their different sociocultural backgrounds.

The main prominent contradictions emerged concern the importance placed on cognitive biases and how much they affect health behavior, the effectiveness of community programs, and digital solutions'/genetic testing acceptance. While some groups emphasized the need for cognitive bias mitigation and tailored community programs, others saw them as less critical or didn't acknowledge them at all. Similarly, digital health literacy and telemedicine received mixed reactions, showing some stakeholders advocating for their expansion and others highlighting resistance to their adoption. Genetic testing received the most opposed views across and within groups; even those in favor of it, were not positive in adopting this solution.

### Implications & Recommendations

To enhance CRC primary prevention, several policy initiatives are recommended. Firstly, improving health literacy across societies and healthcare budget re-establishments are crucial. Training healthcare providers in cultural competence and provision of patient-centered care can build trust and improve preventive behaviors, while embracing telemedicine, digital health platforms, and mobile health apps, supported by digital literacy training, can update prevention efforts. Community engagement through outreach and educational programs, leveraging community leaders, and organizing culturally tailored communication campaigns would tremendously support participation. Moreover, the streamlining of bureaucratic application processes and the expansion of eligibility criteria are necessary as well.

Integrating preventive measures into daily activities, such as embedding wellness programs in workplaces, building safe spaces for physical activity, and establishing school programs is essential. Strengthening public-private partnerships, increasing resource allocation, and adopting holistic health approaches can further support these initiatives. Robust monitoring and evaluation mechanisms are necessary to assess effectiveness and make data-driven adjustments. Ensuring all strategies are inclusive and target vulnerable and marginalized populations is paramount to equitable access to preventive care.

To sum up, indicative policy enhancements should include but not be limited to:

- o Development of comprehensive policies that integrate the strengthening of health literacy and offer financial incentives through community engagement.
- o Implementation of long-term strategies to sustain prevention efforts and monitor their progress.
- o Facilitation of public-private partnerships to leverage resources and expertise for preventive care.
- o Provision of ongoing training for healthcare providers in cultural competence and provision of patient-centered care.
- o Promotion of digital literacy and digital health information literacy among healthcare professionals and patients.
- o Implementation of educational programs in schools and communities to raise awareness about CRC prevention and promote healthy behaviors.
- o Expansion of telemedicine services to increase access to preventive care, especially in remote areas, communities with poor resources, or among vulnerable populations.
- o Development of digital health platforms and mobile apps to provide personalized preventive care and disseminate accurate health information.
- o Utilization of AI and machine learning to analyze patient data and provide tailored preventive interventions as well as inform evidence-based policy making.
- o Strengthen community outreach programs to educate and support individuals in CRC prevention.
- o Engagement of community leaders and culturally relevant ambassadors to improve outreach and participation.
- o Creation of safe spaces and wellness programs in workplaces to integrate preventive behaviors into daily activities.
- o Increase funding for preventive care programs and ensure resource allocation aligns with identified needs.
- o Foster collaboration between public and private sectors to enhance the effectiveness of prevention efforts.
- o Encourage interdisciplinary approaches to address the multifaceted nature of CRC prevention barriers.
- o Incorporate holistic health approaches that address environmental, mental, and physical health issues.
- o Promotion of policies that support healthy dietary guidelines and genetic testing for individuals with increased cancer risk.
- o Address social determinants of health, such as housing conditions and food insecurity, to create a supportive environment for preventive behaviors.
- o Implement robust monitoring and evaluation mechanisms to assess the impact of preventive programs.
- o Ensure transparency and accountability in the implementation of policies and programs.
- o Ensure that all prevention strategies are inclusive and target vulnerable and marginalized populations.
- o Design, implement & monitor tailored interventions to address the specific needs of high-risk groups, such as individuals with low socio-economic status, migrants, and refugees.

- o Reduce stigmatization and create judgment-free environments to encourage participation in preventive measures.

#### 4.4 Next steps

Moving forward is important to ensure that attention to CRC primary prevention is continuously given through the conduction of longitudinal studies to evaluate the effectiveness of interventions as well as provide invaluable insights regarding their sustainability. Considering all that has been previously presented, a wide range of population groups need to partake in longitudinal and implementation research endeavors to assist experts in identifying the appropriate interventions for the different population groups affected by CRC. Behavioral insights are required as well to shed light on the actual aspects of cognitive biases, social influences, and motivational challenges while all future research studies need to take into consideration novel technological solutions including genetic tests and mobile health apps to support their contributions to CRC prevention.

Before designing and implementing new policies, needs assessments and policy impact assessments are required to adequately cater to individual's needs. Outreach community programs and community-based interventions should be promoted in all policies addressing primary prevention to ensure accessibility and participation. Meanwhile, school and workplace initiatives are important for smoothly integrating CRC prevention in peoples' daily lives. The dissemination of future awareness, informational, and educational campaigns ought to take advantage of the diverse mass media platforms comprehensively while addressing the different cultural, linguistic, and social needs of the distinct groups. Telemedicine, mobile health apps, online health platforms, and AI solutions should be embraced and supported as they can guarantee the provision of accessible, equitable, and personalized preventive care. Finally, the introduction of financial incentives will lower the economic barriers and encourage participation in CRC screening and preventive measures from both stakeholders and beneficiaries.

Despite aiming to reduce the limitations and biases of our study to a significant extent, several of them should be examined through future corresponding projects. Larger-scale studies, that also adopt a mixed-methods approach, are needed to investigate the effects of barriers and facilitators to more extensive and diversified samples. Those studies is important to incorporate follow-up elements that our study lacked due to time constraints, as well as standardized evaluation metrics to systematically assess the effectiveness of CRC prevention interventions, if such efficacy assessments lie within their scope.

In conclusion, addressing the multifaceted barriers to CRC primary prevention requires a holistic approach that entangles government's engagement in it and runs through all facets of society. The insights gained from our discussions underline the necessity of policy enhancements, technological advancements, community engagement, and tailored interventions. By improving health & organizational health literacy, providing financial incentives, embracing digital health solutions, and fostering patient-centered care, we can significantly enhance CRC prevention efforts. Ensuring inclusivity and equity in these strategies is paramount for achieving better health outcomes across diverse populations. With research, monitoring, and evidence-based interventions, progress on CRC primary prevention will be sustained. To this end, collaborative efforts and commitment to innovation & inclusivity are cornerstones for truly reducing the burden of colorectal cancer and improve public health.

## 5 Conclusions

The collective insights gained from the various tasks undertaken within the ONCODIR project have significantly contributed to shaping the foundation of this initiative. Through the systematic gathering and analysis of user requirements, the comprehensive literature review, and the identification of barriers to effective health interventions, we have established a robust framework that not only addresses the current landscape of cancer prevention and control but also sets the stage for future developments.

The user requirements sessions have facilitated meaningful engagement with stakeholders, allowing us to capture diverse perspectives and needs. This collaborative approach has ensured that the tools being developed are not only technically sound but also user-centered, aligning closely with the expectations of healthcare professionals, policy-makers, and citizens alike. The feedback collected during these sessions will serve as a guiding light as we refine our tools to enhance their usability and effectiveness in real-world settings.

Moreover, the literature review and meta-analysis of colorectal cancer incidence factors have provided critical insights into the complexities surrounding cancer prevention. By identifying risk factors, we can better inform the design of our interventions, ensuring they are grounded in evidence-based practices. This analysis is vital for understanding the nuanced challenges that various populations face, thereby allowing us to tailor our solutions accordingly.

Additionally, the identification of barriers to health interventions has illuminated the social and economic dynamics that impact health-related quality of life. By addressing these barriers head-on, we can develop tools that not only meet technical requirements but also resonate with the lived experiences of users. This holistic approach is essential for fostering engagement and ensuring the sustained effectiveness of our initiatives.

In conclusion, the tasks carried out thus far have laid a solid foundation for the ONCODIR project, equipping us with the necessary insights and strategies to move forward confidently. As we continue to build on this groundwork, we are committed to ensuring that our tools remain responsive to user needs and contribute effectively to advancing cancer prevention and control efforts across diverse populations. The journey ahead promises to be both challenging and rewarding, and we look forward to leveraging these foundational insights to drive impactful outcomes in the realm of public health.

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## Annexes

Annex Number	Title	Description	Document Format
Annex A	Agenda for Online Consortium User Requirements Session 30.11.2023	Agenda for the online consortium session on user requirements	PDF
Annex B	Updated Agenda and Details for Online Consortium User Requirements Session 30.11.2023	Revised agenda and details for the online consortium session	PDF
Annex C	Document for Collection of Consortium User Requirements	Form for collecting user requirements from consortium members	Excel Spreadsheet Document
Annex D	ONCODIR Basic Tool Descriptions to Support T2.1 and User Requirements Session	Basic tool descriptions to support Task 2.1 and user requirements session	Word Document
Annex E	Agenda for Clinician External Stakeholder User Requirement Session 18.12.2023	Agenda for clinician stakeholder session on user requirements	PDF
Annex F	Agenda for Policy-Maker External Stakeholder User Requirement Session 18.12.2023	Agenda for policy-maker stakeholder session on user requirements	PDF
Annex G	MoHGR - User Requirements for DELI (Policy-makers) 18.12.2023	User requirements document for DELI from the Ministry of Health (policy-makers)	
Annex H	Document for Collection of Consortium User Requirements 23-24.01.2024	Form for collecting user requirements during consortium sessions	Excel Spreadsheet Document
Annex I	Comprehensive Guide to the User Requirements Workshop 01-02.07.2024	Detailed guide for the User Requirements Workshop	PDF
Annex J	Document for Collection of Consortium User Requirements 01-02.07.2024	Form for collecting user requirements during the workshop	Excel Spreadsheet Document
Annex K	NELI ESUS Session Agenda and Structure Guide 22.10.2024	Agenda and structure guide for the NELI ESUS session	Word Document

Annex L	Document of Feedback of External Stakeholders User Requirements Session for Citizens Tool NELI 22.10.2024	Feedback document for external stakeholders' session on the Citizens Tool NELI	Excel Spreadsheet Document
Annex M	DELI ESUS Session Agenda and Structure Guide 06.11.2024	Agenda and structure guide for the DELI ESUS session	Word Document
Annex N	Document of Feedback of External Stakeholders User Requirements Session for Citizens Tool DELI 06.11.2024 (EUREGHA report)	Collected responses from the survey shared with the External Stakeholders that participated in the session	PDF

## Annex A



Annex A\_ Agenda for  
Online Consortium Us

## Annex B



Annex B\_ Updated  
Agenda and Details for

## Annex C



Annex C\_ Document  
for Collection of Cons

## Annex D



Annex D\_ ONCODIR  
Basic Tool Description

## Annex E



Annex E\_ Agenda for  
Clinician External Stakeholders

## Annex F



Annex F\_ Agenda for  
Policy-Maker External Stakeholders

## Annex G



Annex G\_ MoHGR -  
User Requirements for Clinicians

## Annex H



Annex H\_ Document  
for Collection of Consents

## Annex I



Annex I\_ Comprehensive guide  
to the use of the ONCODIR platform

## Annex J



Annex J\_ Document  
for Collection of Consents

## Annex K



Annex K\_ NELI ESUS  
Session Agenda and ?

## Annex L



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of Feedback of Extern

## Annex M



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## Annex N



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