



**ELISA**

*European Linkage of Initiative  
from Science to Action in Health*

# DELIVERABLE

## 3.4

### REPORT ON LIFESTYLE RISK FACTORS

#### VERSION V. 1

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## VERSION CONTROL SHEET

### [1] PROJECT SUMMARY

|                 |                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------|
| Project acronym | ELISAH                                                                                                   |
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### [2] DOCUMENT CONTROL

|                              |                                                                                                                                        |
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|----------|------------|--------|----------|
|          |            |        |          |
|          |            |        |          |

## DISCLAIMER

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## ABBREVIATIONS

|                |                                                                           |
|----------------|---------------------------------------------------------------------------|
| <b>1st Qu.</b> | First quartile                                                            |
| <b>3rd Qu.</b> | Third quartile                                                            |
| <b>ADA</b>     | American Diabetes Association                                             |
| <b>ALT</b>     | Serum alanine aminotransferase                                            |
| <b>AST</b>     | Aspartate transaminase                                                    |
| <b>BC</b>      | Breast cancer                                                             |
| <b>BMI</b>     | Body mass index                                                           |
| <b>C-RP</b>    | C-reactive protein                                                        |
| <b>CI</b>      | Confidence intervals                                                      |
| <b>EU</b>      | European Union                                                            |
| <b>GGT</b>     | Gamma-glutamyl transferase                                                |
| <b>HDL</b>     | High-density lipoprotein                                                  |
| <b>HR</b>      | Hazard ratio                                                              |
| <b>IARC</b>    | International Agency for Research on Cancer                               |
| <b>ICD-O-3</b> | International Classification of Diseases for Oncology, Third Edition      |
| <b>LDL</b>     | Low-density lipoprotein                                                   |
| <b>MAX</b>     | Maximum value                                                             |
| <b>MCV</b>     | Mean corpuscular volume                                                   |
| <b>MIN</b>     | Minimum value                                                             |
| <b>NCI</b>     | National Cancer Institute                                                 |
| <b>TNM</b>     | Tumour-Node-Metastasis, Classification of Malignant Tumours Sixth Edition |
| <b>US</b>      | United States                                                             |
| <b>WHO</b>     | World Health Organization                                                 |

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## EXECUTIVE SUMMARY

**Objectives:** Overweight and alcohol consumption are associated with the development of breast cancer and tobacco smoking is strongly suspected to favour the onset of the disease. The prevalence of these risk factors is well known in the European population but little information is available on their presence in women with a breast cancer diagnosis. One of the aims of the ELISAH project was to assess the prevalence of these risk factors in Greece, Italy and Spain and to compute overall survival figures relative to these factors.

**Methods:** We collected cases from the pilot breast cancer registry of the Attica region in Greece developed by the ELISAH project, from the cancer registries of the Basilicata region and of the Palermo province in Italy, and the Tarragona province in Spain. Data on overweight, alcohol and tobacco use, and fasting glucose and cholesterol levels were collected by cancer registry personnel via direct consultation of clinical records. The prevalence of exposure to risk factors was computed and Cox proportional hazard models were used to evaluate mortality hazards based on risk factors.

**Results:** Information was collected for 2622 women with a BC diagnosis. Considering all cases but null values, the share of overweight women was 60%, the share of drinkers was 5.9%, the share of smokers was 18.6%, and the share of women with elevated blood glucose (ADA criteria,  $\geq 100$  mg/dL) was 57%.

The all-cause mortality hazard for fasting glucose was 1.06 (1.02-1.10) per increase of 5 mg/dL for women with BMI below 22.5 kg/m<sup>2</sup> and 1.03 (1.01-1.05) per increase of 5 mg/dL for women with BMI above 22.5 kg/m<sup>2</sup>. BMI showed a non-linear association with mortality hazard.

**Conclusion:** This pilot study supports the feasibility and importance for cancer registries collecting information, also on a sampling basis, about behavioural risk factors. The results highlight the need for hospital and community-based interventions to reduce population exposure to these risk factors.

## 1. INTRODUCTION

This deliverable is dedicated to the assessment of BMI, fasting glucose, and alcohol and tobacco use in women with a breast cancer (BC) diagnosis and to the computation of mortality risks due to exposure to these risk factors.

Previous systematic reviews and meta-analyses have shown that overweight and obesity before or shortly after a diagnosis of BC [1] [2] are associated with higher risks of all-cause, cancer-specific mortality and recurrence. The share of overweight individuals from the general population aged 16 years or over in the EU varied in 2022 between 31.3% in Italy and 56.7% in Latvia for females and between 51.5% in France and 69.4% in Croatia, Malta and Slovakia for males [3]. Among females aged 15 years and over, the share of daily smokers in the EU in 2019 ranged from 6.7% in Iceland to 25.3% in Serbia.

Studies showed that smoking before or after a BC diagnosis was associated with a higher mortality from BC and several other causes [4]. Smoking cessation support in cancer patients has been recognized as an essential component of cancer care by the US National Cancer Institute (NCI) [5], and the NCI launched an implementation science nationwide effort as part of the Cancer Moonshot to help people undergoing treatment for cancer to quit smoking.

In 2019, 29.9% of the EU female population aged 15 and over reported having at least one alcoholic drink every week [6]. In Europe 40 000 new BC cases occurring in the female population were considered due to alcohol according to IARC [7]. In a recent meta-analysis, alcohol consumption was identified as a significant factor influencing BC recurrence [8].

The combination of a high prevalence of overweight, high fasting glucose, and use of tobacco and alcohol in the European population and the association of these risk factors with wors BC outcomes, prompted ELISAH researchers to plan gap analysis and intervention studies. This document is primarily related to gap analysis. No other European studies have reported on the prevalence of exposure to these risk factors in women diagnosed with BC, limiting the opportunity to highlight the need for interventions. The ELISAH project aims to link gap analysis and interventions to enhance BC prevention in this case tertiary prevention. For this reason, we evaluated interventions that target BMI and address a spectrum of risk factors, many of them focusing mostly on the metabolic syndrome, which is associated with five risk factors: abdominal obesity, high blood pressure, high fasting glucose, high serum triglycerides, and low serum high-density lipoprotein.

Studies have shown that women with metabolic syndrome were at a higher risk of developing BC, and their prognosis following a BC diagnosis tended to be poorer [9]. We collected additional information to be as close as possible to the intervention studies to which we wanted to link our gap analysis. Given that two studies in Europe and one in the United States found an association between fasting glucose levels and mortality in cohorts of women with a BC [10] [11] [12], we used blood tests to collect fasting glucose levels along with other selected metabolic values.

Taking into account all these considerations, we designed this study with the following aims.

- Assess the knowledge gaps in exposure of women with a BC diagnosis to overweight and obesity, as measured by BMI; to alcohol consumption and smoking; and to metabolic alterations such as high values of fasting glucose and abnormal lipid levels.
- Determine the hazard of death based on BMI, alcohol, smoking and fasting glucose.

The results of the study may be useful to plan primary and tertiary prevention interventions. Because of ELISAH's public health design the results of WP3 are linked to the interventions outlined by WP4.

## 2. CONTENT



Figure 1: Study area and participating institutions.

### Breast cancer cases

We performed a retrospective study on a cohort of women diagnosed with primary BC. The cases were archived by the population-based cancer registries participating in the ELISAH call for data-specific tasks: Attica (Greece), Basilicata and Palermo (Italy), and Tarragona (Spain). A search using site code C50 and malignant epithelial morphology codes M8000 to M8575 of the International Classification of Diseases for Oncology (ICDO-3) [13] retrieved a total of 2622 primary BC cases diagnosed in the predetermined study period (2019-2021). For the development of task T3.4, aiming to describe both risk factor prevalence and mortality hazards in a recent period and giving us the possibility to compute survival for at least three years from diagnosis, we selected cases diagnosed in the interval period from 2019 to 2021. Disease stage was as specified by the TNM classification of malignant tumours (6th edition, 2002) [14]. We collected cases from cancer registries in compliance with privacy legislation, classifying morphology into three broad ICDO-3 categories:

- ductal BCs, code 8500;
- lobular BCs, code 8520;
- others in the range not included in the first two.

Similarly, we classified age into three classes: 0-49, 50-69, and 70+; or, when necessary, into two classes: 0-49 and 50+, assuming a pre- and post-menopausal subdivision.

## Collection of exposure variables

Each participating cancer registry accessed patients' clinical records to collect information on the following variables: body weight and height, BMI, smoking status, number of traditional cigarettes smoked every day, how many years a woman had smoked, alcohol use, how many alcoholic drinks per week, how many years a woman had drunk. The following clinical test results were also collected at BC diagnosis (or as near as possible): fasting blood glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, c-reactive protein (C-RP), gamma-glutamyl transferase (GGT), aspartate transaminase (AST), serum alanine aminotransferase (ALT) and mean corpuscular volume (MCV) as a proxy for alcohol consumption. Information collection followed the ELISAH Task 3.4 protocol. The dates associated with the information were recorded; for example, if the smoking habit was documented in a clinical record, the cancer registry personnel collecting the information for ELISAH recorded the dates of the clinical record compilation in accordance with protocol rules. We also collected compilation dates for comparison with the BC diagnosis date in order to identify potential bias resulting from an extended time interval between the diagnosis and the variables reported in the clinical records [15].

Initially, we collected body weight and height to calculate BMI. Where these were absent from the clinical record, we obtained BMI categorized as follows:

- underweight  $< 18.5 \text{ kg/m}^2$
- normal weight  $18.5 \text{ to } < 25 \text{ kg/m}^2$
- overweight  $25.0 \text{ to } < 30 \text{ kg/m}^2$
- obesity  $\geq 30 \text{ kg/m}^2$

Smoking status was classified in this way:

- never smoker
- former smoker
- current smoker (if a person smoked at least one cigarette per day)
- occasional smoker (if a person did not smoke every day but smoked sometimes)

Drinking categories were defined as:

- never drinker
- former drinker
- current drinker (more than a drink per week)
- occasional drinker (up to one drink per week)

## Statistical analysis

We computed the percentage of women according to the categorization we defined for every variable. Associations between patient variables were analysed using the chi-square test, and Spearman and Kendall rank correlation coefficients were determined to examine correlations between selected variables. The study end-point was all-cause mortality. The Kaplan-Meier method was used to visualize the effects of variables on endpoints. Cox proportional hazard modelling was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for all-cause death according to study variable, adjusting by age and stage and stratifying by region of residence. Time to an event or end of follow-up was calculated from the date of diagnosis. Patients alive at the study end were censored. Patients lost to follow-up were censored at the date of loss to follow-up. Cases with missing data (missing disease stage and tumour grade) were assigned to 'not specified' categories in the analyses. We introduced in the model BMI, fasting glucose, triglycerides and LDL cholesterol as continuous variables, and smoking habits and alcohol use as categorical variables. We first tested the functional form of continuous variables by plotting the martingale residuals and superimposing a scatterplot smoother. We also performed additional analyses introducing a restricted cubic spline function to evaluate non-linear associations. The proportional hazards assumption was tested by analysis of scaled Schoenfeld residuals, with p values for each variable estimated. When the hazard for a variable was suspected to be non-proportional over time, we performed additional analyses, substituting the conventional Cox model  $\beta$  coefficient (for a given variable) with a time-dependent function  $\beta(t)$  obtained by adding the smoothed scaled Schoenfeld residuals to the conventional  $\beta$  coefficient [16]. The results were evaluated as suggested by Bellera *et al.* [17]. The analyses were performed using the R statistical package [18].

## Process indicators

To monitor the quality of the data used and produced by us, we defined some indicators based on the percentage of null values for the collected data. The main indicator, percentage of BMI, is directly included in the ELISAH proposal: the percentage of BC cases for which BMI is available must be greater than 75%. The following tables show the percentages of non-null data broken down by geographical area, that were retrieved among the variables required for the study. This analysis was conducted as part of data quality monitoring activities to assess the completeness of the information collected and identify any critical issues in the acquisition process.

Risk factors with robust evidence of a link to disease progression were designated as primary, while risk factors for which there was an indirect link were designated as secondary.

| PRIMARY<br>VARIABLES | ATTICA                        | PALERMO                       | TARRAGONA                      | BASILICATA                    |
|----------------------|-------------------------------|-------------------------------|--------------------------------|-------------------------------|
|                      | N total = 625<br>not null (%) | N total = 599<br>not null (%) | N total = 1072<br>not null (%) | N total = 326<br>not null (%) |
| Alcohol              | 99.20%                        | 85.81%                        | 67.63%                         | 20.25%                        |
| BMI                  | 99.20%                        | 39.23%                        | 80.41%                         | 36.81%                        |
| Fasting glucose      | 86.88%                        | 33.89%                        | 88.71%                         | 83.44%                        |
| Smoke                | 99.20%                        | 99.67%                        | 79.85%                         | 23.31%                        |

*Table 1: Percentage of non-null data for primary variables broken down by geographical area.*

| SECONDARY<br>VARIABLES | ATTICA                        | PALERMO                       | TARRAGONA                      | BASILICATA                    |
|------------------------|-------------------------------|-------------------------------|--------------------------------|-------------------------------|
|                        | N total = 625<br>not null (%) | N total = 599<br>not null (%) | N total = 1072<br>not null (%) | N total = 326<br>not null (%) |
| ALT                    | 85.60%                        | 0.00%                         | 81.53%                         | 81.29%                        |
| AST                    | 86.56%                        | 0.00%                         | 64.27%                         | 81.90%                        |
| GGT                    | 86.56%                        | 10.85%                        | 69.50%                         | 81.29%                        |
| MCV                    | 82.24%                        | 0.00%                         | 91.23%                         | 10.43%                        |
| C-RP                   | 0.64%                         | 0.00%                         | 30.60%                         | 0.00%                         |
| HDL cholesterol        | 81.12%                        | 0.00%                         | 63.71%                         | 0.92%                         |
| LDL cholesterol        | 83.20%                        | 1.00%                         | 62.22%                         | 0.00%                         |
| Total cholesterol      | 85.60%                        | 0.00%                         | 70.43%                         | 1.53%                         |
| Triglycerides          | 85.92%                        | 0.84%                         | 65.58%                         | 0.31%                         |

Table 2: Percentage of non-null data for secondary variables broken down by geographical area.

## Results

This report is based on data made available for the ELISAH project by the cancer registry of Tarragona for Spain, the registries of Palermo province and Basilicata region for Italy, and the pilot breast cancer registry of Greece, that is being developed by the ELISAH research group. Information on the variables under analysis was collected and checked for 2622 cases of BC diagnosed in the period 2019-2021.

### Prevalence of exposure

The prevalence of exposure was assessed by describing the availability of clinical data for each of the primary variables BMI, fasting glucose, smoking and alcohol use stratified by geographical area (Table 3), age group (Table 4) and stage of malignancy (Table 5). Tables 3, 4 and 5 report for each subcategory the distribution of variables retrieved from clinical records and the percentages with respect to the total number of individuals belonging to the same subcategory. This representation allows a comparative view of the prevalence of exposure and the completeness of clinical data in the different subpopulations analysed. Furthermore, Annex 1 contains a comprehensive table of all subdivisions for best comparison.

Annexes 2, 3, 4, 5 and 6 provide a direct depiction of exposure prevalence for the variables BMI, smoking and alcohol use, with representative images for each subcategory.

|                        | Complete dataset | Attica        | Palermo       | Tarragona      | Basilicata    |
|------------------------|------------------|---------------|---------------|----------------|---------------|
|                        | N total = 2622   | N total = 625 | N total = 599 | N total = 1072 | N total = 326 |
| <b>BMI</b>             |                  |               |               |                |               |
| Underweight            | 66 2.52%         | 37 5.92%      | 4 0.67%       | 22 2.05%       | 3 0.92%       |
| Normal weight          | 674 25.71%       | 246 39.36%    | 127 21.20%    | 262 24.44%     | 39 11.96%     |
| Overweight             | 622 23.72%       | 237 37.92%    | 51 8.51%      | 288 26.87%     | 46 14.11%     |
| Obese                  | 475 18.12%       | 100 16.00%    | 53 8.85%      | 290 27.05%     | 32 9.82%      |
| Unknown                | 785 29.94%       | 5 0.80%       | 364 60.77%    | 210 19.59%     | 206 63.19%    |
| <b>Fasting glucose</b> |                  |               |               |                |               |
| <100 mg/dL             | 1116 42.56%      | 257 41.12%    | 117 19.53%    | 625 58.30%     | 117 35.89%    |
| 100-110 mg/dL          | 337 12.85%       | 96 15.36%     | 34 5.68%      | 136 12.69%     | 71 21.78%     |
| 110-125 mg/dL          | 252 9.61%        | 119 19.04%    | 26 4.34%      | 70 6.53%       | 37 11.35%     |
| ≥125 mg/dL             | 264 10.07%       | 71 11.36%     | 26 4.34%      | 120 11.19%     | 47 14.42%     |
| Unknown                | 653 24.90%       | 82 13.12%     | 396 66.11%    | 121 11.29%     | 54 16.56%     |
| <b>Smoke</b>           |                  |               |               |                |               |
| Never                  | 1381 52.67%      | 397 63.52%    | 385 64.27%    | 538 50.19%     | 61 18.71%     |
| Former                 | 331 12.62%       | 105 16.80%    | 99 16.53%     | 126 11.75%     | 1 0.31%       |
| Current                | 393 14.99%       | 83 13.28%     | 112 18.70%    | 184 17.16%     | 14 4.29%      |
| Occasional             | 44 1.68%         | 35 5.60%      | 1 0.17%       | 8 0.75%        | 0 0.00%       |
| Unknown                | 473 18.04%       | 5 0.80%       | 2 0.33%       | 216 20.15%     | 250 76.69%    |
| <b>Alcohol</b>         |                  |               |               |                |               |
| Never                  | 1498 57.13%      | 370 59.20%    | 497 82.97%    | 571 53.26%     | 60 18.40%     |
| Former                 | 40 1.53%         | 36 5.76%      | 1 0.17%       | 3 0.28%        | 0 0.00%       |
| Current                | 114 4.35%        | 25 4.00%      | 16 2.67%      | 68 6.34%       | 5 1.53%       |
| Occasional             | 273 10.41%       | 189 30.24%    | 0 0.00%       | 83 7.74%       | 1 0.31%       |
| Unknown                | 697 26.58%       | 5 0.80%       | 85 14.19%     | 347 32.37%     | 260 79.75%    |

Table 3: Prevalence of exposure to primary variables broken down by geographical area.

|                        | Complete dataset | Age 0-49      | Age 50-69      | Age 70+       |
|------------------------|------------------|---------------|----------------|---------------|
|                        | N total = 2622   | N total = 764 | N total = 1147 | N total = 711 |
| <b>BMI</b>             |                  |               |                |               |
| Underweight            | 66 2.52%         | 23 3.01%      | 27 2.35%       | 16 2.25%      |
| Normal weight          | 674 25.71%       | 272 35.60%    | 283 24.67%     | 119 16.74%    |
| Overweight             | 622 23.72%       | 213 27.88%    | 256 22.32%     | 153 21.52%    |
| Obese                  | 475 18.12%       | 76 9.95%      | 256 22.32%     | 143 20.11%    |
| Unknown                | 785 29.94%       | 180 23.56%    | 325 28.33%     | 280 39.38%    |
| <b>Fasting glucose</b> |                  |               |                |               |
| <100 mg/dL             | 1116 42.56%      | 383 50.13%    | 480 41.85%     | 253 35.58%    |
| 100-110 mg/dL          | 337 12.85%       | 95 12.43%     | 155 13.51%     | 87 12.24%     |
| 110-125 mg/dL          | 252 9.61%        | 70 9.16%      | 101 8.81%      | 81 11.39%     |
| ≥125 mg/dL             | 264 10.07%       | 44 5.76%      | 113 9.85%      | 107 15.05%    |
| Unknown                | 653 24.90%       | 172 22.51%    | 298 25.98%     | 183 25.74%    |
| <b>Smoke</b>           |                  |               |                |               |
| Never                  | 1381 52.67%      | 409 53.53%    | 517 45.07%     | 455 63.99%    |
| Former                 | 331 12.62%       | 89 11.65%     | 180 15.69%     | 62 8.72%      |
| Current                | 393 14.99%       | 132 17.28%    | 227 19.79%     | 34 4.78%      |
| Occasional             | 44 1.68%         | 19 2.49%      | 19 1.66%       | 6 0.84%       |
| Unknown                | 473 18.04%       | 115 15.05%    | 204 17.79%     | 154 21.66%    |
| <b>Alcohol</b>         |                  |               |                |               |
| Never                  | 1498 57.13%      | 438 57.33%    | 617 53.79%     | 443 62.31%    |
| Former                 | 40 1.53%         | 16 2.09%      | 14 1.22%       | 10 1.41%      |
| Current                | 114 4.35%        | 25 3.27%      | 70 6.10%       | 19 2.67%      |
| Occasional             | 273 10.41%       | 101 13.22%    | 140 12.21%     | 32 4.50%      |
| Unknown                | 697 26.58%       | 184 24.08%    | 306 26.68%     | 207 29.11%    |

Table 4: Prevalence of exposure to primary variables broken down by age groups.

|                 | Dataset complete |        | Stage 0      Stage 1      Stage 2      Stage 3      Stage 4      Stage null |        |     |        |               |        |               |        |               |        |              |        |                |  |
|-----------------|------------------|--------|-----------------------------------------------------------------------------|--------|-----|--------|---------------|--------|---------------|--------|---------------|--------|--------------|--------|----------------|--|
|                 | N total = 2622   |        | N total =75                                                                 |        |     |        | N total = 604 |        | N total = 544 |        | N total = 137 |        | N total = 51 |        | N total = 1211 |  |
| BMI             |                  |        |                                                                             |        |     |        |               |        |               |        |               |        |              |        |                |  |
| Underweight     | 66               | 2.52%  | 5                                                                           | 6.67%  | 22  | 3.64%  | 16            | 2.94%  | 2             | 1.46%  | 1             | 1.96%  | 20           | 1.65%  |                |  |
| Normal weight   | 674              | 25.71% | 31                                                                          | 41.33% | 186 | 30.79% | 132           | 24.26% | 48            | 35.04% | 9             | 17.65% | 268          | 22.13% |                |  |
| Overweight      | 622              | 23.72% | 30                                                                          | 40.00% | 157 | 25.99% | 162           | 29.78% | 43            | 31.39% | 9             | 17.65% | 221          | 18.25% |                |  |
| Obese           | 475              | 18.12% | 9                                                                           | 12.00% | 112 | 18.54% | 114           | 20.96% | 26            | 18.98% | 12            | 23.53% | 202          | 16.68% |                |  |
| Unknown         | 785              | 29.94% | 0                                                                           | 0.00%  | 127 | 21.03% | 120           | 22.06% | 18            | 13.14% | 20            | 39.22% | 500          | 41.29% |                |  |
| Fasting glucose |                  |        |                                                                             |        |     |        |               |        |               |        |               |        |              |        |                |  |
| <100 mg/dL      | 1116             | 42.56% | 33                                                                          | 44.00% | 276 | 45.70% | 219           | 40.26% | 71            | 51.82% | 17            | 33.33% | 500          | 41.29% |                |  |
| 100-110 mg/dL   | 337              | 12.85% | 13                                                                          | 17.33% | 71  | 11.75% | 92            | 16.91% | 18            | 13.14% | 9             | 17.65% | 134          | 11.07% |                |  |
| 110-125 mg/dL   | 252              | 9.61%  | 19                                                                          | 25.33% | 73  | 12.09% | 50            | 9.19%  | 16            | 11.68% | 3             | 5.88%  | 91           | 7.51%  |                |  |
| ≥125 mg/dL      | 264              | 10.07% | 8                                                                           | 10.67% | 53  | 8.77%  | 60            | 11.03% | 13            | 9.49%  | 7             | 13.73% | 123          | 10.16% |                |  |
| Unknown         | 653              | 24.90% | 2                                                                           | 2.67%  | 131 | 21.69% | 123           | 22.61% | 19            | 13.87% | 15            | 29.41% | 363          | 29.98% |                |  |
| Smoke           |                  |        |                                                                             |        |     |        |               |        |               |        |               |        |              |        |                |  |
| Never           | 1381             | 52.67% | 49                                                                          | 65.33% | 353 | 58.44% | 315           | 57.90% | 74            | 54.01% | 27            | 52.94% | 563          | 46.49% |                |  |
| Former          | 331              | 12.62% | 13                                                                          | 17.33% | 75  | 12.42% | 79            | 14.52% | 17            | 12.41% | 7             | 13.73% | 140          | 11.56% |                |  |
| Current         | 393              | 14.99% | 7                                                                           | 9.33%  | 97  | 16.06% | 72            | 13.24% | 22            | 16.06% | 8             | 15.69% | 187          | 15.44% |                |  |
| Occasional      | 44               | 1.68%  | 6                                                                           | 8.00%  | 18  | 2.98%  | 11            | 2.02%  | 4             | 2.92%  | 0             | 0.00%  | 5            | 0.41%  |                |  |
| Unknown         | 473              | 18.04% | 0                                                                           | 0.00%  | 61  | 10.10% | 67            | 12.32% | 20            | 14.60% | 9             | 17.65% | 316          | 26.09% |                |  |
| Alcohol         |                  |        |                                                                             |        |     |        |               |        |               |        |               |        |              |        |                |  |
| Never           | 1498             | 57.13% | 48                                                                          | 64.00% | 362 | 59.93% | 331           | 60.85% | 81            | 59.12% | 35            | 68.63% | 641          | 52.93% |                |  |
| Former          | 40               | 1.53%  | 4                                                                           | 5.33%  | 23  | 3.81%  | 9             | 1.65%  | 2             | 1.46%  | 0             | 0.00%  | 2            | 0.17%  |                |  |
| Current         | 114              | 4.35%  | 5                                                                           | 6.67%  | 32  | 5.30%  | 20            | 3.68%  | 4             | 2.92%  | 1             | 1.96%  | 52           | 4.29%  |                |  |
| Occasional      | 273              | 10.41% | 18                                                                          | 24.00% | 97  | 16.06% | 79            | 14.52% | 17            | 12.41% | 2             | 3.92%  | 60           | 4.95%  |                |  |
| Unknown         | 697              | 26.58% | 0                                                                           | 0.00%  | 90  | 14.90% | 105           | 19.30% | 33            | 24.09% | 13            | 25.49% | 456          | 37.65% |                |  |

Table 5: Prevalence of exposure to primary variables broken down by stage.

Among the main variables, fasting glucose, one of the five components of the metabolic syndrome, was analysed separately, as it was identified as the variable with the greatest impact on mortality analysis. Table 6 provides a comprehensive delineation of the available data categorized into clinically significant classes (critical values) and age groups, facilitating a more nuanced evaluation of exposure distribution.

To complement the tabular presentation, a histogram of relative frequencies (Figure 2), built from the entire dataset of available values, was added to illustrate the overall distribution of the variable and the concentration of observations in specific risk ranges. The combination of tabular and graphical representations allows us to capture both the clinical categorization of exposure and the continuous distribution of the observed values.

Annexes 7, 8, 9 and 10 display the same representation for the four geographical areas in the study.

| Area       | Fasting glucose |         |        | Age group | Fasting glucose |         |        |
|------------|-----------------|---------|--------|-----------|-----------------|---------|--------|
|            | 100-110         | 110-125 | ≥125   |           | 100-110         | 110-125 | ≥125   |
| Attica     | 17.68%          | 21.92%  | 13.08% | Over 50   | 17.63%          | 24.10%  | 13.31% |
|            |                 |         |        | Under 50  | 17.74%          | 19.62%  | 12.83% |
| Palermo    | 16.75%          | 12.81%  | 12.81% | Over 50   | 18.88%          | 15.38%  | 18.18% |
|            |                 |         |        | Under 50  | 11.67%          | 6.67%   | 0.00%  |
| Tarragona  | 14.30%          | 7.36%   | 12.62% | Over 50   | 14.72%          | 8.36%   | 15.12% |
|            |                 |         |        | Under 50  | 12.69%          | 3.55%   | 3.05%  |
| Basilicata | 26.10%          | 13.60%  | 17.28% | Over 50   | 27.23%          | 14.85%  | 21.29% |
|            |                 |         |        | Under 50  | 22.86%          | 10.00%  | 5.71%  |
| Complete   | 17.12%          | 12.80%  | 13.41% | Over 50   | 17.57%          | 13.22%  | 15.98% |
|            |                 |         |        | Under 50  | 16.05%          | 11.82%  | 7.43%  |

Table 6: Fasting glucose prevalence of exposure broken down by geographical area, critical values and age groups.

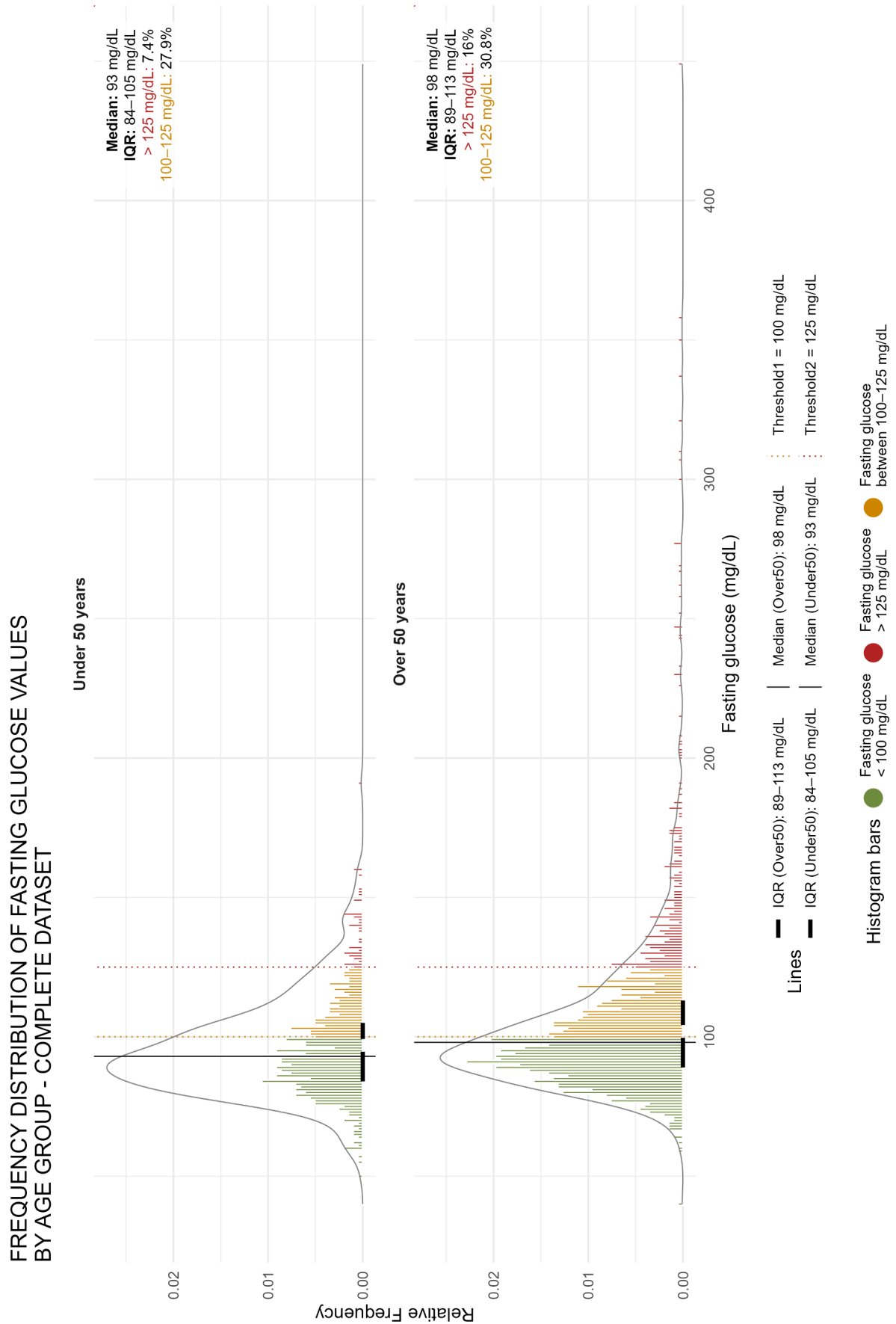


Figure 2: Relative frequency distribution of fasting glucose values, complete dataset.

To complete the description of the primary variables, an analysis was performed to determine the number of women presenting with none, one, or more concomitant risk factors.

For each woman, the number of primary variables exceeding the risk thresholds was calculated, defined as: overweight or obesity for BMI, fasting glucose  $\geq 100$  mg/dL, and belonging to the "current" class for both smokers and alcohol consumers. Table 7 shows the distribution of patients based on the number of above thresholds risk factors, presented in both absolute figures and percentage, illustrating the occurrence of null values.

| Primary risk factors availability | Number of risk factors above thresholds |         |      |         |     |         |    |        |   |        |
|-----------------------------------|-----------------------------------------|---------|------|---------|-----|---------|----|--------|---|--------|
|                                   | 0                                       |         | 1    |         | 2   |         | 3  |        | 4 |        |
| complete 2622                     | 915                                     | 34.90 % | 1038 | 39.59 % | 591 | 22.54 % | 75 | 2.86 % | 3 | 0.11 % |
| none null 1371                    | 283                                     | 20.64 % | 569  | 41.50 % | 454 | 33.11 % | 62 | 4.50 % | 3 | 0.22 % |

Table 7: Number of women with the four concomitant primary risk factors above thresholds.

Similarly, the concomitance between BMI and glucose was assessed; the results are reported in Table 8.

| BMI and glucose data availability | N. risk factors above thresholds |         |      |         |     |         |
|-----------------------------------|----------------------------------|---------|------|---------|-----|---------|
|                                   | 0                                |         | 1    |         | 2   |         |
| complete 2622                     | 1147                             | 43.75 % | 1000 | 38.14 % | 475 | 18.11 % |
| none null 1642                    | 435                              | 26.49 % | 732  | 44.58 % | 475 | 28.93 % |

Table 8: Number of women BMI and glucose simultaneously above thresholds.

For the secondary variables, a more concise and comprehensive description of the available data was adopted. Table 8 reports, for each variable, the main descriptive indicators: first quartile (1st Qu), median, mean and third quartile (3rd Qu). This summary provides an overall picture of the data distribution, useful for contextualizing the variability of the measures and supporting the interpretation of the results of subsequent analyses.

| SECONDARY VARIABLES | 1st Qu. | Median | Mean   | 3rd Qu. |
|---------------------|---------|--------|--------|---------|
| ALT                 | 15      | 20     | 23.55  | 28      |
| AST                 | 17      | 21     | 24.23  | 27      |
| GGT                 | 15      | 22     | 33.57  | 36      |
| MCV                 | 85      | 90     | 87.60  | 94      |
| C-RP                | 4       | 4      | 22.84  | 17      |
| HDL Cholesterol     | 50      | 58     | 59.69  | 67      |
| LDL Cholesterol     | 86      | 114    | 112.13 | 135     |
| Total cholesterol   | 174     | 197    | 197.20 | 221     |
| Triglycerides       | 91      | 125.5  | 132.56 | 163     |

Table 9: Main descriptive indicators of secondary variables.

To assess the association between the variables considered in the study, the chi-square ( $\chi^2$ ) test and Spearman and Kendall nonparametric correlation measures were applied where reasonably possible. The results of the statistical analyses are reported in Tables 9 and 10; please note that, in these tables, BMI written in uppercase refers to the categorization of the variable, while BMI written in lowercase indicates the continuous variable.

Table 9 includes, for each pair of variables analysed, the  $\chi^2$  test values, the degrees of freedom, the corresponding p values, and the number of data on which the test was performed. Table 10 reports, for each pair of variables analysed, the Spearman and Kendall correlation coefficients with their respective significance levels and the number of data on which the measurements were carried out.

The same statistical analyses can be found in the annexes (Annex 11 and 12) for each of the four geographical areas under consideration.

| VARIABLES |       |           | $\chi^2$ | df | P value   | n    |
|-----------|-------|-----------|----------|----|-----------|------|
|           | BMI   | - Alcohol | 14.15    | 9  | 0.117     | 1455 |
| *         | Smoke | - Alcohol | 159.92   | 9  | 7.711E-30 | 1922 |
| *         | BMI   | - Smoke   | 38.05    | 9  | 1.708E-05 | 1572 |
|           | BMI   | - Stage   | 21.38    | 12 | 0.045     | 1077 |

Table 10: Chi-square ( $\chi^2$ ) test between variables.

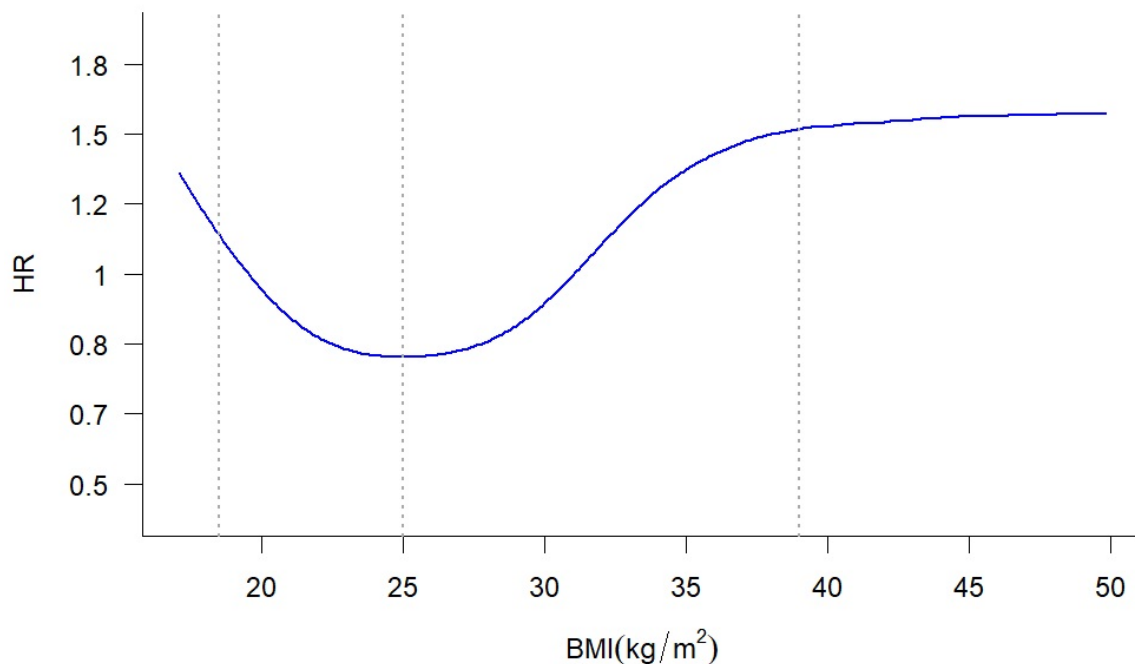
| VARIABLES |                   | n    | Spearman<br>(α=0.05) | ρ      | Kendall<br>(α=0.05) | τ      |
|-----------|-------------------|------|----------------------|--------|---------------------|--------|
| *         | Alcohol - n_drink | 500  | p<0.05               | 0.906  | p<0.05              | 0.866  |
| *         | smoke - n_cig     | 932  | p<0.05               | 0.827  | p<0.05              | 0.702  |
| *         | smoke - Alcohol   | 1922 | p<0.05               | 0.251  | p<0.05              | 0.235  |
| *         | n_cig - n_drink   | 477  | p<0.05               | 0.372  | p<0.05              | 0.341  |
| *         | BMI - bmi         | 1720 | p<0.05               | 0.944  | p<0.05              | 0.830  |
| *         | BMI - Alcohol     | 1455 | p<0.05               | -0.059 | p<0.05              | -0.053 |
|           | BMI - Grade       | 1159 | ns                   | 0.042  | ns                  | 0.037  |
| *         | BMI - smoke       | 1572 | p<0.05               | -0.093 | p<0.05              | -0.083 |
| *         | BMI - Stage       | 1077 | p<0.05               | 0.082  | p<0.05              | 0.071  |
| *         | Grade - Stage     | 1344 | p<0.05               | 0.218  | p<0.05              | 0.196  |

Table 11: Spearman and Kendall measures between variables.

## Mortality analysis

We selected 962 cases of BC with complete follow-up from the total archive of 2622 women. The median follow-up was 23.8 months and the total number of deaths was 91. We performed univariate analysis for all available covariates. Here we present the results of multivariate modelling including BMI and fasting glucose, with age and stage as confounding variables. When applying a method to detect non-linearity, we found the association of BMI and all-cause mortality to be J-shaped; a change point was identified at the value of 25 kg/m<sup>2</sup>. Hence, we analysed two cohorts separately: women with BMI below and women with BMI above the change point.

Figure 3 shows the trend of the hazard according to BMI.



*Figure 3: Trend of all-cause mortality HR according to BMI*

The functional form of the all-cause mortality HR in women with a BC diagnosis is similar to what shown by a paper investigating the same HR in the general population [19].

An increase in fasting glucose was associated with an increase in all-cause mortality both in women with BMI below 25 kg/m<sup>2</sup> and women with BMI above the threshold value. In the first cohort (BMI <25 kg/m<sup>2</sup>), an increase in BMI showed a protective effect, while in the second cohort an increase in BMI was associated with an increase in mortality risk. The effect of fasting glucose proved independent of BMI values.

| Exposure                 | Breast cancer cases (N) | All-causes deaths (N) | HR (95%CI) for all-causes death, bmi below 23           | HR (95%CI) for all-causes death, bmi above 23           |
|--------------------------|-------------------------|-----------------------|---------------------------------------------------------|---------------------------------------------------------|
| Fasting glucose (mg/dL)  | 962                     | 91                    | 1.06 (1.02-1.10)<br>per increase of 5 mg/dL             | 1.03 (1.01-1.05)<br>per increase of 5 mg/dL             |
| BMI (kg/m <sup>2</sup> ) | 962                     | 91                    | 0.82 (0.55-1.21)<br>per increase of 1 kg/m <sup>2</sup> | 1.02 (0.96-1.08)<br>per increase of 1 kg/m <sup>2</sup> |

Table 12: Hazard ratios (HR) and 95% confidence intervals (CI) for all causes of death according to peridiagnostic BMI and fasting glucose.

## Limitations and strengths of the study

The main limitation of the study is the number of null values for some variables. The researchers who collected the data read the clinical records of the women selected for inclusion in the study based on the date of incidence. Sometimes information on certain variables, for example BMI, was lacking and the researchers could only record null in such cases. The main strength of the study is the population-based design, enabling us to assess the prevalence of risk factors in a sample of the European population.

## Synergies with other ELISAH Work Packages

The activities described in this deliverable (D3.4) were developed in synergy with the following ELISAH WPs:

WP2 - Breast cancer impact, risk factors and prevention in European countries. We made use of the review and meta-analysis established by WP2.

WP4 - Holistic intervention involving society. The results of the D3.4 observational study are linked to the intervention studies of WP4 that aimed to reduce the same behavioural risk factors.

WP5 - Action to reduce health inequalities. A study is ongoing to analyse the results of this study in relation to the area deprivation index.

WP6 - Urban environment and risk of BC. The results of the D3.4 observational study are connected to the actions of WP6. Our aim was to fill the gap identified in this observational study by suggesting improvements in the built environment related to physical activity, thereby improving BMI control.

### 3. CONCLUSIONS

#### Study key points

The principal findings of this retrospective study on 2622 women with invasive BC are the following:

- Prevalence of risk factors in women with a BC diagnosis:
  - the share of smokers ranged from 13.4% to 21.5%
  - the share of women using alcohol ranged from 3.1% to 9.4%
  - the share of women with overweight was high, ranging from 44.3% to 67.1%
  - the share of women with elevated fasting glucose levels ( $\geq 100$  mg/dL, ADA criteria) was high, ranging from 34.3% to 57%
- Mortality risk in women with a BC diagnosis:  
we observed a mortality hazard for women at increasing fasting glucose values. Despite not reaching statistical significance, BMI  $\geq 22.5$  was associated with a mortality hazard. Conversely, in women with BMI  $< 22.5$ , an increase in BMI had a protective effect.

#### Recommendation for EU-level, national and regional policymakers

In this report we have presented an analysis focusing on the prevalence of behavioural risk factor exposure among women and on all-cause mortality in women diagnosed with BC. The high prevalence in the general population and in women with BC as well as the association between risk factor exposure and all-cause mortality highlight the need for public health interventions. We analysed all-cause mortality because of the holistic structure of the ELISAH project, as we aim to prevent all causes of death rather than BC deaths only. Importantly, cardiovascular diseases are the second leading cause of death in women with BC and share many risk factors with BC, including overweight, smoking, alcohol consumption and hyperglycaemia. The proposed interventions seek to mitigate all-cause mortality, encompassing deaths due to BC, cardiovascular diseases, and other conditions.

We suggest four kinds of interventions:

- a) pre-diagnosis interventions
- b) post-diagnosis hospital-based interventions
- c) post-treatment community-based interventions
- d) interventions for a health-promoting environment

The pre-diagnosis interventions are to be applied to the general population. Hospital-based interventions may be applied during the active phase of BC, for example in the course of treatment or during initial follow-up. Community-based interventions are aimed at individuals who have been cured. All interventions are favoured by a “health-promoting environment”, which will be described in a dedicated paragraph.

a) Pre-diagnosis interventions targeting the general population

We observed a large proportion of women exposed to behavioural risk factors at diagnosis as a result of their lifestyle before the BC diagnosis. Addressing the prevalence of the analysed risk factors prior to diagnosis is crucial to lower the incidence of new cases, as certain risk factors contribute to the onset and progression of BC as well as all-cause mortality. This approach aims to improve women’s survival and quality of life by reducing the proportion of women exposed to behavioural risk factors.

Interventions targeting the general population are needed for maintaining a healthy body weight, engaging in physically activity and consuming a healthy diet.

b) Hospital-based interventions

Post-diagnosis hospital interventions are needed to limit the exposure of women to behavioural risk factors. A gold standard example are the accredited cancer programs of the American College of Surgeons, which participated in the nationwide Beyond ASK quality improvement initiative to increase the proportion of active smokers with cancer who receive cessation support as part of cancer care provision. Scaled improvement in smoking cessation support across accredited cancer programs proved to be feasible and achievable relatively quickly [20]. Similar initiatives could be planned for other risk factors.

We recommend hospital-based interventions to help patients quit smoking and consuming alcohol and modify their diet to reduce BMI and hyperglycaemia.

c) Post-diagnosis community-based interventions

Behavioural interventions should be included in the broader framework of the clinical governance of survivorship. Over the last few decades we have observed an increase in survival among women diagnosed with BC.

Effective clinical governance of survivorship care has become increasingly important to ensure successful transition from active treatment to post-treatment follow-up. When the active disease phase ends, it is very important to proceed with follow-up to monitor comorbidities deriving from cancer treatments, enhance patients' quality of life and promote a healthy lifestyle.

Many models of survivorship interventions have been proposed [21], but their application is still pending. The main survivorship models are the "Shared Model", the "Pathology Model" and the "Multidisciplinary-Comprehensive Model". The Shared Model is defined as the management of a patient's health through the collaboration between medical specialists and general practitioners. The Pathology Model refers to the activity of a group of disease-specific oncologists dedicated to the planning of correct patient follow-up.

The Multidisciplinary-Comprehensive model is the most complex, involving many different professionals, mainly oncologists and general practitioners, supported by a network of consulting specialists such as cardiologists and nutritionists. Some authors [21] have proposed the use of innovative models for effective clinical governance of survivorship care based on the possible role of the "community oncologist", defined as a trained health professional acting as a link between hospital specialists and general practitioners. We emphasize the necessity to implement clinical governance of survivorship, advocating for the adoption of a model that aligns with local health organizations and social assets. Additionally, it is important to govern survivorship also by incorporating strategies for managing risk factors such as smoking, alcohol consumption and lack of physical activity. As a pragmatic model to enhance tertiary cancer prevention, we highlight a proposal by a group of Italian scientists [22]. Given the strong link between risk factors for cardiovascular disease and BC, the model of "Cardio-Oncology Rehabilitation" has been proposed as a physical exercise-based multi-component intervention that builds on the Cardiac Rehabilitation model to improve the care and prognosis of persons with a cancer diagnosis. The model is particularly interesting because it could be swiftly implemented for cardio-oncological rehabilitation by employing the network of professionals dedicated to cardiac rehabilitation.

d) Interventions for a health-promoting environment

Physical activity helps to prevent excess weight gain and high BMI, major risk factors for BC development and progression. Many key policy areas have been identified to support a built environment for increased physical activity by the World Cancer Research Fund (WCRF) [23]. We highlight the following items in relation to the ELISAH results:

1. walking and cycling infrastructure and transport policies that prioritize walking, cycling and use of public transport
2. healthy schools: initiatives that optimize opportunities for physical activity, including walking and cycling to and from school
3. active policies for the involvement of urban planners and architects in the planning of green space promoting physical activity

### **Practical advice for women with a diagnosis of breast cancer**

Find out how diet and lifestyle can support your health and wellbeing if you're living with and beyond BC. [24] [25]

## 4. REFERENCES

- [1] Kong YH, Huang JY, Ding Y, Chen SH, Li QS, Xiong Y, The effect of BMI on survival outcome of breast cancer patients: a systematic review and meta-analysis, 2025 Feb, 27(2):403-416. doi: 10.1007/s12094-024-03563-9. Epub 2024 Jul 16. PMID: 39012453
- [2] Wen H, Deng G, Shi X, Liu Z, Lin A, Cheng Q, Zhang J, Luo P, Body mass index, weight change, and cancer prognosis: a meta-analysis and systematic review of 73 cohort studies., 2024 Mar, 9(3):102241. doi: 10.1016/j.esmoop.2024.102241. Epub 2024 Mar 4. PMID: 38442453; PMCID: PMC10925937
- [3] Eurostat, Overweight and obesity - BMI statistics,  
[https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Overweight and obesity - BMI statistics](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Overweight_and_obesity_-_BMI_statistics)
- [4] Passarelli MN, Newcomb PA, Hampton JM, Trentham-Dietz A, Titus LJ, Egan KM, Baron JA, Willett WC., Cigarette Smoking Before and After Breast Cancer Diagnosis: Mortality From Breast Cancer and Smoking-Related Diseases., 2016 Apr 20, 34(12):1315-22. doi: 10.1200/JCO.2015.63.9328. Epub 2016 Jan 25. PMID: 26811527; PMCID: PMC4872346
- [5] Lowy DR, Fiore MC, Willis G, Mangold KN, Bloch MH, Baker TB, reating Smoking in Cancer Patients: An Essential Component of Cancer Care-The New National Cancer Institute Tobacco Control Monograph, 2022 Dec, 18(12):e1971-e1976. doi: 10.1200/OP.22.00385. Epub 2022 Nov 7. PMID: 36343305; PMCID: PMC10166433
- [6] EUROSTAT, Alcohol consumption statistics, [https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Alcohol consumption statistics](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Alcohol_consumption_statistics)
- [7] IARC, Cancers Attributable to Alcohol, <https://gco.iarc.who.int/causes/alcohol/en>
- [8] Park S, Ko E, Lee y, Impact of Lifestyle Factors on Breast Cancer Recurrence: A Meta-Analysis of Prospective Cohort Studies, 2025 Jul 16, doi: 10.1097/ANS.0000000000000578. Epub ahead of print. PMID: 40668143.
- [9] Djuric O, Bonvicini L, Pellegrini M, Bruno E, Pasanisi P, Gargano G, Curtosi P, Berrino F, Giorgi Rossi P, Villarini A, Diet, body composition and metabolic and hormonal profile in women at high risk of breast cancer recurrence: A secondary mediation analysis of the DIANA-5 trial, 2026 Jan, 56:106537. doi: 10.1016/j.clnu.2025.11.021. Epub 2025 Dec 4. PMID: 41483481

- [10] Contiero P, Berrino F, Tagliabue G, Mastroianni A, Di Mauro MG, Fabiano S, Annulli M, Muti P, Fasting blood glucose and long-term prognosis of non-metastatic breast cancer: a cohort study, 2013 Apr, 138(3):951-9. doi: 10.1007/s10549-013-2519-9. Epub 2013 Apr 9. PMID: 23568483; PMCID: PMC3664213.
- [11] Minicozzi P, Berrino F, Sebastiani F, Falcini F, Vattiato R, Cioccoloni F, Calagreti G, Fusco M, Vitale MF, Tumino R, Sigona A, Budroni M, Cesaraccio R, Candela G, Scuderi T, Zarcone M, Campisi I, Sant M, High fasting blood glucose and obesity significantly and independently increase risk of breast cancer death in hormone receptor-positive disease, 2013 Dec, 49(18):3881-8. doi: 10.1016/j.ejca.2013.08.004. Epub 2013 Sep 3. PMID: 24011933.
- [12] Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Taylor SK, Hood N, Insulin and obesity related variables in early-stage breast cancer: correlations and time course of prognostic associations, 2012 Jan, 10;30(2):164-71. doi: 10.1200/JCO.2011.36.2723. Epub 2011 Dec 12. PMID: 22162568.
- [13] International Classification of Diseases for Oncology, Third Edition, First Revision, Geneva, World Health Organization, 2013
- [14] Sobin LH, Wittekind C, International Union Against Cancer (UICC) , TNM Classification Of Malignant Tumors, 2002, 6th ed. New York, NY: Wiley-Liss.
- [15] Tyczynski JE, Démaret E, Parkin DM, Standards and Guidelines for Cancer Registration in Europe, 2003, ISBN-13978-92-832-2422-8; ISBN-13978-92-832-2422-8
- [15] Therneau TM, Grambsch PM, Testing proportional hazards In Modeling Survival Data: Extending The Cox Model, 2000, Springer-Verlag; New York
- [16] Bellera CA, MacGrogan G, Debled M, de Lara CT, Brouste V, Mathoulin-Pélissier S, Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer, 2010, 10:20. doi: 10.1186/1471-2288-10-20.
- [17] R Development Core Team, R: a language and environment for statistical computing, 2026, <http://www.r-project.org/>
- [18] Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L, Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK, 2018 Dec, 6(12):944-953. doi: 10.1016/S2213-8587(18)30288-2. Epub 2018 Oct 30; PMID: 30389323; PMCID: PMC6249991.

[19] Pu T, Burris JL, Matulewicz RS, McCarthy DE, Ostroff JS, Reilly EM, Shelton RC, Warren GW, Weigel RJ, Mullett TW, Beyond ASK Quality Improvement Task Force. National Quality Improvement Initiative to Increase Smoking Cessation Assistance in Commission on Cancer Programs and National Accreditation Program for Breast Centers, 2026 Feb 25, JCO2501815. doi: 10.1200/JCO-25-01815. Epub ahead of print. PMID: 41740088.

[20] Tralongo P, Gebbia V, Mercadante S, Bordonaro R, Ferraù F, Barni S, Firenze A, Cancer: New Needs, New Models. Is It Time for a Community Oncologist? Another Brick in the Wall, 2021 Apr 16, 13(8):1919. doi: 10.3390/cancers13081919. PMID: 33923380; PMCID: PMC8071576.

[22] Venturini E, Iannuzzo G, D'Andrea A, Pacileo M, Tarantini L, Canale ML, Gentile M, Vitale G, Sarullo FM, Vastarella R, Di Lorenzo A, Testa C, Parlato A, Vigorito C, Giallauria F, Oncology and Cardiac Rehabilitation: An Underrated Relationship, 2020 Jun 10, 9(6):1810. doi: 10.3390/jcm9061810. PMID: 32532011; PMCID: PMC7356735.

[22] World Cancer Research Fund, Policy factsheet: Physical activity and cancer prevention, <https://www.wcrf.org/research-policy/library/policy-factsheet-physical-activity-cancer-prevention/>

[24] World Cancer Research Fund International's Global Cancer Update Programme provides an analysis of international scientific research into how diet, nutrition and physical activity affect cancer risk and survival, More information is available at: [wcrf.org/about\\_cupglobal, https://www.wcrf.org/preventing-cancer/cancer-types/breast-cancer/living-with-breast-cancer/#eating-well-after-a-breast-cancer-diagnosis](https://www.wcrf.org/preventing-cancer/cancer-types/breast-cancer/living-with-breast-cancer/#eating-well-after-a-breast-cancer-diagnosis)

[25] American Diabetes Association (ADA), Standards of Care in Diabetes, <https://professional.diabetes.org/standards-of-care#:~:text=The%20Standards%20of%20Care%20in%20Diabetes%20%28Standards%20of,and%20tools%20to%20evaluate%20the%20quality%20of%20care>

## 5. ANNEXES

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|                 | Dataset complete |        |                          |        |                           |        |                              |        |                              |        |                            |        |                              |        |                           |        |                          |        |                           |        |                           |        |                           |        |                          |        |                               |        |
|-----------------|------------------|--------|--------------------------|--------|---------------------------|--------|------------------------------|--------|------------------------------|--------|----------------------------|--------|------------------------------|--------|---------------------------|--------|--------------------------|--------|---------------------------|--------|---------------------------|--------|---------------------------|--------|--------------------------|--------|-------------------------------|--------|
|                 | N total<br>2622  |        | Attica<br>N total<br>625 |        | Palermo<br>N total<br>599 |        | Tarragona<br>N total<br>1072 |        | Basilicata<br>N total<br>326 |        | Age 0-49<br>N total<br>764 |        | Age 50-69<br>N total<br>1147 |        | Age 70+<br>N total<br>711 |        | Stage 0<br>N total<br>75 |        | Stage 1<br>N total<br>604 |        | Stage 2<br>N total<br>544 |        | Stage 3<br>N total<br>137 |        | Stage 4<br>N total<br>51 |        | Stage null<br>N total<br>1211 |        |
| BMI             |                  |        |                          |        |                           |        |                              |        |                              |        |                            |        |                              |        |                           |        |                          |        |                           |        |                           |        |                           |        |                          |        |                               |        |
| Underweight     | 66               | 2.52%  | 37                       | 5.92%  | 4                         | 0.67%  | 22                           | 2.05%  | 3                            | 0.92%  | 23                         | 3.01%  | 27                           | 2.35%  | 16                        | 2.25%  | 5                        | 6.67%  | 22                        | 3.64%  | 16                        | 2.94%  | 2                         | 1.46%  | 1                        | 1.96%  | 20                            | 1.65%  |
| Normal weight   | 674              | 25.71% | 246                      | 39.36% | 127                       | 21.20% | 262                          | 24.44% | 39                           | 11.96% | 272                        | 35.60% | 283                          | 24.67% | 119                       | 16.74% | 31                       | 41.33% | 186                       | 30.79% | 132                       | 24.26% | 48                        | 35.04% | 9                        | 17.65% | 268                           | 22.13% |
| Overweight      | 622              | 23.72% | 237                      | 37.92% | 51                        | 8.51%  | 288                          | 26.87% | 46                           | 14.11% | 213                        | 27.88% | 256                          | 22.32% | 153                       | 21.52% | 30                       | 40.00% | 157                       | 25.99% | 162                       | 29.78% | 43                        | 31.39% | 9                        | 17.65% | 221                           | 18.25% |
| Obese           | 475              | 18.12% | 100                      | 16.00% | 53                        | 8.85%  | 290                          | 27.05% | 32                           | 9.82%  | 76                         | 9.95%  | 256                          | 22.32% | 143                       | 20.11% | 9                        | 12.00% | 112                       | 18.54% | 114                       | 20.96% | 26                        | 18.98% | 12                       | 23.53% | 202                           | 16.68% |
| Unknown         | 785              | 29.94% | 5                        | 0.80%  | 364                       | 60.77% | 210                          | 19.59% | 206                          | 63.19% | 180                        | 23.56% | 325                          | 28.33% | 280                       | 39.38% | 0                        | 0.00%  | 127                       | 21.03% | 120                       | 22.06% | 18                        | 13.14% | 20                       | 39.22% | 500                           | 41.29% |
| Fasting glucose |                  |        |                          |        |                           |        |                              |        |                              |        |                            |        |                              |        |                           |        |                          |        |                           |        |                           |        |                           |        |                          |        |                               |        |
| < 100 mg/dL     | 1116             | 42.56% | 257                      | 41.12% | 117                       | 19.53% | 625                          | 58.30% | 117                          | 35.89% | 383                        | 50.13% | 480                          | 41.85% | 253                       | 35.58% | 33                       | 44.00% | 276                       | 45.70% | 219                       | 40.26% | 71                        | 51.82% | 17                       | 33.33% | 500                           | 41.29% |
| 100-110 mg/dL   | 337              | 12.85% | 96                       | 15.36% | 34                        | 5.68%  | 136                          | 12.69% | 71                           | 21.78% | 95                         | 12.43% | 155                          | 13.51% | 87                        | 12.24% | 13                       | 17.33% | 71                        | 11.75% | 92                        | 16.91% | 18                        | 13.14% | 9                        | 17.65% | 134                           | 11.07% |
| 110-125 mg/dL   | 252              | 9.61%  | 119                      | 19.04% | 26                        | 4.34%  | 70                           | 6.53%  | 37                           | 11.35% | 70                         | 9.16%  | 101                          | 8.81%  | 81                        | 11.39% | 19                       | 25.33% | 73                        | 12.09% | 50                        | 9.19%  | 16                        | 11.68% | 3                        | 5.88%  | 91                            | 7.51%  |
| ≥ 125 mg/dL     | 264              | 10.07% | 71                       | 11.36% | 26                        | 4.34%  | 120                          | 11.19% | 47                           | 14.42% | 44                         | 5.76%  | 113                          | 9.85%  | 107                       | 15.05% | 8                        | 10.67% | 53                        | 8.77%  | 60                        | 11.03% | 13                        | 9.49%  | 7                        | 13.73% | 123                           | 10.16% |
| Unknown         | 653              | 24.90% | 82                       | 13.12% | 396                       | 66.11% | 121                          | 11.29% | 54                           | 16.56% | 172                        | 22.51% | 298                          | 25.98% | 183                       | 25.74% | 2                        | 2.67%  | 131                       | 21.69% | 123                       | 22.61% | 19                        | 13.87% | 15                       | 29.41% | 363                           | 29.98% |
| Smoking         |                  |        |                          |        |                           |        |                              |        |                              |        |                            |        |                              |        |                           |        |                          |        |                           |        |                           |        |                           |        |                          |        |                               |        |
| Never           | 1381             | 52.67% | 397                      | 63.52% | 385                       | 64.27% | 538                          | 50.19% | 61                           | 18.71% | 409                        | 53.53% | 517                          | 45.07% | 455                       | 63.99% | 49                       | 65.33% | 353                       | 58.44% | 315                       | 57.90% | 74                        | 54.01% | 27                       | 52.94% | 563                           | 46.49% |
| Former          | 331              | 12.62% | 105                      | 16.80% | 99                        | 16.53% | 126                          | 11.75% | 1                            | 0.31%  | 89                         | 11.65% | 180                          | 15.69% | 62                        | 8.72%  | 13                       | 17.33% | 75                        | 12.42% | 79                        | 14.52% | 17                        | 12.41% | 7                        | 13.73% | 140                           | 11.56% |
| Current         | 393              | 14.99% | 83                       | 13.28% | 112                       | 18.70% | 184                          | 17.16% | 14                           | 4.29%  | 132                        | 17.28% | 227                          | 19.79% | 34                        | 4.78%  | 7                        | 9.33%  | 97                        | 16.06% | 72                        | 13.24% | 22                        | 16.06% | 8                        | 15.69% | 187                           | 15.44% |
| Occasional      | 44               | 1.68%  | 35                       | 5.60%  | 1                         | 0.17%  | 8                            | 0.75%  | 0                            | 0.00%  | 19                         | 2.49%  | 19                           | 1.66%  | 6                         | 0.84%  | 6                        | 8.00%  | 18                        | 2.98%  | 11                        | 2.02%  | 4                         | 2.92%  | 0                        | 0.00%  | 5                             | 0.41%  |
| Unknown         | 473              | 18.04% | 5                        | 0.80%  | 2                         | 0.33%  | 216                          | 20.15% | 250                          | 76.69% | 115                        | 15.05% | 204                          | 17.79% | 154                       | 21.66% | 0                        | 0.00%  | 61                        | 10.10% | 67                        | 12.32% | 20                        | 14.60% | 9                        | 17.65% | 316                           | 26.09% |
| Alcohol         |                  |        |                          |        |                           |        |                              |        |                              |        |                            |        |                              |        |                           |        |                          |        |                           |        |                           |        |                           |        |                          |        |                               |        |
| Never           | 1498             | 57.13% | 370                      | 59.20% | 497                       | 82.97% | 571                          | 53.26% | 60                           | 18.40% | 438                        | 57.33% | 617                          | 53.79% | 443                       | 62.31% | 48                       | 64.00% | 362                       | 59.93% | 331                       | 60.85% | 81                        | 59.12% | 35                       | 68.63% | 641                           | 52.93% |
| Former          | 40               | 1.53%  | 36                       | 5.76%  | 1                         | 0.17%  | 3                            | 0.28%  | 0                            | 0.00%  | 16                         | 2.09%  | 14                           | 1.22%  | 10                        | 1.41%  | 4                        | 5.33%  | 23                        | 3.81%  | 9                         | 1.65%  | 2                         | 1.46%  | 0                        | 0.00%  | 2                             | 0.17%  |
| Current         | 114              | 4.35%  | 25                       | 4.00%  | 16                        | 2.67%  | 68                           | 6.34%  | 5                            | 1.53%  | 25                         | 3.27%  | 70                           | 6.10%  | 19                        | 2.67%  | 5                        | 6.67%  | 32                        | 5.30%  | 20                        | 3.68%  | 4                         | 2.92%  | 1                        | 1.96%  | 52                            | 4.29%  |
| Occasional      | 273              | 10.41% | 189                      | 30.24% | 0                         | 0.00%  | 83                           | 7.74%  | 1                            | 0.31%  | 101                        | 13.22% | 140                          | 12.21% | 32                        | 4.50%  | 18                       | 24.00% | 97                        | 16.06% | 79                        | 14.52% | 17                        | 12.41% | 2                        | 3.92%  | 60                            | 4.95%  |
| Unknown         | 697              | 26.58% | 5                        | 0.80%  | 85                        | 14.19% | 347                          | 32.37% | 260                          | 79.75% | 184                        | 24.08% | 306                          | 26.68% | 207                       | 29.11% | 0                        | 0.00%  | 90                        | 14.90% | 105                       | 19.30% | 33                        | 24.09% | 13                       | 25.49% | 456                           | 37.65% |

**Annex 1:** Prevalence of exposure to primary variables broken down by geographical area, age groups and stage.

## LEGENDS

All percentages in the annexes refer to women:

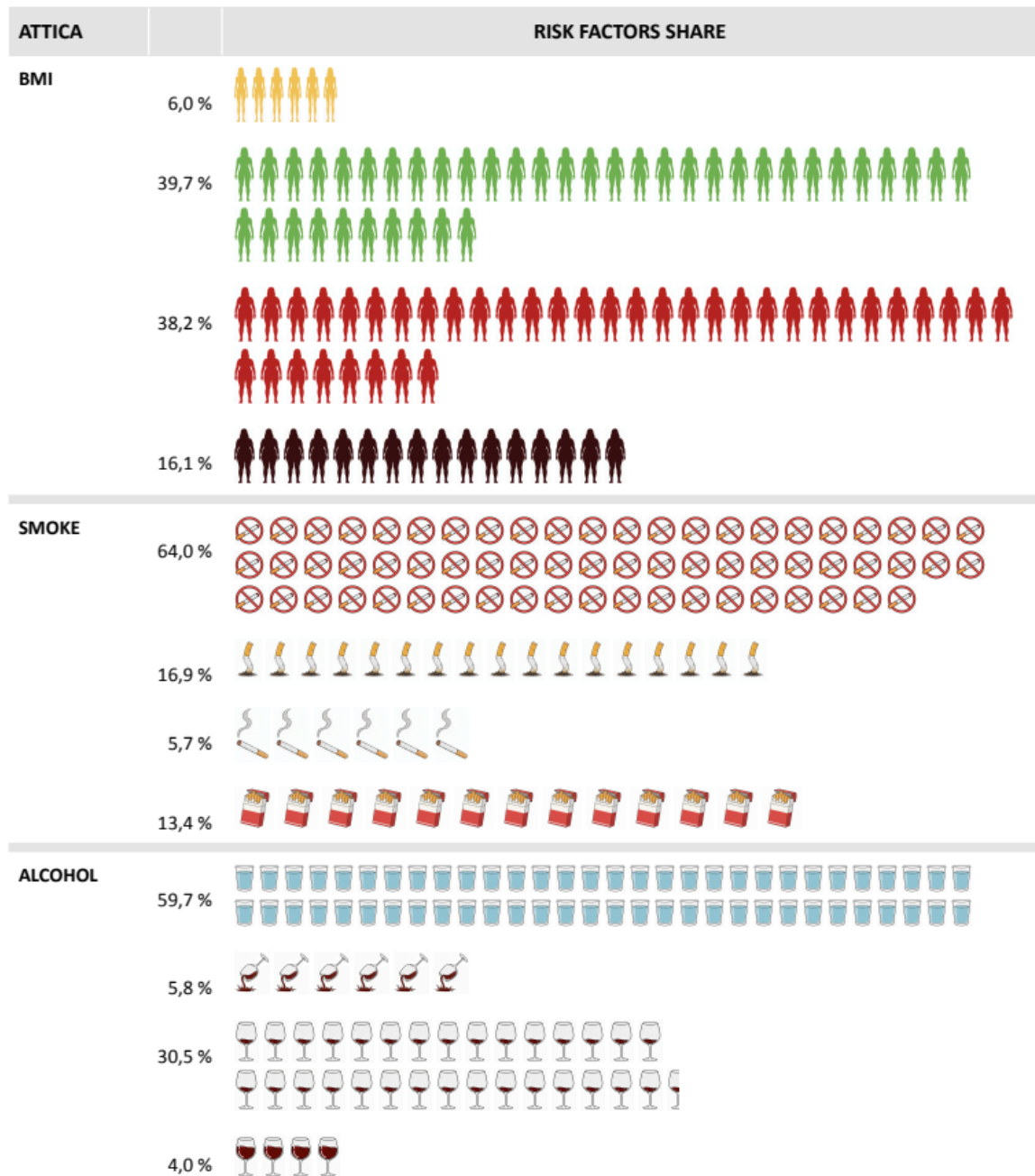
- diagnosed with breast cancer
- from the indicated geographical region
- for whom information regarding the individual risks considered were available

(The reported percentages were calculated based on the total number for each region, avoiding null data.)

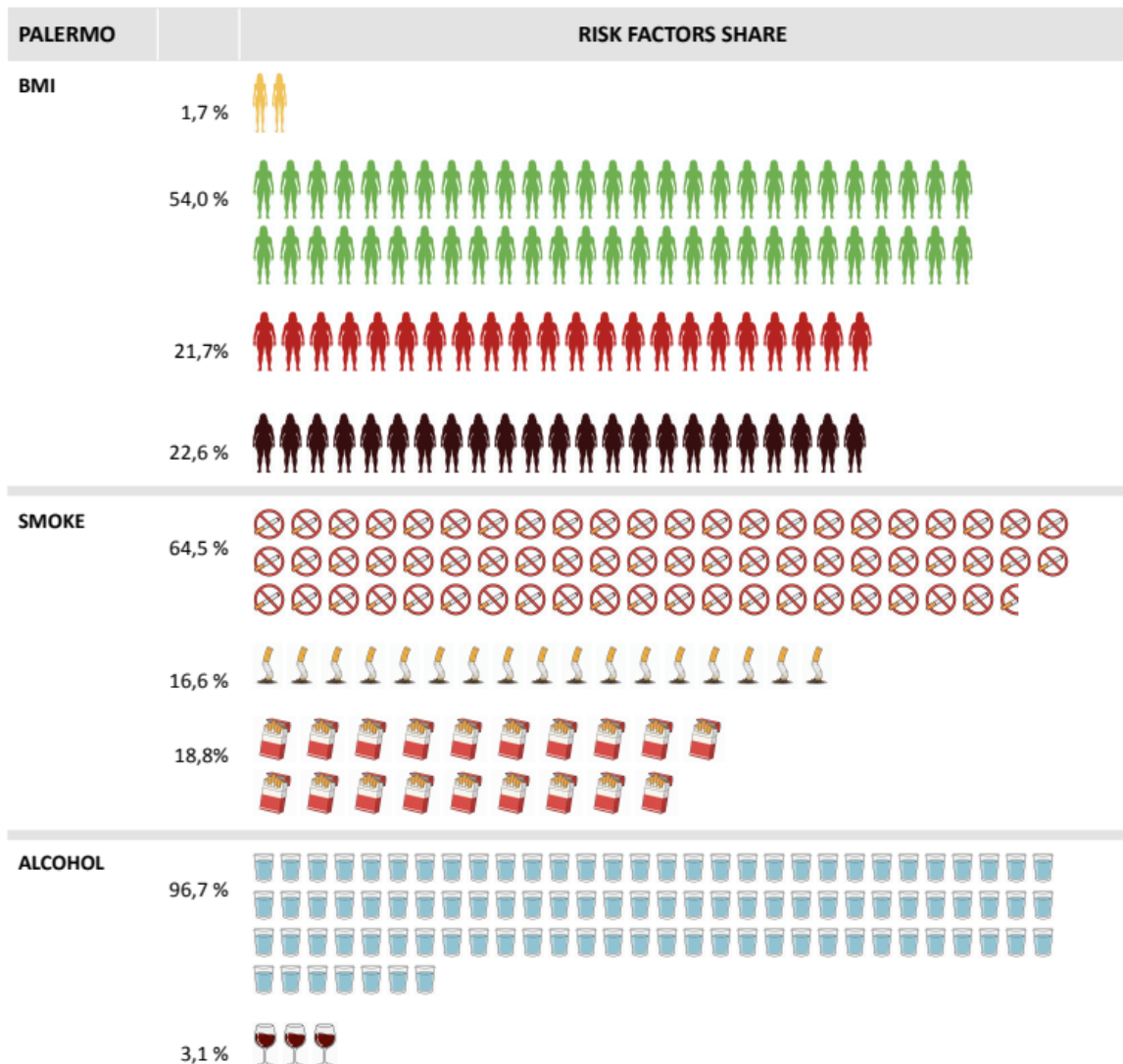
Please note: Classes with percentages below 0.5% were not represented.

| BMI CLASSES                                                                                                      | SMOKING CLASSES                                                                                                                        | ALCOHOL CLASSES                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
|  Underweight<br>BMI 18.5        |  Never smoker                                         |  Never drinker                                     |
|  Normal weight<br>18.5 < BMI 25 |  Former smoker                                        |  Former drinker                                    |
|  Overweight<br>25 < BMI 30     |  Occasional smoker<br>(only sometimes)               |  Occasional drinker<br>(up to one drink per week) |
|  Obese<br>BMI > 30            |  Current smoker<br>(at least one cigarette per day) |  Current drinker<br>(more than a drink per week) |

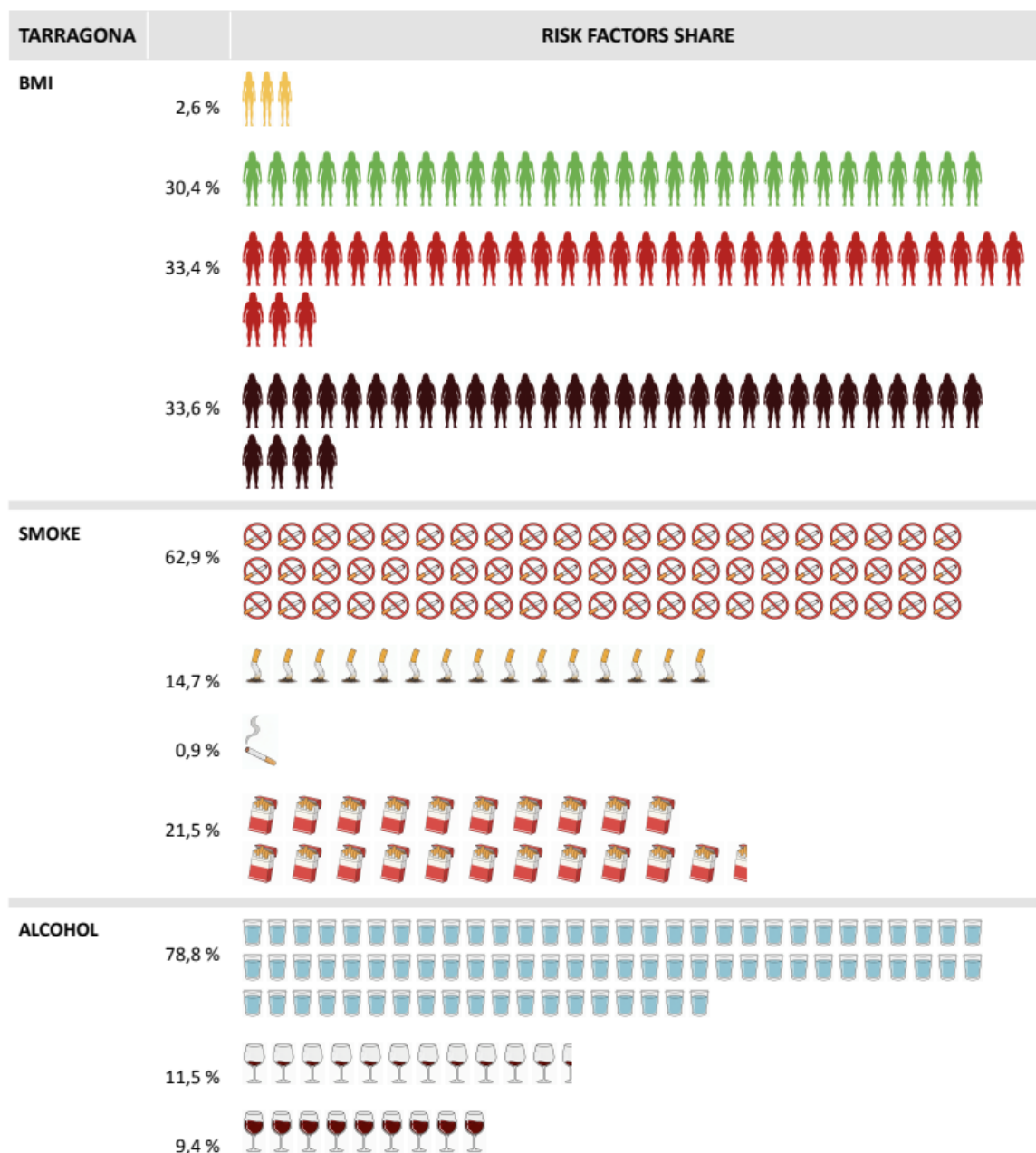
**Annex 2:** Legend for the exposure prevalence of BMI, smoking and alcohol.



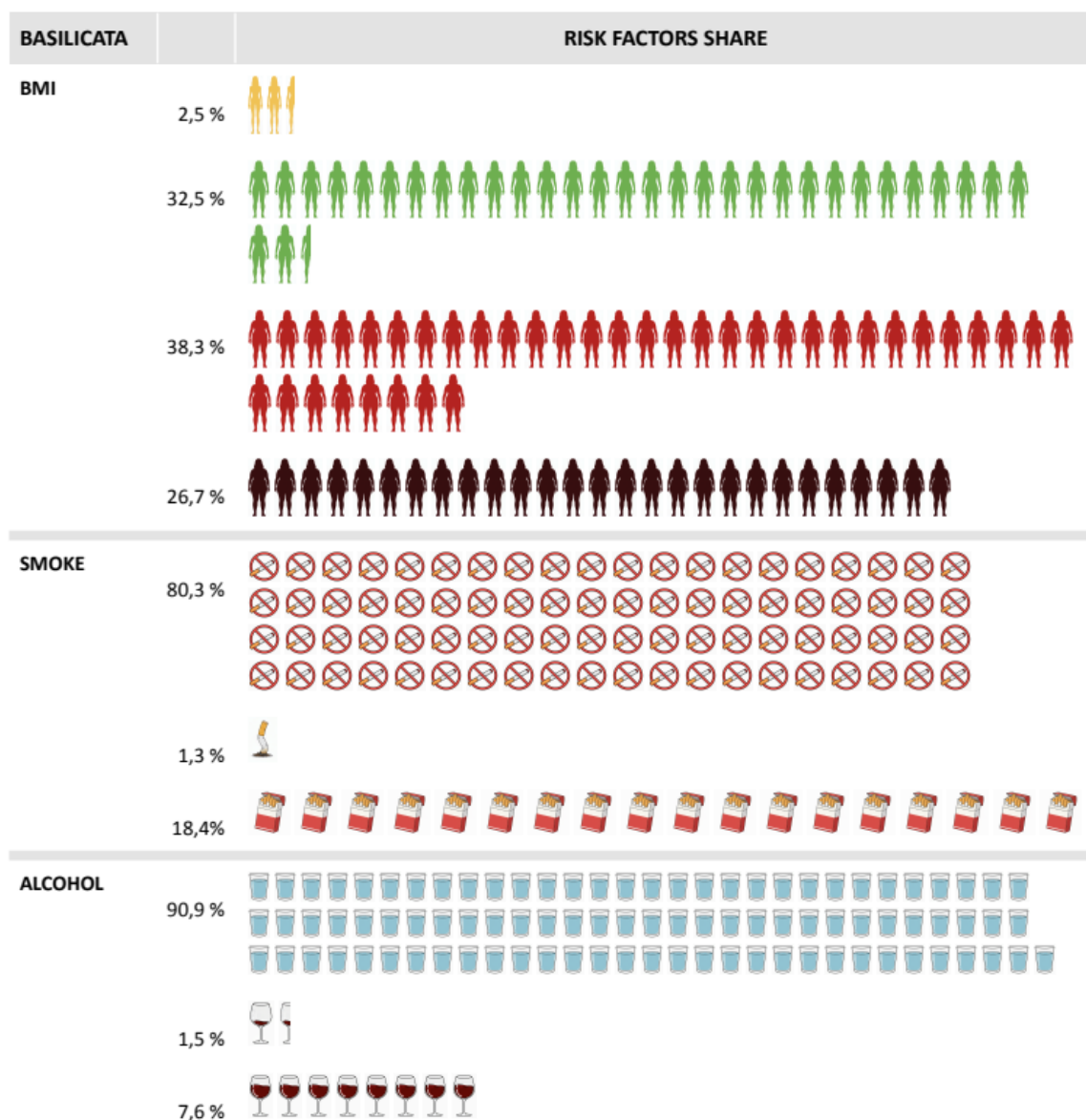
**Annex 3:** Visual representation of exposure prevalence for the variables BMI, smoking and alcohol; Attica dataset.



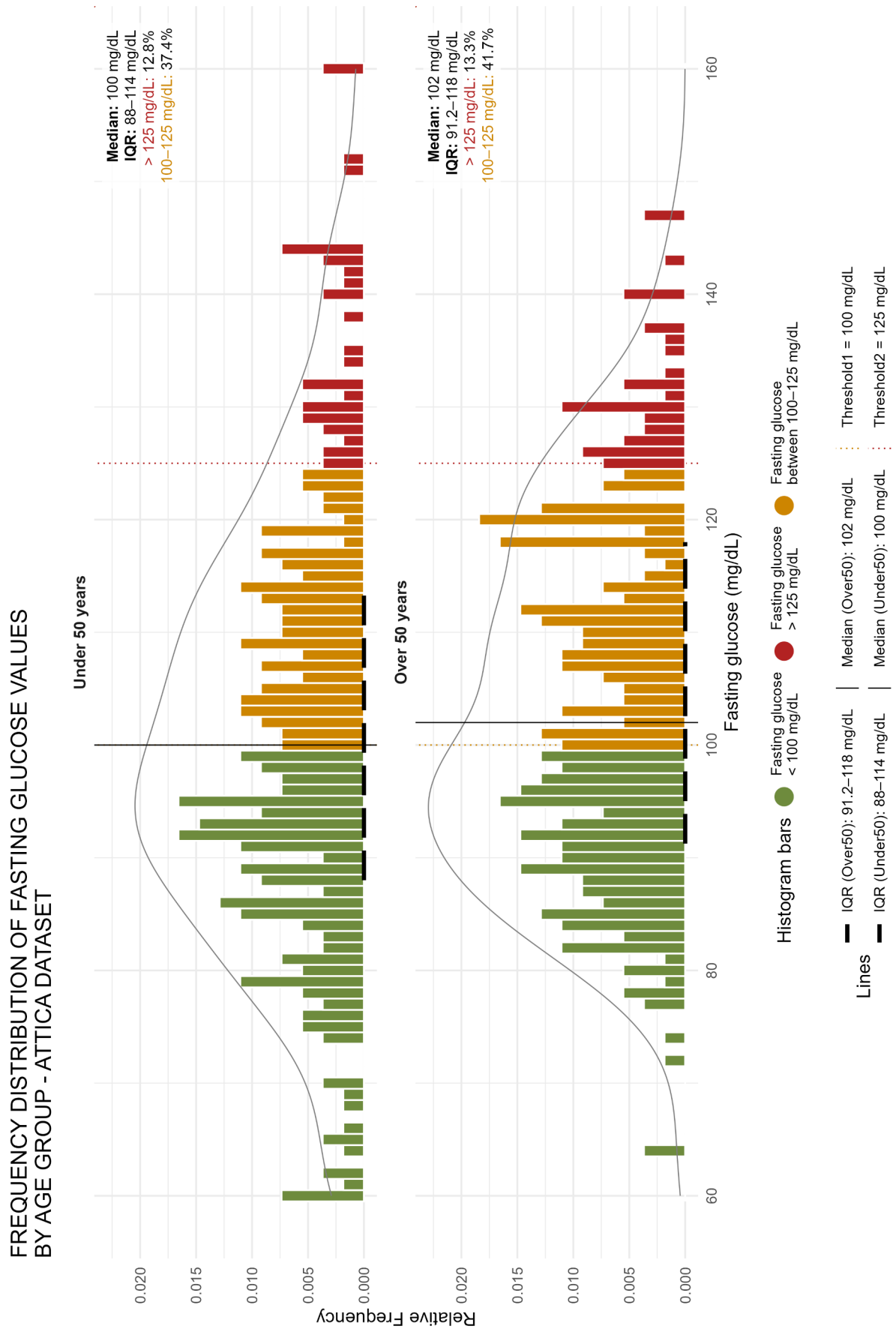
**Annex 4:** Visual representation of exposure prevalence for the variables BMI, smoking and alcohol; Palermo dataset.



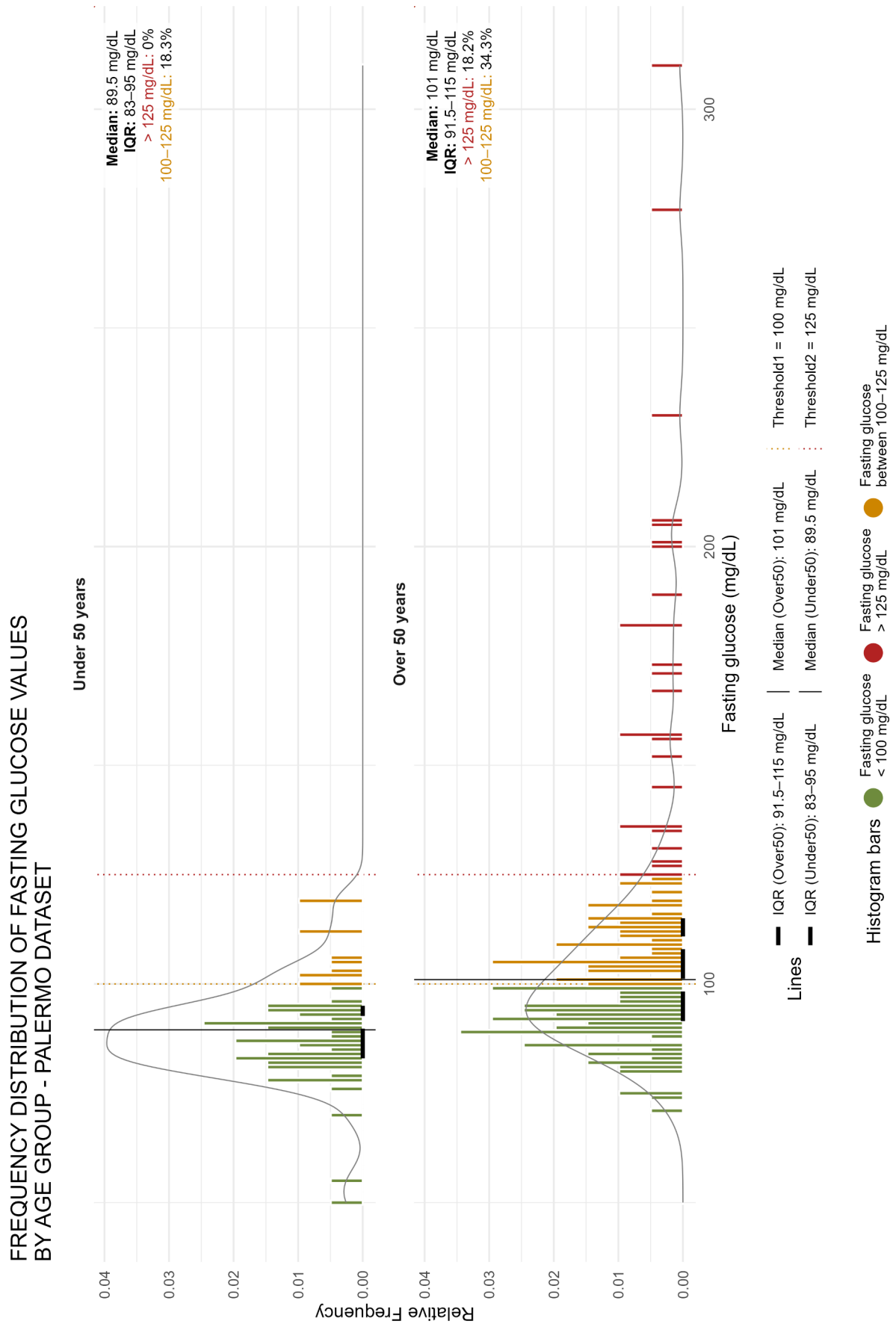
**Annex 5:** Visual representation of exposure prevalence for the variables BMI, smoking and alcohol; Tarragona dataset.



**Annex 6:** Visual representation of exposure prevalence for the variables BMI, smoking and alcohol; Basilicata dataset.

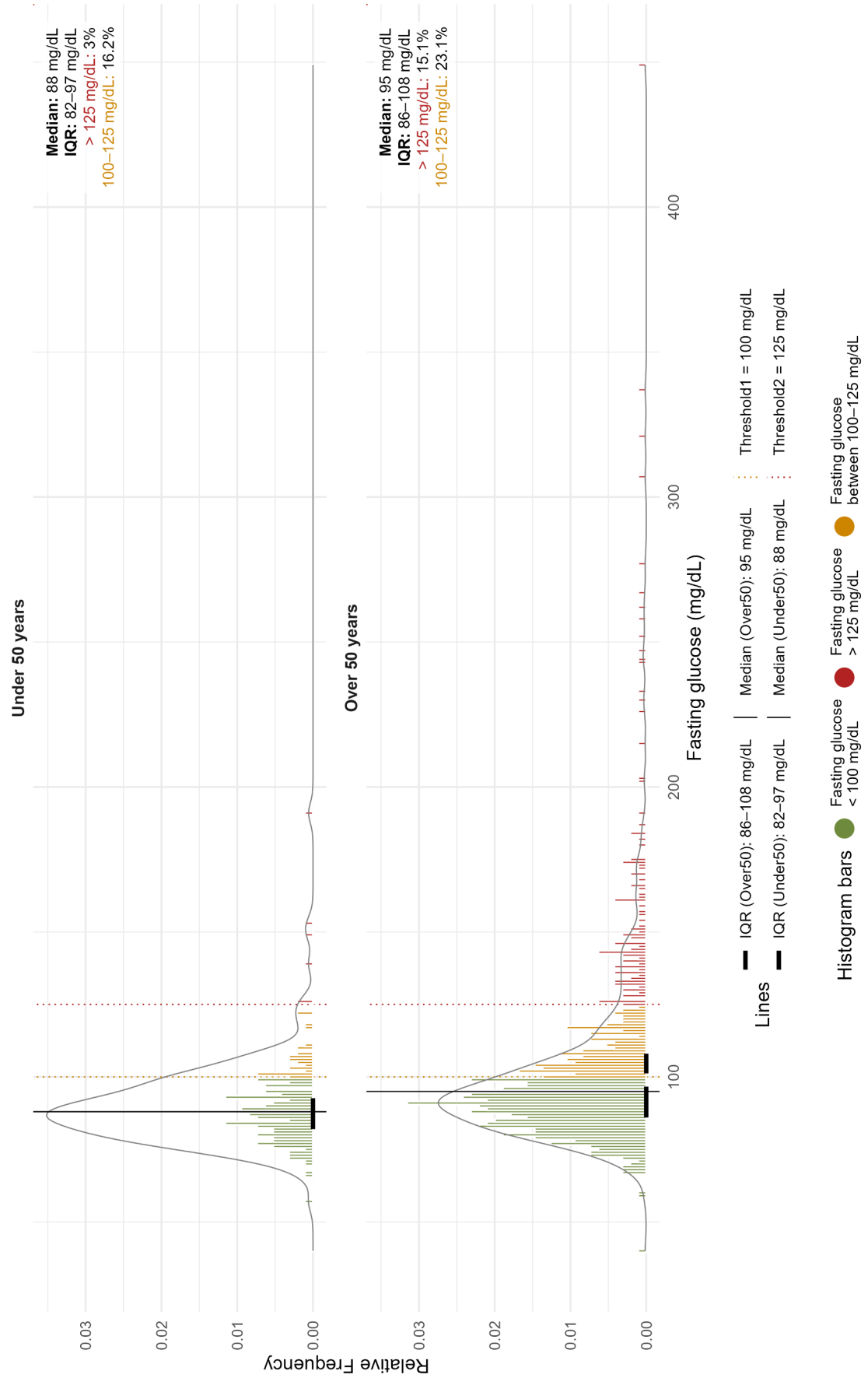


**Annex 7:** Relative frequency distribution of fasting glucose values, Attica dataset.



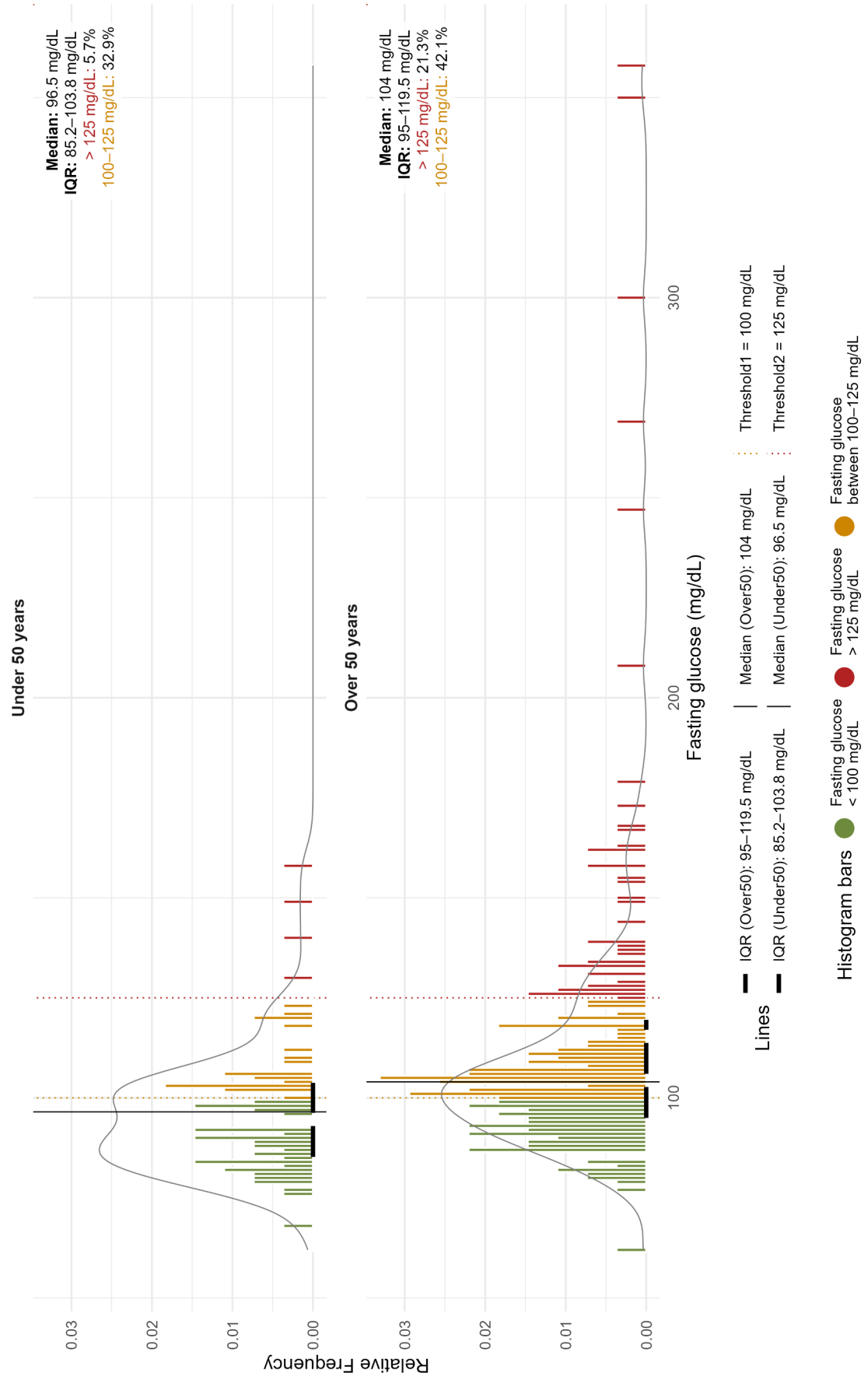
**Annex 8:** Relative frequency distribution of fasting glucose values, Palermo dataset.

## FREQUENCY DISTRIBUTION OF FASTING GLUCOSE VALUES BY AGE GROUP - TARRAGONA DATASET



**Annex 9:** Relative frequency distribution of fasting glucose values, Tarragona dataset.

# FREQUENCY DISTRIBUTION OF FASTING GLUCOSE VALUES BY AGE GROUP - BASILICATA DATASET



**Annex 10:** Relative frequency distribution of fasting glucose values, Basilicata dataset.

| ATTICA     |                   | $\chi^2$ | df | P value   | n   |
|------------|-------------------|----------|----|-----------|-----|
|            | BMI - Alcohol     | 13.29    | 9  | 0.150     | 620 |
| *          | Smoking - Alcohol | 58.44    | 9  | 2.675E-09 | 620 |
|            | BMI - Smoking     | 9.83     | 9  | 0.364     | 620 |
|            | BMI - Stage       | 12.13    | 12 | 0.436     | 602 |
| PALERMO    |                   | $\chi^2$ | df | P value   | n   |
|            | BMI - Alcohol     | 5.22     | 3  | 0.156     | 226 |
|            | Smoking - Alcohol | 11.95    | 6  | 0.063     | 513 |
|            | BMI - Smoking     | 2.72     | 6  | 0.847     | 234 |
|            | BMI - Stage       | 8.69     | 9  | 0.466     | 94  |
| TARRAGONA  |                   | $\chi^2$ | df | P value   | n   |
|            | BMI - Alcohol     | 6.70     | 9  | 0.669     | 651 |
| *          | Smoking - Alcohol | 146.86   | 9  | 3.943E-27 | 724 |
| *          | BMI - Smoking     | 41.62    | 9  | 3.851E-06 | 764 |
|            | BMI - Stage       | 11.59    | 12 | 0.479     | 391 |
| BASILICATA |                   | $\chi^2$ | df | P value   | n   |
|            | BMI - Alcohol     | 3.26     | 6  | 0.776     | 50  |
| *          | Smoking - Alcohol | 9.50     | 2  | 0.009     | 65  |
|            | BMI - Smoking     | 1.94     | 3  | 0.585     | 53  |
|            | BMI - Stage       | 6.11     | 4  | 0.191     | 39  |

**Annex 11:** Chi-square ( $\chi^2$ ) test between variables, broken down by geographical area.

| ATTICA |         |           | n   | Spearman<br>( $\alpha=0.05$ ) | $\rho$ | Kendall<br>( $\alpha=0.05$ ) | $\tau$ |
|--------|---------|-----------|-----|-------------------------------|--------|------------------------------|--------|
| *      | Alcohol | - n_drink | 457 | p<0.05                        | 0.857  | p<0.05                       | 0.820  |
| *      | Smoking | - n_cig   | 597 | p<0.05                        | 0.942  | p<0.05                       | 0.829  |
| *      | Smoking | - Alcohol | 620 | p<0.05                        | 0.246  | p<0.05                       | 0.224  |
| *      | n_cig   | - n_drink | 456 | p<0.05                        | 0.245  | p<0.05                       | 0.226  |
| *      | BMI     | - bmi     | 620 | p<0.05                        | 0.940  | p<0.05                       | 0.845  |
|        | BMI     | - Alcohol | 620 | ns                            | -0.054 | ns                           | -0.048 |
|        | BMI     | - Grade   | 609 | ns                            | 0.040  | ns                           | 0.036  |
|        | BMI     | - Smoking | 620 | ns                            | -0.074 | ns                           | -0.066 |
|        | BMI     | - Stage   | 602 | ns                            | 0.014  | ns                           | 0.011  |
| *      | Grade   | - Stage   | 596 | p<0.05                        | 0.196  | p<0.05                       | 0.177  |

| PALERMO |         |           | n   | Spearman<br>( $\alpha=0.05$ ) | $\rho$ | Kendall<br>( $\alpha=0.05$ ) | $\tau$ |
|---------|---------|-----------|-----|-------------------------------|--------|------------------------------|--------|
| *       | Smoking | - Alcohol | 513 | p<0.05                        | 0.131  | p<0.05                       | 0.126  |
| *       | BMI     | - bmi     | 162 | p<0.05                        | 0.892  | p<0.05                       | 0.770  |
| *       | BMI     | - Alcohol | 226 | p<0.05                        | -0.139 | p<0.05                       | -0.132 |
|         | BMI     | - Grade   | 116 | ns                            | 0.109  | ns                           | 0.100  |
|         | BMI     | - Smoking | 234 | ns                            | -0.065 | ns                           | -0.059 |
|         | BMI     | - Stage   | 94  | ns                            | -0.036 | ns                           | -0.033 |
| *       | Grade   | - Stage   | 217 | p<0.05                        | 0.244  | p<0.05                       | 0.226  |

| TARRAGONA |         |           | n   | Spearman<br>( $\alpha=0.05$ ) | $\rho$ | Kendall<br>( $\alpha=0.05$ ) | $\tau$ |
|-----------|---------|-----------|-----|-------------------------------|--------|------------------------------|--------|
| *         | Alcohol | - n_drink | 42  | p<0.05                        | 0.607  | p<0.05                       | 0.545  |
|           | Smoking | - n_cig   | 237 | ns                            | 0.031  | ns                           | 0.028  |
| *         | Smoking | - Alcohol | 724 | p<0.05                        | 0.343  | p<0.05                       | 0.325  |
| *         | n_cig   | - n_drink | 21  | p<0.05                        | 0.525  | p<0.05                       | 0.393  |
| *         | BMI     | - bmi     | 823 | p<0.05                        | 0.946  | p<0.05                       | 0.827  |
|           | BMI     | - Alcohol | 651 | ns                            | -0.023 | ns                           | -0.021 |
|           | BMI     | - Grade   | 382 | ns                            | 0.046  | ns                           | 0.041  |
| *         | BMI     | - Smoking | 764 | p<0.05                        | -0.110 | p<0.05                       | -0.098 |
|           | BMI     | - Stage   | 391 | ns                            | 0.065  | ns                           | 0.057  |
| *         | Grade   | - Stage   | 439 | p<0.05                        | 0.234  | p<0.05                       | 0.210  |

| BASILICATA |         |           | n   | Spearman<br>( $\alpha=0.05$ ) | $\rho$ | Kendall<br>( $\alpha=0.05$ ) | $\tau$ |
|------------|---------|-----------|-----|-------------------------------|--------|------------------------------|--------|
| *          | Smoking | - Alcohol | 65  | p<0.05                        | 0.263  | p<0.05                       | 0.262  |
| *          | BMI     | - bmi     | 115 | p<0.05                        | 0.943  | p<0.05                       | 0.828  |
|            | BMI     | - Alcohol | 50  | ns                            | -0.139 | ns                           | -0.129 |
|            | BMI     | - Grade   | 112 | ns                            | -0.112 | ns                           | -0.103 |
|            | BMI     | - Smoking | 53  | ns                            | -0.135 | ns                           | -0.126 |
|            | BMI     | - Stage   | 39  | ns                            | 0.137  | ns                           | 0.123  |
| *          | Grade   | - Stage   | 92  | p<0.05                        | 0.255  | p<0.05                       | 0.241  |

**Annex 12:** Spearman and Kendall measures between variables, broken down by geographical area.