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D2.3 - REPORT OF THE RISK FACTORS AT THE COMMUNITY LEVEL IN PILOT COMMUNITIES IN NORWAY, ROMANIA, SPAIN

Due date	M18	**Delivery date**	M18
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Responsible Author(s)	Ana-Maria Forsea		
Contributor(s)	Meghan Bradway, Thomas Schopf, Marit B. Veierød, Inger Torhild Gram, Maja-Lisa Løchen, Guri Skeie, Kari Dyb, Cristina Ruano Rodriguez, Cristina Soguero Ruiz, Anna M.C. Wägner, Andreea Catarina Popescu, Sorin Ioacara, Luana Bosoteanu, Irina Batir-Jipa		
Version	2.1		

DISSEMINATION LEVEL

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WATCHING THE RISK FACTORS
WARIFA
ARTIFICIAL INTELLIGENCE AND THE PERSONALIZED PREVENTION AND MANAGEMENT OF CHRONIC CONDITIONS

LIST OF ABBREVIATIONS

Abbreviation	Significance
CVD	Cardiovascular diseases (for the purpose of WARIFA restricted to stroke, myocardial infarction, coronary/ ischemic heart disease)
COPD	Chronic Obstructive Pulmonary Disease
DM	Diabetes Mellitus
T1/T2 DM	Type 1/Type 2 Diabetes Mellitus
CM	Cutaneous Melanoma
NCDs	Non-transmittable Chronic Diseases
WHO	World Health Organization
CCs	Chronic Conditions
MI	Myocardial infarction
IARC	International Agency for Research on Cancer
OECD	The Organization for Economic Cooperation and Development
RCTs	Randomized Controlled Trials
DALY	Disability-adjusted life years

1 INTRODUCTION

The current deliverable is the main output of the task ***Task 2.3. Map the community risk factors,*** which aimed to map the risk factors for the main chronic conditions in the 3 countries studied (Norway, Romania, Spain), analyzing in further detail the presence and co-occurrence of relevant risk factors for the major NCDs that are the focus of WARIFA, while paying special attention to identifying the vulnerable subpopulations, taking into account the geographical and cultural context.

It builds on the rich information regarding the distribution of the major chronic diseases burden and their determinants in Europe gathered in the *Deliverable D.7.1 Health outcomes*, and *D.2.1 Evidence basis report on existing validated risk calculators and preventive digital systems for the studied CCs*

It integrates the data available through the Global Burden of Disease Report [1], the nationally-relevant available epidemiology reports/databases, and the expertise of leading specialists in clinical and preventive medicine, epidemiology, social and behavioral sciences in the three countries that are serving as pilot for the development of the WARIFA preventive tool proof of concept and policy framework.

It further provides new knowledge, based on the analysis of emerging evidence, on potential new risk determinants at individual behavioral level as well as at the community level and environment-related. These new possible determinants of disease risk open new directions of research for improving our understanding of the complex, interrelated behavioral, socio-economic, cultural and environmental factors that influence the development of major chronic diseases.

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This new knowledge will be supplemented through in-field analysis, and direct observation in communities in each of the 3 pilot countries, in the following phases of the project.

D.2.3 will provide a succinct, comparative overview of:

I. The burden of the major NCDs that are the focus of WARIFA (CVD, DM, COPD, skin cancer) in the particular countries studied: Norway, Romania, Spain.

II Known risk factors for the mentioned NCDs– their prevalence, distribution, co-occurrence in the three study countries, with particular detail given on the population categories at highest risk for disease and highest level of exposure to those risk factors- the geographical or demographical "hotspots" for the occurrence of the risk factors/ diseases. Special focus will be on the modifiable risk factors

III. Potential new risk determinants, relevant for the 3 studied countries for the studied NCDs

These include individual or community-level characteristics that appear to have a significant association with the risk of developing any of the studied NCDs, not yet established by extensive population studies, but supported by emergent evidence at least in one of the studied countries.

Through this, the present deliverable fulfils its objectives to:

- Provide context information needed to build the WARIFA tool as relevant as possible for the improvement of prevention efforts, tailored to the target populations. This will support the work in WPs 3 and 4, as well as the personalization and co-creation efforts in WP7
- Provide new information for the extended list of input variables list for WARIFA AI system– supply for D.2.4 and WP4
- Provide basis information for the formulation of the policy- making framework in WARIFA, that needs to be anchored in the reality of epidemiologic situation of the studied NCDs, and in the larger socio-economic, cultural and governance context of the 3 countries studied and further at European level.

2 BACKGROUND

Cardiovascular diseases (CVD) are the leading cause of mortality and a major cause of morbidity in Europe. Currently, there are more than 6 million new cases of CVD in the EU and more than 11 million in Europe as a whole, every year. With almost 49 million people living with the disease in the EU, the cost to the EU economies is high at €210 billion a year[2].

In 2019, the number of adults diagnosed with **diabetes** in the European Union had reached 32.3 million persons. Additionally, in 2019, the number of diabetic but undiagnosed persons was also estimated at 24.2 million in Europe in 2019[2]. Diabetes prevalence among adults (diagnosed and age-standardized) was 6.2% on average in EU countries in 2019 [2].
The health expenditure allocated to treat diabetes and prevent complications are estimated at about EUR 150 billion in 2019 in the EU, with the average expenditure per diabetic adult estimated at about EUR 3 000 per year [3].

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COPD is a large, growing public health problem. According to the World Health Organization, its expected burden will increase in the coming decades, mostly due to continued exposure to risk factors, population growth and aging, to become the third leading cause of death by 2030. Despite being a major health problem, existing data on COPD prevalence are limited. Only 19 (38%) of the 50 sovereign European countries, have available reliable data on COPD prevalence. In this context, the prevalence of COPD in Europe is estimates at 12.4%[2].

Cutaneous melanoma (CM) is the sixth most frequently occurring cancer in Europe (after breast, colorectal, prostate, lung, and bladder cancers) with estimated over 100 000 new cases, and about 16 500 deaths in 2020 in European Union[4].

Melanoma burden is unequally distributed across Europe, with estimated incidence rates in 2020 varying six-fold across EU-27, and mortality rates varying three-fold. The overall incidence and mortality of CM are increasing for most EU countries, with national and regional exceptions and large variability among countries.

The five-year survival of skin melanoma patients diagnosed in 2000-2007 is in average 86% for the EU, with the highest rates in Western Europe and lowest, diving below 50% in some Eastern European countries. These disparities reflect variations in prevention, early detection and treatment.[4]

The main risk factors for these diseases have been reviewed extensively in Deliverables D.2.1 and D.7.2, and are summarized in Table 1. Among those, the principal modifiable factors include unhealthy diet and sedentary lifestyle, alcohol consumption, smoking and – for melanoma-excessive sun exposure.

Further risk determinants, in the areas of individual behaviors and lifestyle, socio-economic and cultural context of the individual, community characteristics and dynamics, and living environment are increasingly being explored worldwide, benefiting from the support of the booming new technologies of big data analysis and artificial intelligence.

The pilot countries chosen for the study within the WARIFA project are representative for different European regions **Norway** (Northern Europe); **Spain** (Southern Europe), **Romania** (Central & Eastern Europe). As such they illustrate the different demographic, socio-economic, cultural, epidemiological and healthcare systems governance configurations within the European landscape, as well as the well documented disparities in disease burden and outcome, access to quality healthcare, level of health literacy and digital literacy between these regions and across the European continent[1, 2, 5].

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Table 1. Established Risk Factors for the NCDs studied in WARIFA

Variables associated with risk	Disease for which the risk variable is relevant (for risk prediction or risk reduction)							Modifiable through behavior yes/no
	CM	CVD	T1 DM	T2 DM	COPD	Mortality overall	Morbidity overall	
DEMOGRAPHICS								NO
Age	Yes	Yes		Yes		Yes	Yes	NO
Sex	Yes	Yes				Yes	Yes	NO
Ethnicity	Yes	Yes	Yes	Yes				NO
Education level		yes		yes	yes	Yes	Yes	YES
Socio-economic level		yes		yes	yes	Yes	Yes	YES
Location	yes							YES
PHENOTYPIC MARKERS								NO
Phototype (skin reaction to sun exposure	Yes							NO
Natural Hair color	Yes							NO
Presence of freckling	Yes							NO
Total Number of nevi on body	Yes							NO
Presence of atypical nevi	Yes							NO
MEDICAL SITUATION								NO
Personal medical history								NO
Diabetes		Yes				Yes	Yes	Yes (T2DM)
CVD			Yes*	Yes		Yes	Yes	
Hypertension (HTA)		Yes	Yes*	Yes		Yes	Yes	yes
COPD		yes				Yes	Yes	no
Cancer	Yes					Yes	Yes	no
Immuno-suppressive treatment	Yes							
FAMILY HISTORY								NO
- of skin cancer	Yes							NO
- of cancer	Yes					Yes	Yes	NO
- of CVD (coronary heart disease, MI, stroke, hypertension)		Yes				Yes?	Yes?	no
- of T1/T2 Diabetes		Yes		Yes				no
LABORATORY PARAMETERS								YES
serum cholesterol total		Yes		Yes			Yes	YES
Serum cholesterol LDL HDL		Yes	Yes*	Yes			Yes	YES
Fasting plasma glucose		Yes	Yes	Yes				YES
VARIABLES for T1DM tertiary prevention								YES
HbA1c *			Yes*	Yes			Yes	
Kidney function (creatinine, estimated glomerular filtration rate, proteinuria) *			Yes*	Yes*			Yes	
Previous hypoglycemia (from sensor automatically) *		Yes*	Yes*					
Time in range (70-180mg/dl glucose) *			Yes*					
Hypoglycemia unawareness*			Yes*					

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Variables associated with risk	Disease for which the risk variable is relevant (for risk prediction or risk reduction)							Modifiable through behavior yes/no
	CM	CVD	T1 DM	T2 DM	COPD	Mortality overall	Morbidity overall	
Average glucose concentration*			Yes*					
Time below glucose 70mg/dl*			Yes*					
Coefficient of variation in glucose (%) *			Yes*					
CURRENT BEHAVIOR/ Lifestyle								
BMI/OBESITY		Yes	Yes*	Yes		Yes	Yes	YES
DIET		Yes	Yes*	Yes		Yes	Yes	YES
1.-Diet low in fruits (frequency?)		Yes	Yes*	Yes		Yes	Yes	YES
2.-Diet Low in vegetables (frequency?)		Yes				Yes	Yes	YES
3.-Diet high in red meat		Yes		Yes		Yes	Yes	YES
4.-Diet high in processed meat		Yes		Yes		Yes	Yes	YES
5.-Diet high in sugar-sweetened beverages		Yes		Yes				YES
6.Diet high in sodium		Yes		Yes?		Yes	Yes	YES
Carbohydrate (g in a meal)			Yes					YES
PHYSICAL ACTIVITY		Yes	Yes*	Yes		Yes	Yes	YES
ALCOHOL		Yes	Yes*	Yes		Yes	Yes	YES
TOBACCO EXPOSURE		Yes	Yes*	Yes	Yes	Yes	Yes	YES
CURRENT SUN EXPOSURE	yes							YES
recreational	Yes							YES
professional	Yes							YES
tanning beds use	Yes							YES
Location UV index								NO
SLEEP PATTERNS		Yes		Yes				YES
AIR POLLUTION EXPOSURE		Yes	Yes*	Yes	Yes	Yes		YES
EXPOSURE HISTORY								NO
History of Sun exposure	Yes							NO
Sunburn history	Yes							NO
History of Indoor tanning sessions	Yes							NO
Past Exposure to carcinogens								NO
Past tobacco exposure		yes			YES	Yes	Yes	NO

* relevant for tertiary prevention, related to the risk of worse course/outcome of the disease, not for primary prevention

3 NCDS BURDEN AND RISK FACTORS DISTRIBUTION IN THE THREE STUDIED COUNTRIES

3.1 NORWAY

3.1.1 Burden of the studied NCDs (CVD, DM, COPD, skin cancer) in Norway.

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Table 2.1. Standardized rates per 100.000 by sex and cause of death, Norway 2020.

	Total	Men	Women
All deaths	840.1	992.0	723.0
Cancer	228	279.9	192.9
CVD	198.5	241.1	163.2
COPD	44.2	49.9	41.2
DM	15.6	19.1	12.8

*Data from Norway Public Health Report, 2020, Norwegian Institute of public Health

3.1.1.1 Main points Diabetes

(taken from [6])

- 1 in 20 Norwegians have been diagnosed with diabetes (245,000 individuals). Of these, estimates show that 28,000 have type 1 diabetes and 216,000 have type 2 diabetes.
- In addition, many may be unaware that they have diabetes.
- Among 80-year-olds, 1 in 9 have diabetes.
- Drug statistics suggest that the number of new cases of type 2 diabetes are no longer increasing.
- Diabetes is associated with serious complications and contributes significantly to the disease burden in Norway and worldwide.
- People with type 1 and type 2 diabetes have increased mortality and risk of complications in the cardiovascular system, kidneys, eyes and nerves. Gestational diabetes is linked with an increased risk of complications during pregnancy for mother and child.
- Estimates show that diabetes constitutes a significant part of the disease burden in Norway. For diabetes, years of life lost made up about 25 per cent of the number of disability adjusted years of life, while morbidity accounted for the remaining disease burden in 2015. Diabetes ranks as number seven in terms of morbidity, after for instance neck- and back pain, common mental disorders and migraines[7].

3.1.1.2 Key points CVD

(taken from [8])

- Every year, approximately 40,000 people receive specialist healthcare services related to angina or myocardial infarction; 16,000 for heart failure; and 11,000 for stroke.
- A fifth (21 per cent) of the entire population currently lives with established cardiovascular disease or with a high risk of developing the disease. Approximately 1.1 million Norwegians use therapeutic drugs to either prevent or treat cardiovascular disease.
- The number of new cases of myocardial infarction per 100,000 inhabitants per year is declining. Of those affected, fewer people are suffering serious myocardial infarction.
- The reduction in smoking and improvements in treatment account for much of the decline in the number of new cases of infarction.

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- Mortality due to cardiovascular disease has shifted to higher age groups in the population. Half of all deaths occur after the age of 83 years among men and after 89 years among women.
- During the 1970s, cardiovascular mortality in Norway was among the highest in the world. This situation has changed dramatically, and Norway is now on a par with the Mediterranean countries.

3.1.1.3 Main points COPD

(taken from [9])

- According to the latest Tromsø Study, about 6 per cent of the population over 40 years old has COPD. This corresponds to 150,000 people in the country as a whole.
- Chronic diseases in the lower respiratory tract (which include COPD) were the third most frequently reported cause of death in 2016.
- The number of people living with COPD will remain high in the coming years because the number of older people is increasing.
- Smoking is the main cause of COPD.

3.1.1.4 Key Points Melanoma and Non-melanoma Skin Cancer

- A worldwide total of 325 000 new cutaneous melanoma cases and 57 000 deaths were estimated for 2020, estimated to increase to 510 000 new cases and 96 000 deaths by 2040[10]. Norway is ranked fifth in the world in melanoma incidence and second in melanoma mortality[11]
- Melanoma and non-melanoma skin cancer are among the most frequent types of cancer in Norway[12] (Note 95% of non-melanoma is cutaneous squamous cell cancer since cutaneous basal cell carcinoma is not routinely registered in the Cancer Registry of Norway). For the most common cancers in Norwegian women and men, the largest increase in incidence from 2011-2015 to 2016-2020 was observed for melanoma (11.4% in men and 10.9% in women) and non-melanoma skin cancers (26.6% in men and 29.9% in women). The Norwegian incidence rate of melanoma in 2020 was 23.2 in men and 25.1 in women, and for non-melanoma skin cancer 22.2 and 16.2, respectively (age standardized rates, world std.). In 2020, the median age at diagnosis was 66 for melanoma and 79 years for non-melanoma skin cancer. The cumulative risk (%) of developing melanoma by age of 80 years, 2016-2020, is 3.6 in men and 3.2 in women. Corresponding cumulative risks were 3.4 and 2.3 for non-melanoma skin cancer.

- Age-standardization by the Norwegian std. is mainly used by the Cancer Registry of Norway. Using the Norwegian std., the Norwegian age-standardized incidence rate of melanoma in 2020 was 44.3 in men and 39.6 in women, and for non-melanoma skin cancer 56.9 and 37.1, respectively[12].

  Melanoma incidence varies by age and for men/women it is 2.9/8.2 for 20-24, 8.0/16.7 for 30-34, 22.7/35.2 for 40-44, 44.5/56.9 for 50-54, 81.9/72.9 for 60-64, 162.1/107.4 for 70-74 and 220.8/130.7 for 80-84. For non-melanoma skin cancer incidence rates for men/women

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were 0.8/1.6 for 20-24, 1.5/1.5 30-34, 3.4/3.9 for 40-44, 10.5/12.6 for 50-54, 44.8/35.2 for 60-64, 183.3/117.2 for 70-74 and 571.4/329.2 for 80-84 years.

There is also a large variation in incidence by county. The male/female melanoma 2020 incidence rates were 50.0/50.5 in southern Norway (Agder), 45.0/34.7 in Oslo, 46.5/41.2 in western Norway (Vestland), 39.8/36.0 in eastern Norway (Innlandet) and 29.6/30.2 in northern Norway (Troms and Finmark).
For non-melanoma skin cancer, the male/female melanoma incidence rates were 77.1/56.4 in southern Norway (Agder), 55.3/29.2 in Oslo, 64.7/47.1 in western Norway (Vestland), 41.9/24.5 eastern Norway (Innlandet) and 40.2/29.1 in northern Norway (Troms and Finmark).

Men are diagnosed in a more serious stage than women. The age-standardized incidence rate in men in 2016-2020 was 36.7 for localized, 4.1 for regional and 1.6 for distant. Corresponding rates for women were 35.0, 2.6, and 0.8, respectively. Norwegian skin cancer incidence rates also vary by country of origin. Melanoma (non-melanoma) incidence 2016-2020 in Norwegian born men was 47.2 (57.7), while it was 37.0 (57.4) for men from the Nordic countries, 32.1 (59.4) for those born in Western Europe/North America/Oceania, 13.9 (14.4) for those born in other European countries, 0.6 (16.6) for those born in Middle East and Africa and 2.7 (12.7) for those born in Asia. Melanoma (non-melanoma) incidence 2016-2020 in Norwegian born women was 43.4 (37.8), while it was 34.9 (30.8) for women from the Nordic countries, 24.9 (34.4) for those born in Western Europe/North America/Oceania, 14.8 (13.8) for those born in other European countries, 3.4 (13.4) for those born in Middle East and Africa and 1.2 (6.1) for those born in Asia.

- Per December 31st 2020, 30 034 and 12 137 individuals were alive in Norway and previously diagnosed with melanoma and non-melanoma skin cancer, respectively[12].

- Long-term survival of melanoma varies between men and women (Cancer Registry of Norway, 2020). Five-year relative survival for 2016-2020 was 95.7 in Norwegian men and 94.9 in Norwegian women and the rates for men/women were 102.0/98.1 for localized, 95.8/75.9 regional and 44.5/55.1/ for distant melanoma[12].

3.1.2 The prevalence and distribution of main risk factors for the studied NCDs in the population of Norway

Table 2.2. Prevalence and distribution of main lifestyle risk factors in Norway

From [13]

Prevalence of Smoking in Norway	**2021**		
Current Smoking	Both sexes % of the population	Males (%)	Females (%)
Daily	8	6	9

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Occasionally	8	9	7
Current Smoking	16	15	16
Alcohol consumption in Norway	**2021**		
Current alcohol drinking	Both sexes (% of population)	Males (%)	Females (%)
Percentage which drinks alcohol once a week or more often	35	42	28
Percentage that has drunk six or more units on one and the same occasion weekly	5	8	2
https://www.ssb.no/helse/helseforhold-og-levevaner/statistikk/royk-alkohol-og-andre-rusmidler			
Proportion fulfilling dietary advice (%)		Males	Females
Vegetables		15	13
Fruits and berries		34	41
Whole grains		27	25
Fish		39	31
Fatty fish		24	21
Red meat		45	67
	Based on the latest national dietary survey (2010-2011) From https://www.regjeringen.no/contentassets/fab53cd681b247bfa8c03a3767c75e66/handlingsplan_kosthold_2017-2021.pdf		

3.1.2.1 "Hotspots" of risk factors in Norway (demographic or geographic)

Individuals from South Asia and Africa have a higher risk of type 2 diabetes than other ethnic groups in the population. There is considerable variation in CVD risk between immigrant groups. Some immigrant groups in Norway are at lower risk of suffering cardiovascular disease than the population as a whole, while other groups are at greater risk. [14, 15]

- Immigrants from South Asia (India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan and Myanmar) are at considerably greater risk of suffering both myocardial infarction and stroke compared with the ethnic Norwegian population[16]
- Immigrants from the former Yugoslavia are also at greater risk of suffering myocardial infarction. Men in this group are also at greater risk of stroke[16]
- Immigrants from East Asia are at less risk of contracting cardiovascular disease than the ethnic Norwegian population[16]

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- With regards to risk factors in many immigrant groups, few people have raised blood pressure and few smoke, particularly among women. This is offset by an increased tendency to be overweight and physically inactive, as well as a greater tendency to develop diabetes, among the same groups[17, 18].

Historically, northern Norway (particularly Finnmark) has had higher cardiovascular mortality than the national average. Mortality has been lowest in Western Norway. These differences are now much less marked than they were earlier. There were no differences between those with Sámi and non-Sámi backgrounds as regards the proportion with previous myocardial infarction and stroke, but a higher proportion of Sámi than non-Sámi reported angina pectoris and chest pain[19, 20]

As described above age, sex, region of residence and origin are important for melanoma and non-melanoma skin cancer risk.

3.1.2.2 Information on co-occurrence/co-variance of risk factors in Norway

Most studies, both from Norway and other countries, show that type 2 diabetes is more common in groups with lower education than in higher education groups. Among those with low education, a higher proportion experience myocardial infarction than among those with higher education. [6]

People with a primary education have a three times higher risk of COPD than people with a higher education. This is still the case when differences in smoking habits and occupation are accounted for [9]

3.2 SPAIN

3.2.1 Burden of the studied NCDs (CVD, DM, COPD, skin cancer) in Spain.

Table 3.1. Standardized rates per 100 000 by sex and cause of death, Spain 2020 [National Institute of Statistics (INE, 2020)

	Total	Men	Women
All deaths	1042.7	1075.8	1011.0
Cancer	238.1	279.96	180.379
CVD	279.1	241.05	264.659
COPD	77	77.71	54.007
DM	23.85	21.90	25. 73

3.2.1.1 Main points in CVD

According to the National Institute of Statistics (INE, 2020)[21], in 2018 (latest consolidated data and validated) a total of 120,859 people died in Spain (53.7% women and 46.3% men) as a consequence of CVD, which assumes a standardized rate of CVD mortality of 230.5 deaths per 100,000 inhabitants. The average age of death in men was 78 years, while that of women was 84 years. The ischemic heart disease leads the ranking of deaths from CVD in men; stroke, in women. All this makes CVD the main cause of death in Spain (explaining 28.3% of all deaths), followed by cancer (26.4%) and respiratory diseases (12.6%).

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Regarding the prevalence of ischemic heart disease, according to the same source, Spain is in the group of European countries with the lowest rates (1000-1400 cases per 100,000) only surpassed by Portugal with 1156 cases per 100,000, although the rate is similar to that of Portugal in women (874 cases per 100,000). Contrary to for the global prevalence of CVD, the trend in the prevalence of ischemic heart disease seems to have decreased slightly between 1990 and 2017, both in the EU as a whole Like in Spain[21].

Regarding stroke, the prevalence in Spain was slightly higher among men (800- 1,100 cases per 100,000) than among women, with a rate of less than 800 cases, among the lowest in Europe. The prevalence of stroke has decreased significantly in Spain and in the whole of the EU since 1990, except in some Eastern countries and in Portugal.

The prevalence of other relatively common and important cardiovascular disorders such as atrial fibrillation, stood at 735 cases per 100,000 inhabitants in men and in 448 in women, in the average of the European set.[21]

3.2.1.2 Main points COPD

Results from recent epidemiological study conducted in Spain (EPSICAN II) [22]: A total of 12,825 subjects were initially contacted, and 9433 (73.6%) agreed to participate, of whom 9092 performed a valid spirometry. Baseline characteristics were: 52.6% women, mean ± SD age 60±11 years, 19.8% current- and 34.2% former-smokers. The prevalence of COPD measured by post-BD fixed ratio FEV1/FVC<0.7 was 11.8% (95% C.I. 11.2-12.5) with a high variability by region (2.4-fold). Prevalence was 14.6% (95% C.I. 13.5-15.7) in males and 9.4% (95% C.I. 8.6-10.2) in females; according to the lower limit of normal (LLN) was 6.0% (95% C.I. 5.5-6.5) overall, by sex being 7.1% (95% C.I. 6.4-8.0) in males and 4.9% (95% C.I. 4.3-5.6) in females. Underdiagnosis of COPD was 74.7%. Cases with COPD were a mean of seven years older, more frequently male, of lower attained education, and with more smokers than the non-COPD population (p<0.001). However, the number of cigarettes and pack-years in non-COPD participants was substantial, as it was the reported use of e-cigarettes (7.0% vs. 5.5%) (p=0.045). There were also significant social and clinical differences including living alone, previous respiratory diagnoses, more comorbidities measured with the Charlson index, greater BODE and COTE scores, cognitive impairment, and depression (all p<0.001).

3.2.1.3 Main points diabetes

The estimated incidence of diabetes adjusted for the age and sex structure of the Spanish population and the form of detection of diabetes was of 11.6 cases/1000 person-years (IC95% = 11.1–12.1). The incidence of known diabetes was 3.7 cases/1000 person-years (IC95% = 2.8–4.6) and, therefore, the incidence of unknown diabetes was 7.9 cases/1000 person-years (IC95% = 5.3–8.1).[23, 24]

As expected, the incidence of diabetes increased with age and was higher among men (13.4 cases/1000 person-years IC95% = 12.6–14.2) than among women (9.9 cases/1000 person-years 95% CI = 9.3–10.4) adjusted for the form of detection of diabetes[25]. Nevertheless, the overall incidence adjusted for the Spanish population, and calculated taking into account that not all subjects underwent all diagnostic tests, was of 11.6 cases/1000 person-years. The incidence of known diabetes has only been a fraction of the total diabetes detected: 3.71 cases/1000 person-years, a

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figure that can be assimilated to the incidence of diabetes diagnosed in the national health system. For people older than 75 years there was no difference between sexes[23, 24]

The variables associated with the presence of diabetes in the cross-sectional study were age, sex, educational level, obesity, abdominal obesity, hypertension, low levels of HDL cholesterol, and high levels of triglycerides as well as the family history of diabetes[23]. In the current work, most of these variables are also associated with incident diabetes, except for hypertension and dyslipidaemia. This may be due to the fact that these variables are not causative of diabetes, but they rather share a common pathophysiology, probably linked to the loss of insulin sensitivity

3.2.1.4 Main Points on Melanoma in Spain

Spain has one of Europe's lowest melanoma incidence and mortality rates. Nevertheless, it is one of the fastest-growing pathologies in our country, with a 181.3 % increase in the incidence rate in men and 205.3 % increase in women. It represents 1.3 % and 2.5 % of malignant tumours in men and women, respectively, while the current standardized worldwide rate is respectively 2.4 % and 4.9 %. The highest incidence levels correspond to Tarragona for men (6.81 %) and Gerona for women (8.24 %), and lowest to the Canary Islands and Zaragoza (3.55 % and 4.27 % for women and men, respectively). This higher incidence among females differentiates Spain from the rest of Europe, where the opposite occurs[26].

Mortality has also increased in Spain in the last few decades (1.76 % in males and 1.26 % in females), although this rising trend has stabilized in recent years. Spain's mortality rate is the lowest in Europe, as the EUROCARE-III study revealed. This study found an increase of 70.4 % in the survival rate for men and 84.1 % for women in the 1980s, while the figures for the 1990s were 73.9 % for men and 89.8 % for women. This low mortality rate in Spain may be due to the increase in thin melanomas, due to early diagnosis and surgical treatment[4]

3.2.2 The prevalence and distribution of the known risk factors for the 4 NCDs in the population of Spain

Table 3.2. The prevalence and distribution of main risk factors for the studied NCDs in the population of Spain (%)

Smoking in Spain (% of the population)	**2020_21**		
Current Smoking	Both sexes	Males	Females
Daily	19.8	23.3	16.4
Occasionally			
Alcohol consumption in Spain (% of the population)	**2020_21**		
Current alcohol drinking	Both sexes	Males	Female
Percentage which drinks alcohol once a week or more often	35.1	46.4	24.5
Percentage of heavy drinkers	1.3	1.5	1
https://www.sanidad.gob.es/estadEstudios/estadisticas/sisInfSanSNS/tablasEstadisticas/InfAnualSNS2020_21/INFORME_ANUAL_2020_21.pdf			
Diet	Homes (% reporting daily intake)	Males (% reporting	Female (% reporting

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		daily intake)	daily intake)
Vegetables		63.9	71.2
Fruits and berries		41	52
Grains	69.1		
Fish	11.1		
Fatty fish	32.0		
Red meat	11.2		
https://www.mapa.gob.es/es/alimentacion/temas/consumo-tendencias/panel-de-consumo-alimentario/ultimos-datos/	Based on the latest Annual Report on Food Consumption 2020		

Adult obesity rates in Spain are higher than the OECD average, but child rates are amongst the highest in the OECD. Two out of 3 men are overweight and 1 in 6 people are obese in Spain. One in 3 children aged 13 to 14 are overweight. The proportion of adults who are overweight is projected by the OECD to rise a further 10% during the next 10 years[27].

3.2.2.1 "Hotspots" of risk factors in Spain (demographic or geographic)

Older age, male sex and lower attained education, were associated with smoking and with COPD ($p<0.001$). Smoking in increasing in younger adults and adolescents, and the proportion of women taking up the habit is increasing.

Women with poor education in Spain are 3.5 times more likely to be overweight than more educated women. Disparities are substantially smaller in men

3.2.2.2 Information available on co-occurrence/co-variance/interdependence of risk factors in Spain

Low socio-economic status, low education level are associated with most of lifestyle risk factors

3.3 ROMANIA

3.3.1 Summary- the burden of the studied NCDs (CVD, DM, COPD, skin cancer) in Romania.

3.3.1.1 Cardiovascular Diseases

Cardiovascular diseases are the main cause of deaths in Romania. In 2019 deaths causes in Romania were represented by circulatory system diseases (55.9% of deaths), of which 19.2% - ischemic heart disease and 14.9% - cerebro-vascular diseases, responsible for a higher number among the female population (62.9% vs. 49.6%)[28].

Ischemic heart disease and stroke are the leading causes of death. Together they account for more than 550 deaths per 100 000 population (2016). The death rate from ischaemic heart disease is almost triple in Romania than in the EU as a whole. Despite a marked reduction since 2000, stroke

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remains the second leading cause of death at 256 deaths per 100 000 population in 2016, well above the EU average of 80.[29]

According to data reported by the National Institute of Public Health in Romania, the most important cardiovascular risk factors are hypertension –correlated with 31.8% of cardiovascular deaths, smoking -16.3%, dyslipidemia – 14.4%, obesity – 13.9%, alcohol consumption – 12.4%, low fruit and vegetable intake – 7.1% and physical inactivity – 6.6% [30]

3.3.1.2 Diabetes

Romania reports a prevalence of Diabetes (1 and 2) of 6.9%, close to the European average of 6.2% in the population aged 20-79, in 2019[2]. The prevalence trend is a slight increase in Southern European and Central and Eastern Europe countries, partly due to the increasing prevalence of obesity and sedentary lifestyle, overlapping with a phenomenon of population aging[2].

The mortality estimates in 2019 Ages standardized mortality rates were 5.20/100 000 for women and 6.85 in men[31].

However, when analyzing the cases of deaths where diabetes was the underlying *or* the first secondary cause of death, as a local study did in 2015, the figures increased to ASMRs of 35.42 in women and 48.41in men[32]. Differences between sexes were most marked in the middle age groups: In the 50-59 age group ASMRs were 22.37 for women and 47.77 for men, in the 60-69 years old group 85.02 for women vs 137.03 for men. Above 70 years, the rates tended to close: 241 vs 283 in 70-79 years old and 418 vs 421 in 80-89years old groups respectively.
Due to methods of reporting death causes and cases registration, the mortality data are likely underestimated for Romania[32] .

The diabetes mortality rates have been increasing in Romania up to 2019, with stronger trend before 2010, and slower growth (+0.9 estimated annual percentage change) in the last decade[31].

The disease burden translated in age standardized DALY (Disability adjusted life years) rates reached 426.5/100 000 for women and 545.4 DALYs/ 100 000 for men in 2019

The costs of DM treatment are estimated for Romania to 581 mil. euro/ year, with an average of 586 Euro/year/ patient. It is estimated that 70% of diabetes diagnosis occur in advanced stages, with complications already developed. Most frequent complications are ophthalmological 40%, cardiovascular 37.5%, 136.6% diabetic neuropathy and 18% renal disease[32].

In terms of health care system characteristics related to Diabetes in Romania, Romania belongs to a cluster of Central and Eastern European countries sharing the characteristics of state health insurance system, no or late adoption of National Diabetes Plan (2013), health expenditure for diabetes over 9% of the total health expenditure, and increasing, with increasing mortality[33].

Romania adopted the National Diabetes Program in 2013, focused on providing medical care for diabetic patients and based on screening, treatment and providing resources for care.

Diabetes prevention program is included in the National Program for treatment of (2021), and there is a National Diabetes Registry established in 2011, with partial coverage.

3.3.1.3 Chronic obstructive pulmonary disease

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It is estimated that COPD affects 8.3% of the population of Romania aged over 40 years old (COPD Prevalence Study in Romania, 2019, Romanian Society of Pneumology), with a slight increase of prevalence from 8.13% in 2012. Alarmingly, 89% of the general population and 85% of smokers never heard of this disease. Only 2in 5 patients with COPD are regularly followed by a physician and 3 of 20 patients treated for COPD use self-medication.

3.3.1.4 Melanoma

The epidemiological surveillance of melanoma in Romania is suboptimal. Cutaneous melanoma is officially reported to the National population-based cancer registry, of which however only 2 out of the 8 regional units are currently functional and of sufficient quality to provide data to IARC. Moreover, since reporting to the regional Cancer registry occurs mainly through oncological centers, early stages melanoma, which are normally diagnosed and treated outside oncological centers, escape reporting. Therefore incidence, mortality, prevalence and survival figures for melanoma in Romania relay on estimates from 2 partial regional cancer registries and neighboring countries. Strong signals of underreporting have been raised[34, 35]

The estimative data available through the European Cancer Information Systems (ECIS) for Romania indicate an age-standardized incidence of 7,6 and mortality 2.6, the lowest in Europe for 2020[4]

Overall Incidence is higher men than in women for all ages, and for ages older than 55 years old. In age groups younger than 55 years old, incidence is higher in women than in men.

All ages mortality is 1.5 folds higher in men then in women, with lower differences in younger age and highest difference over 60 years old (double)[4].

Incidence and mortality increase with age in both sexes.

There are no estimates of CM survival for Romania, but Eastern Europe has a 5-years survival rate of 73%, with the neighboring Bulgaria estimates falling as low as 49%[[4]ECIS]

3.3.2 The prevalence and distribution of the known risk factors for the studied NCDs in the population of Romania

It is estimated that more than half of all deaths in Romania can be attributed to a selection of behavioral risk factors[29] The proportion of deaths attributable to lifestyle risk factors in Romania is 27% for unhealthy diet, 17% smoking, 14% alcohol consumption, and 4% to sedentary lifestyle.

Romania has implemented policies to combat smoking and excessive alcohol consumption, and did not report plans to counteract other risk factors such as overweight, obesity, inadequate nutrition and sedentary lifestyle[36].

Obesity – Romania self-reported obesity prevalence was 10%, the minimum rate in Europe, compared with 17% average for EU 27, for 2018. The trend is a slight increase from 2000. More alarming it is alarming that overweight and obesity rates in children have increased over the last decade to reach 15 %[2, 29].

Also, the Europe-reported difference of obesity prevalence rates between low-education and high education level groups is minimum in Romania and neighboring Balkan countries (5%)

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Overweight is estimated in the lowest quadrant (<60%) for males and 2nd lowest tier (50-59%) for females

However, self-reported rates are usually underestimated, compared with BMI values, which are measured and reported only in a few EU countries[29].

Thus, an epidemiological study conducted in Romania in 2015-2016 SEPHAR III revealed that 20% of the obese participants in the study and 75% of the overweight ones believed they had a normal weight[37].

The PREDATORR (PREvalence of DiAbeTes mellitus, prediabetes, overweight, Obesity, dyslipidemia, hyperuricemia and chronic kidney disease in Romania) study[38] is the first national study analyzing the prevalence of diabetes mellitus (DM) and prediabetes, and their association with cardiometabolic, sociodemographic, and lifestyle risk factors in the Romanian population aged 20-79 years (2014).

Over 75% of the 40-79 age group of the PREDATORR study had a BMI above the upper limit of normal: 40.3% overweight and 35.1% obese. Obesity was more common in women compared to men: 39.2% vs. 30.2%. Nearly half of men were overweight (48.4%) and a third of women (33.7%)[38, 39]

The overall prevalence of obesity, adjusted for sex and age, in the Romanian adult population was 31.9%, and that of overweight was 34.7%. The highest percentage of obesity was found in the 40-59-years age group and in men, while the highest percentage of overweight people was in the 60-79-years age group and in women.

Abdominal obesity had a 73.9% prevalence in the general Romanian population, predominantly in the 60-79-years age group and among women, with 91%.[38]

Physical activity

Romania reported the lowest proportion of adults involved in moderate weekly physical activity of more than 150 minutes in 2014 in Europe (38%), with rates lower for women 30%, than for men (46%)[40, 41]. The average Europe is 65%

Differences in moderate weekly physical activity by population groups, depending on the level of education and the country in which they live, with sedentary lifestyle more prevalent in higher education groups. These differences were largest in Bulgaria, France and Romania, in the later the maximum of over 20%(4% average Europe)[2]

Sedentary lifestyle is associated with obesity and Diabetes risk, this combination disfavors women. European states structures need to be more involved in ensuring women's access to sports, removing socio-cultural barriers, increasing safety and making timely investments for infrastructure favoring walking/pedestrians.

According to the statistics provided by the EU Eurobarometer 2017[42] on the territory of Romania, the opinion of Romanians regarding the opportunities for physical activities is among the most negative among European populations.

Alcohol

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Romania has the highest alcohol-related mortality rate in the European Union for women and is ranked 4th for men, with 17,000 Romanians dying annually due to alcohol consumption. [3] In terms of excessive alcohol consumption, Romania ranks 5th.

Romania reported an average of liters of pure alcohol consumption/inhabitant/year very close to the European average of 10l/person, with a reduce of about 3l/person over the decade 2008-2018[2]. However, men consume 4 times more alcohol than women. Excessive drinking (binge drinking) is reported by 35% of the population, and over 50% of men[2].

Beer is the favorite alcoholic drink of Romanians, being consumed by 67% of them, wine is consumed by 57% of Romanians, and spirits are consumed by 39% of drinkers under 35 years and about 42% by those aged 35-65 years[43].

Tobacco

Tobacco consumption is a major public health challenge in Romania. Despite a slight reduction in smoking rates since 2008, one in five adults still smoked daily in 2014, in line with the EU average. There is a large gender gap in smoking, with smoking rates among men (32 %) four times higher than among women (8 %)[2, 29].

Regular tobacco consumption in adolescents is a matter of concern, with nearly one third of 15- and 16-year-olds reporting having smoked during the preceding month in 2015, among the highest rates in the EU. The effects of the 2016 Law on Prevention and Control of Tobacco are yet to be seen.

Nearly 13.5 % of people in the lower education groups are regular smokers compared to nearly 21 % in the highest education groups. However, the smoking rate was similar for both high- and low-income groups (18-20 %).

Diet

Fruit

In the European Union, on average, 57% of adults say they eat fruit every day. The distribution of *fruit consumption* in the European Community is uneven. Thus, in countries such as: Bulgaria, Latvia and Romania, less than 40% of the adult population reported daily fruit consumption. Women tend to eat more fruit then men, the differences between gender are among the smallest in Europe for Romania[2, 29]

Vegetables

Romania reported the lowest daily consumption of vegetables, only 30% of the adult population 16 *Daily consumption of vegetables among adults in 2014[41]*, compared to 51% European average. The differences between men and women are the same as for fruit consumption. The vegetables intake increases in elderly

Proportion of adults consuming at least five portions of fruits and vegetables daily in 2014 was in Romania the lowest in Europe, at 2.5% in men and 4% in women, 5.5% in higher education level group vs 2.4% in the lower education group. Source: Eurostat EHIS 2014[41]. The main content of diet is based on potato and cereals.

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Macronutrients in diet

Regarding the content of the diet stratified on main macronutrient, the The report on Heath and Environment elaborated in 2020 by the National Institute of Public Health[44] revealed that:

- *Total daily calories intake* in men was within the recommendations limit, except for the age group over 62 years which is 30% higher than the recommendations. For women the energy intake was in line with the recommendations only in the age group 45-60 years, while it was lower in the group 20-45 years by 13.6% and higher in the group over 60 years by 35%.
- *Lipids intake*. High intake of total fats and in particular saturated fats and cholesterol (saturated fats account for more than 80% of the total) was found, which means that the percentage of the energy intake covered by fats is 41% compared with the recommended 15-30%. Cholesterol intake was more than double (714 g/day) the limit considered tolerable in the diet (300 mg/day).
- C*arbohydrate intake* was insufficient, with only 40.1% of the energy intake being covered by carbohydrates compared with 55% as would be recommended.
- *Sugar intake* was high, with 60% of the population intaking sugar daily, 12% of the population 2-3/week and further 5% 1/week. Sugar products consumption was reported daily by 23,6% of the population, 2-3/week by 26.9% and 1/week by 18.6%.
- *Dietary fiber* intake was of only 12.1 g/day compared with the 25-30 g/day recommended
- *Protein intake* was higher than recommended, predominantly of animal origin, with 18.6% of the energy ration covered by protein compared to the recommended 15%. The animal to vegetal protein content ratio was 2.6 in men and 2.24 in women (vs. 1.1. recommended)
- *Salt intake* was increased, over 6.57 g/day - added salt - leading to an estimated total intake of almost 12 g/day total consumption
- *Micronutrients* deficiencies were reported only in the case of calcium and magnesium intake for women

Analysis of eating habits by frequency of consumption shows the Romanian subjects' preferences for certain products they consume more often, namely: meat and meat preparations, eggs and milk products and cheese, bread and sugary products, and at the opposite pole those they consume rarely, namely: legumes, nuts and seeds, and natural juices, the preferences remaining mainly the same as in previous years. An improvement was noted in fish consumption, which is increasing[44].

Dyslipidemia

Approximately 67.1% of the Romanian adult population have at least one abnormal value of the lipid profile: 47.8% have elevated LDL-C, 29.4% have low HDL-C and 27.5% have elevated TG. The overall prevalence of mixed dyslipidemia in the adult population of Romania was 30%[38, 39].

The association of all three lipid abnormalities was found in 7.6%, with a maximum prevalence in the 60-79-years age group and in women. The overall age-and gender-adjusted prevalence of isolated low HDL dyslipidemia was 9.3%, of high LDL was 23.7%, and of isolated hypertriglyceridemia was 4.1%. The highest prevalence of low HDL-C levels was found in the 20-39 years age group and in women, while high LDL-C and TG levels were found predominantly in the 40-79 years age group and in men. 26.2% of the patients with high LDL-C levels had LDL-C ≥ 2.58 mmol/l, associated with cardiovascular disease or equivalent cardiovascular risk (10-year risk >20%). The prevalence of high levels of non-HDL cholesterol was 15.2% in the adult Romanian population and 12.6% have high or very high values of non-HDL-C, according to the NCEP definition[37].

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Hypertension

The overall prevalence of hypertension in the Romanian population is 45.1%, increasing with age: from 15.4% in the 18-24-years age group, up to 66.9% in the over 65 years age group, independent of gender or residence. Among hypertensive patients, 19.1% are newly diagnosed and 80.9% are known to have high blood pressure. Despite the fact that most of them (72.2%) received antihypertensive treatment, only 30.8% have controlled blood pressure values. Significant differences in the prevalence of hypertension were observed in urban areas, being higher in men (48.9 vs. 40.4%). The prevalence of newly diagnosed hypertension was higher in men (urban – men: 25.1 vs. women: 10.8%; rural – men: 24.7 vs. women: 16%) while the prevalence of known hypertension is higher in women (urban – men: 74.9% vs. women: 89.2%; rural – men: 75.3 vs. women: 84%), regardless of the environment. The presence of antihypertensive treatment in the urban environment differed between the two genders, being more frequent in women (81.9 vs. 68.2%). Overall, antihypertensive treatment was more frequent in urban than rural areas (74.8 vs. 68.6%)[37, 39].

Metabolic syndrome

Metabolic syndrome is a group of metabolic risk factors for cardiovascular disease, such as insulin resistance, impaired glucose tolerance, abdominal obesity, dyslipidemia and prothrombotic/ proinflammatory status. The prevalence of metabolic syndrome in Romania was reported to be about 40% [38, 45], higher in males (43.2 vs 34.2%) and increasing with age, from 20% in the 20-39-years age group, to 56.6% in the 60-79-years age group, with equal prevalence between the genders in the elders. In order to investigate the relationship between unhealthy lifestyle and the risk of metabolic syndrome in the Romanian population, a study was conducted on a group of 181 patients of a rehabilitation hospital, which identified living in rural areas, lower education, smoking history, excessive alcohol consumption, and no fruits and vegetable consumption as risk factors for metabolic syndrome[46].

Sun exposure

There are no studies on the sun exposure habits in Romania.

Natural UV exposure is quite high, as Romania is situated at 45* Latitude, in continental temperate climate, with an UV index average over 7 for 4 months (May-August), and 3-7 for 4 months (March-April, September- October)

Romania has a high proportion of rural population, working in agriculture.

Skin cancer due to outdoor professional UV exposure is not recognized as occupational disease, protection regulation for outdoor professions UV exposure is not in place. Low awareness of skin cancer risks and UV risks is prevalent, especially in low income and low education population segments, among those performing unqualified work in construction and agriculture.

Summer holidays at the seaside are common in the population, especially urban, and sunbathing is popular, with sunburns being reported frequently, including in children.

Sunbeds use is rapidly increasing, with only moderate regulation regarding type of UV lamps, information for users, personal training. Sunbed use is by law forbidden under 18 years. However,

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compliance to regulations, the correctness of information to users and the handling of high-risk groups is not systematically controlled[47].

Data from the population structure, empirical data about skin cancer patients, small scale center-based studies[48, 49] [50]suggest that the main source of excessive UV exposure related to melanoma risk is the chronical exposure in rural areas and in professional setting related mainly to agriculture followed by outdoor professions such as construction, infrastructure maintenance, navy, and other partially outdoor professions. Sunburns are highly prevalent in melanoma patients reports.

Sunbeds use history is very rare in melanoma patients, but sunbeds use is increasing rapidly, especially in urban areas, and in young women.

Phenotypical markers of melanoma risk

There are no national or regional studies on melanoma-specific risk factors/markers prevalence. Small center-based observational studies suggest that melanoma patients in Romania exhibit the same risk factors as for European population, with higher risk in people with fair phototypes, higher nevi count, history of sunburns or chronic sun exposure.

There is no data on the prevalence of the phenotypical risk factors in the population. The majority of the population exhibits phototypes II and III. Phototype I is more frequent in German and Hungarian-descendance minorities in the West of the country, as well as in North-East (Moldavia). Phototype IV, the least exposed to skin cancer risk is prevalent in Roma minority.

Psychosocial risk factors

Psychosocial factors are commonly found in patients with cardio-vascular disease, with significant differences between genders. The most frequently observed were social isolation (72.2%), low socioeconomic status (63.8%), work-related stress (65.2%) and hostility (65.9%). A higher frequency was observed in women for: lack of social support (79.8 vs. 72.2%), depression (43.9 vs. 31.6%), anxiety (58.3 vs. 45.2%), hostility (70 vs. 65.9%), D-type personality (64.1 vs. 55.5%), post-traumatic stress (65.5 vs. 57.3%) and other psychiatric conditions (11.2 vs. 8.8%), while men were more often exposed to occupational stress (65.2 vs. 61.4%)[51].

3.3.3 "Hotspots" of risk factors in Romania (demographic or geographic)

Compared to EU average, Romania shows high prevalence in unhealthy diet, sedentary lifestyle, drinking, average tobacco consumption and lower prevalence of obesity and overweight.[2, 29]

Low socio-economic status and low level of education are catalysts for cardio-vascular risks, diabetes risks, and other lifestyle factors including drinking, unhealthy diet, smoking.

Both socially assisted women and men had the highest cardiovascular risk, 14.3% of women and 33.3% of men belonging to the cardiovascular risk category >40%, while the minimum risk (<10%) was recorded among students, unmarried women, women working in agriculture and people with unemployment benefits. Cardiovascular risk of >40% was recorded more frequently in people with low educational level compared to people with higher education: 9.7% vs. 3.3% among men and 3.6% vs. 1% among women[38, 39, 46]

Drinking, smoking, unhealthy diet, overweight is more prevalent in men than in women.

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Chronic sun exposure is common in rural areas, in agricultural and other outdoor professional settings. Sunbathing is a popular recreation, across all categories. The use of sunbeds is increasing, mainly in urban areas and for younger women.

3.3.4 Co-occurrence/co-variance/interdependence of risk factors in Romania

Sedentary lifestyle is more prevalent in women and high education

High education level is associated with sedentary lifestyle and smoking, but less drinking, less overweight and better diet, less frequency of metabolic syndrome.

Low socio-economic level has more prevalent drinking and unhealthy diet, similar smoking rates as higher income, higher cardiovascular and diabetes risk.

Drinking, smoking, unhealthy diet, overweight is more prevalent in men than in women

4 POTENTIAL NEW RISK VARIABLES

The established risk factors described previously are based upon large and repeated studies, often focusing on one or few factors at a time. While reliable, the traditional validation process is slow to evolve our understanding of factors that influence the risk of developing CVD, DM, COPD or skin cancer. Further, this process primarily focuses on clinical factors [52] For example, the INTERHEART study recently highlighted nine factors that contribute to the vast majority of myocardial infarction, all but three of which (i.e. physical activity, diet and psychosocial factors) are clinical [53]. In 2022 the European Association of Preventive Cardiology (EAPC) still focuses on bringing “topics like hypertension, diabetes, dyslipidemia and smoking to the forefront of attention” [52, 54].

Beyond those, individual behavioral and psycho-social factors as well as community/environmental level characteristics do exercise an influence on risk of developing diseases, but their role and true impact is less explored and only begin to be elucidated; Therefore, these are often not included in the risk calculators (see Deliverable 2.1) and the guidelines of prevention practices used by health authorities and healthcare providers in addressing the public health problem of major NCDs prevention.

However, the rapidly evolving technologies of artificial intelligence – as it is proposed in WARIFA – can integrate a high number of variables, and thus have the potential to reveal possible new associations between some of the emerging, non-traditional variables and the risk of developing the diseases, or between new variables and the established risk factors for chronic diseases. Thus, integrating new variables, beyond established risk factors, into the WARIFA AI tool, may reveal new risk determinants, improve our understanding of how these illnesses develop, and highlight the directions for further epidemiological studies, to validate this new knowledge.

The challenge in this context is to select the set of input variables to integrate into the WARIFA AI tool, from the colossal range of possible information about the individuals and their environment. In order to narrow down this selection to the variables most likely to show a relationship with the risk of developing the NCDs studied in WARIFA, we proceeded to review the scientific evidence available so far regarding individual or community-level variables that have shown some degree of association

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with the risk of the studied NCDs, in the population of any of the three countries (Norway, Spain Romania), beyond the established risk factors (listed Table 1)

4.1 Methodology of Review

For this aim we performed a scoping scientific literature search, in the databases: PubMed/ Medline and Web of Science in the period 03-04.2022. The search terms were established through consensus of the experts of clinical and preventive medicine, epidemiology, and social and behavioral sciences of the Consortium. These included:

Population *(adults in any one of the consortium countries)*: Norway OR Norwegian OR Spain OR Spanish OR Romania OR Romanian

Exposure *(risk variables)*: Behavioral OR behavior OR lifestyle OR habit **AND** risk **AND** variable OR factor OR influence OR determinant.

Community OR neighborhood OR environment AND risk AND variable OR factor OR influence OR determinant

Outcomes *(development of any of the studied NCDs)*: Diabetes OR metabolic syndrome OR chronic obstructive pulmonary disease OR COPD OR cardiovascular disease OR coronary heart disease OR ischemic heart disease OR myocardial infarction OR stroke OR Blood hypertension OR CVD morbidity OR CVD mortality OR Skin cancer OR Melanoma

Only literature in English, that described studies performed in at least one of our Consortium countries (i.e., Norway, Spain, and Romania) within the last 12 years, were included.

We retained the articles that addressed variables of interest, identified as those that:

1. Were at individual level (biological, phenotypical, behavioral, socio-cultural), or related to the community/environment in which the individuals were situated (i.e., climate/ natural life environment, social/cultural/economical characteristics of the community, physical features of the residence place.)
2. Were not already included in the aforementioned list of established risk factors (Table 1)
3. Demonstrated a statistically significant or qualitatively significant association with the risk of developing at least one of the NCDs studied in WARIFA

4.2 Results

We identified 1694 articles, corresponding to the search. After applying the criteria of selection (3 independent reviewers M.B, I.J-B, L.B) we retained 109 articles filling our criteria, from which we identified relevant, novel variables associated with risk.

The results are summarized in Table 4 (4.1-4.2)

Many of the identified studies explored the impact of more than one risk variable on the studied NCDs, separately or in combination. Most reports addressed only one of the studied NCDs.

Some studies reported only on new variables, some other reported on a combination of new and established risk factors.

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Table 4.1. New variables associated with risk of developing NCDs (cohort/case-control/review studies)

N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
	COPD	• Pollution level • Climatological factors • Temperature • Humidity • Ozone (o3) • Carbon monoxide (co) • Particulate matter • Nitrogen dioxide (no2)	Spain	162338	18+	16.5	Cross-sectional	[55]
	CVD	• Previous hospital admission	Spain (Alicante)	303	18+	48.8	Cohort	[56]
	CVD	• Socioeconomic status (education, employment status (except those who had retired or had a permanent disability)/rural population/gender	Spain (Badajoz, Extremadura)	2833	25-79	53.5	Cross-sectional	[57]
	CVD	• Total number of negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and conversation flow, motor retardation, and active social avoidance)	Spain (Barcelona)	1120	18+	41.6	Cohort	[58]
	CVD	• Ethnicity (South Asians living in Europe)	Spain (Catalonia)	N/A	20–64	N/A	Review	[59]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
	CVD	• Occupation (professional driver)	Spain (Different Spanish geographical areas)	24787	18+	5	Cross-sectional	[60]
	CVD	• Access to small stores for buying healthy foods • Drinking as a socialization mechanism • Accessibility to public open spaces • Availability of destinations to walk to for the elderly	Spain (Madrid)	15000	45+	55.1	Exploratory study	[61]
	CVD	• Mediterranean lifestyle (Rest (napping for 30mins or less) X Social habits X Conviviality)	Spain (Navarra)	18419	18+	60.5	Cohort	[62]
	CVD	• Olive oil consumption • Low Mediterranean diet adherence	Spain (Northern regions; Basque country; Cordillera Cantabria; Central Spain; Peninsular Spain; Southern Spain & Canary Islands; Eastern Spain)	1732	37-65	54	Cross-sectional	[63]
	CVD	• Ethnicity (South Asians living in Europe)	Norway (Norway National data)	2637057	35–64	N/A	Cohort	[59]
	CVD	• Active travel (walking or cycling for travel) X low SES (favorable)	Norway (Oslo)	2445	18+	56.4	Cross-sectional	[64]
	CVD	• Antipsychotic drugs X gender	Norway (Oslo)	1791	16-65	48	Case control	[65]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
	CVD	• Eating speed	Spain (Reus-Tarragona)	792	55-80	57	Cross-sectional	[66]
	CVD	• Sociocultural level (low sociocultural level)	Spain (Southern Spain (Malaga))	2270	18-80	50.3	Cross-sectional	[67]
	CVD	• Ethnicity (South Asians living in Europe)	Spain (Spanish National data)	799446	60-79	100	Cross-sectional	[59]
	CVD	• Road noise • Outdoor light pollution	Spain	N/A	N/A	N/A	Review	[68]
	CVD	• Poor adherence to the Mediterranean Diet X Little education, single, divorced or separated	Spain	7305	55-80	58.9	Cross-sectional	[69]
	CVD	• Intervention: Obese men on antihypertensive medications X advice/counseling, exercise sessions	Norway	568	40-74	0	2X2 Factorial trial	[70]
	CVD	• Oral tobacco use	Norway (Nord-Trondelag)	1592	20+	0	Cross-sectional	[71]
	CVD	• Socioeconomic status (education) • Smoking practice x nonmanual occupation • Manual occupations x gender	Spain	2699	60+	53	Cross-sectional	[72]
	CVD	• Socioeconomic position (race, education, income, social class)	Spain	20406	18+	52.5	Cohort	[73]
								[74]
	CVD	• Social interaction	Spain	4008	60+	56.4	Cross-sectional	[75]
	CVD	• Education level • Childhood environment	Norway	228346	40-45	52	Cross-sectional	[76]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
	CVD (Coronary heart disease)	• Living alone X men • Education level X women	Norway (Hordaland)	17361	40-67	N/A	Cohort	[77]
	CVD (coronary heart disease; CVD morbidity and mortality)	• Traffic pollution • Long-term exposure to traffic pollution • Indoor exposure • Indoor air pollution due to biomass smoke	Spain (Barcelona)	N/A	N/A	N/A	Review	[78]
	CVD (CVD mortality)	• Socioeconomic indicators (employment, education level, education level X age, manual vs. non-manual work, temporary work status) • City size	Spain	8375477	18+	N/A	Cross-sectional	[79]
	CVD (CVD Mortality)	• Socioeconomic position	Norway	398297	40-50	61.1	Cohort	[80]
	CVD (CVD Mortality)	• Unemployment rate • Crude divorce rate • Available beds in hospital	Norway	N/A	18+	N/A	Cohort	[81]
	CVD (hypertension)	• Knowledge of cardiovascular disease • Living alone/social support • Quality of life	Spain (Alicante)	303	18+	48.8	Cohort	[56]
	CVD (hypertension)	• Level of education • Civil status	Romania (Bucharest)	806	18-83	63.2	Cross-sectional	[82]
	CVD (hypertension)	• Depression (treatment vs. Not adequately treated)	Spain (Navarra and Basque country; Catalonia; Valencia and Balearic Islands;	5954	55-80	60.5	Cross-sectional	[83]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
			Andalusia and Canary Islands)					
	CVD (hypertension)	• Increased levels of stress	Romania (North)	2659	18+	53.22	Cross-sectional	[84]
	CVD (hypertension)	• Socioeconomic level (education and occupational activity) • Psychological well-being • Emotional stress • Disease awareness X duration since diagnosis • Depression	Romania	1970	18-80	53	Cross-sectional	[85]
	CVD (ischaemic heart disease)	• (Favorable factors) Residence of low population density • Residence of areas with less farming • Residence of areas with less unemployment • Residence of area with adequate supply of healthcare resources/services	Spain (Burgos; Cuenca; Cantabria; Palencia; Teruel; Navarre; Pontevedra; Lugo; Orense; Tarragona; Salamanca; Segovia; and Soria; Suances in Cantabria, and Deltebre in Tarragona)	32 (towns)	N/A	N/A	Cohort	[86]
	CVD (ischemic heart disease)	• Health anxiety	Norway	7052	18+	49	Cohort	[87]
	CVD (mortality; ischemic heart disease; Stroke)	• Parental socioeconomic position • Parental practices • Housing • Neighborhood	Norway	271643	18+	51.3	Cohort	[88]
	CVD (myocardial infarction)	• Urban greenness • Air pollution • Daytime traffic noise levels • Walkability	Spain (Barcelona; Catalonia)	41463	18+	50	Cohort	[89]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
	CVD (myocardial infarction)	• Educational level	Norway	70506	35-85	32.4	Cross-sectional	[90]
	CVD (myocardial infarction; stroke)	• Education level • Pensioner status • Geography (urban vs rural) • Employment	Romania	15138	41-64	N/A	Cross-sectional	[91]
	CVD (stroke)	• Traffic-related air pollution	Spain (Barcelona)	2742	18+	50.6	Case-crossover study	[92]
	CVD (stroke)	• Air pollutants • Residential surrounding greenness • Exposure to fine particulate matter, black carbon • Nitrogen dioxide (no2)	Spain (Catalonia)	3 521 274	18+	52	Cohort	[93]
	CVD (stroke)	• Socioeconomic status (income)	Spain (Catalonia)	16344	18+	46.5	Cohort	[94]
	CVD (stroke)	• Temperatures • Humidex	Spain (Galicia)	50 (weather stations)	N/A	N/A	Comparison of weather station data over time	[95]
	CVD (stroke)	• Psycho-physical stress • Socioeconomic level (civil status, employment)	Spain (Madrid)	150	18-65	22.7	Case control	[96]
	CVD (stroke)	• COCs		16 (studies)	18+	100	Integrative review	[97]
	Diabetes	• Deprivation	Spain (Barcelona)	2978	18+	N/A	Cross-sectional	[98]
	Diabetes	• Depression/anxiety	Norway (Nord-Trøndelag)	37291	20+	N/A	Cross-sectional	[99]
	Diabetes	• Active travel (walking or cycling for travel) X low SES (favorable)	Norway (Oslo)	2445	18+	56.4	Cross-sectional	[64]
	Diabetes	• Ambient temperature	Spain	5072	18+	57.1	Cross-sectional	[100]
	Diabetes	• SES (educational level, social class	Spain	N/A	N/A	N/A	Cohort	[101]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
		based on occupation)						
	Diabetes	• Marital status (widower vs. Single vs. Divorced)	Romania	2728	20-79	52.1	Cross-sectional	[102]
	Diabetes (metabolic syndrome)	• Total number of negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and conversation flow, motor retardation, and active social avoidance)	Spain (Barcelona)	1120	18+	41.6	Cohort	[58]
	Diabetes (Metabolic syndrome)	• Income • Crowding • Education	Spain (Canary Island; Tunisia)	6729	18-75	56.7	Cross-sectional	[103]
	Diabetes (Metabolic syndrome)	• Rural environment Lower education level	Romania (Cluj-Napoca)	181	36+	70.2	Cross-sectional	[104]
	Diabetes (Metabolic syndrome)	• Evening chronotypes	Spain (Murcia)	2748	18-29	83.3	Cross-sectional	[105]
	Diabetes (Metabolic syndrome)	• Lifestyle **x** stress X psychoses	Spain (Tarragona)	81	18-29	39.5	Cohort	[106]
	Diabetes (Metabolic syndrome)	• Residence of an area in a geographically higher altitude (favorable)	Spain	6860	25+	59.8	Cohort	[107]
	Diabetes (Metabolic syndrome)	• Perceived stress level	Romania	254	18+	40.2	Cross-sectional	[108]
	Diabetes (T1D)	• Socioeconomic status (education)	Norway (Nord-Trøndelag)	76885	20+	59.1	Cohort	[109]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
	Diabetes (T2D)	• Socioeconomic status (education)	Spain (Las Margaritas; Lista; Arévalo)	5278	65+	40.8	Cohort	[110]
	Diabetes (T2D)	• Number of healthy lifestyle habits • Nap length during the day (favorable <30mins) • Marriage status • Tv watching • Working hours per week (favorable <40)	Spain (Navarra)	11005	18-80	43.1	Cohort	[111]
	Diabetes (T2D)	• Lack of available info about the preventive health services • Time pressure • Lack of financial affordability for training facilities • Absence of gender-exclusive gyms	Norway (Oslo)	30	25+	100	Cohort	[112]
	Diabetes (T2D)	• Duration of stay in Norway (≥11 years)	Norway (Oslo; Akershus)	302	25+	100	Cross-sectional	[113]
	Diabetes (T2D)	• Higher concentrations of persistent organic pollutants • Low level exposure to persistent organic pollutants	Spain (Southern Spain, Granada))	386	18+	49	Cross-sectional	[114]
	Diabetes (T2D)	• Inorganic arsenic exposure	Spain (Valladolid, northwestern Spain)	1451	20+	51	Cohort	[115]
	Diabetes (T2D)	• Country of residence	Spain	3596	18+	55	Cohort	[116]
	Diabetes (T2D)	• Blue collar social status • Former smoker status	Spain	23293	20-65	27	Cohort	[117]

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N	Disease	Risk variables	Country (geographic area)	Population	age	Sex (%F)	Study type	reference
	Skin cancer	• Pharmacist-Dermatologist collaboration for screening (awareness)	Spain (Barcelona, Catalonia)	5530	18+	74.7	Cross-sectional	[118]
	Skin cancer	• Attitudes • Beliefs • Knowledge • Actions taken to avoid sun exposure	Spain (Canary Islands)	286	N/A	68.8	Cross-sectional	[119]
	Skin cancer	• Sunburn X students • Knowledge (UV lamps association w/ skin cancer) • Knowledge (sun exposure association w/ skin cancer)	Spain (Madrid)	2007	18-64	51	Cross-sectional	[120]
	Skin cancer	• Teledermatology	Spain (Western Costa del Sol)	393	18+	65.4	Transversal descriptive study	[121]
	Skin cancer	• Secondary/university education	Spain	1054	18+	61.2	Cross-sectional	[122]
	Skin cancer (melanoma)	• College or university education • Higher income	Norway	9775	25+	49.2	Cross-sectional	[123]
	Skin cancer (melanoma)	• Psychological factors (stress-prone personality or unfavorable coping styles, negative emotion, depression) • Social factors	Spain	467	18+	52.2	Case control	[124]
	Skin cancer (melanoma)	• Use of Antidepressants	Norway	130566	18-85	50.5	Cohort	[125]
	Skin cancer (melanoma)	• Use of Immunomodulating drugs (immunosuppressants and corticosteroids)	Norway	130670	18-85	50.5	Case control	[126]

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Our selection of articles included a small number of RCTs and intervention trials. Although they are not aiming primarily to identify risk variables or quantify their impact, studying their points of intervention can bring valuable information on hypothesized risk variables, beyond established risk factors, in the studied population subgroups. Therefore, we kept them for our analysis and summarize them in the **Table 4.2**

Table 4.2. New variables associated with risk of developing NCDs (from RCTs and intervention studies)

Disease	Risk Variables	Country (geographic area)	Population	age	Sex (%F)	ref...
CVD	Blood pressure hyperreactivity defined as a combined stress-induced change in SBP (>20 mmHg) and DBP (>15 mmHg)	Romania (Arad County)	35	40-50	N/A	[127]
CVD	Social Cognitive Theory (continuous interaction of: personal factors, environmental influences, and behavior, i.e. observational learning, reinforcement, self-control, and self-efficacy via healthy lifestyle choices)	Spain (Barcelona; Cambrils; Guadix; Manresa; Molina de Segura; San Fernando de Henares; Villanueva de la Cañada)	543	25-50	71	[128]
CVD	persistent organic pollutants (POPs)	Spain (Navarra and Basque country; Catalonia; Valencia and Balearic Islands; Andalusia and Canary Islands)	343	55-80	65.8	[129]
CVD	Intervention: sociocultural participation	Spain	364	18+	76.8	[130]
CVD	Elderly men X advice/counseling	Norway	563	65-75	0	[70]
CVD	Chronodisruption X diet (evening chronotype (i.e., the preference to wake up late and feel more active during evenings or nights, are more prone to have chronodisruption)	Spain	857	20-76	17.2	[131]
Diabetes (Metabolic syndrome)	Intervention: knowledge (culturally adapted lifestyle education programme)	Norway (Oslo)	198	25-62	100	[132]
Diabetes (T2D)	Factors represented in the intervention: knowledge, empowerment, including participation and cooperation without assuming responsibility for the other person's performance, and accepting without judging the other's feelings and choices.	Norway (Oslo)	198	25-60	100	[133]

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	Intervention: culturally adapted and non-directive intervention. Since many of the participants had low levels of literacy, mainly culturally adapted pictures and figures were used during the education sessions. All communication in the intervention group went through the preferred language, either with multilingual personnel or with an interpreter. All research personnel were female.					

In summary, the variables most frequently associated with the risk of diseases identified in our review were:

- Living spaces (air and green spaces that are healthy, clean, etc.), which were associated with all except skin cancer;
- Mental stress (depression, anxiety, social or occupational stress), which were associated with CVD and Diabetes (not T1D). Moreover, comorbid depression and diabetes have synergistic effects on the risk of all-cause mortality and risk of cancer- and cardiovascular disease- specific mortality.

We mention that Socio-economic status (income, occupation, education etc.) appeared repeatedly in our search results, were associated with all diseases risk, except COPD; but since these are already established variables of risk, included in our table 1, we do not repeat them here.

With respect to factors most commonly reported for each disease, from this review:

- COPD was only associated with Living spaces;
- CVD studies explored the risk posed by (in order of frequency) Living spaces, Socio-economic status, and Mental stress;
- Diabetes (with no distinction as to which type) was reported in association with Socio-economic status, living spaces and Mental stress; T1D was only explored in relation to Socio-economic status; T2D was studied in association (equally) with Socio-economic status, Living spaces, and Health behaviour;
- Skin cancer was most commonly studied in association with Health beliefs, attitudes and knowledge, followed by Socio-economic status and Medication.

A combination of factors was studied primarily for CVD (e.g., Mediterranean lifestyle, which included naps in addition to diet, socializing and conviviality, and one's gender in association with co-habitation or occupation),

One study of combination factors explored Diabetes (i.e., stress in the presence of psychosis) and one study addressed skin cancer (i.e., sunburn amongst students). One study of interest – an outlier in terms of unique factors studied- was that which explored psychological factors such as stress-prone personality etc. in related to increased risk of skin cancer.

4.3 Discussion

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In this scoping review of the literature, we identified several variables and combinations of variables that were associated with the risk of developing at least one of the chronic diseases that are the focus of our WARIFA project, in the countries of the pilot study.

A rapidly accumulating body of scientific data confirm the empirical knowledge that our health, and especially health choices, are impacted by factors beyond our biological measurements; our beliefs, experiences, surroundings and access to resources can facilitate or hinder our capacity to pursue healthy options or the availability of healthy environments. These factors exist, evolve and impact differently depending on their context, i.e., the geographical region with the related climate and resources, cultural and socioeconomic context therein. Whereas an individual of Asian descent, living in Norway has access to certain foods, societal influence and health-related resources, that same individual may have a different experience in Romania, which may translate to a different health status. The findings of this review highlight factor that have not yet been fully explored, but provide potential for a more comprehensive understanding of the mechanisms of disease development in Norway, Spain and Romania, as well as interesting hypotheses for further public health interventions aimed at enhancing major NCDs prevention.

As previously mentioned, artificial intelligence may be a powerful tool to explore the relationships between these factors with the development of the major NCDs in a novel way, thereby potentially giving researchers, individuals and policy makers a greater understanding of disease prevention. It is important to build upon existing knowledge; supplementing our understanding of established factors with future population-based studies that explore and validate these novel factors, also in different national or regional contexts.

4.4 CONCLUSION

The information gathered herein will inform two main parts of WARIFA: 1) the development of the AI tool for comprehensive risk predictor across multiple major NCDs, by providing a list of additional input variables 2) The formulation of the policy framework within WARIFA, supporting the inclusion of complex, behavioral, socio-economical and community- and environment related aspects of citizens life into consideration for public health programs designed to enhance the prevention of major NCDs, and reduce the exposure to major risk factors for morbidity and mortality in Europe

5 CONCLUSION

The current deliverable offers a succinct but comprehensive overview of how the major NCDs studied in WARIFA together with their principal determinants burden, distribute and aggregate within different European countries that are illustrative for different geographical, socio-political, economical and cultural-demographic configurations within the European landscape. Further, it highlights new individual and community- related aspects that may play a role in modulating the risk of disease development, as possible targets for future larger studies, but also for future more personalized and adapted prevention interventions.

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