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D7.1 – REVIEW OF THE LITERATURE ON HEALTH-RELEVANT OUTCOMES

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List of Abbreviations

Abbreviation	Definition
AMI	Acute myocardial infarction
BMI	Body mass index
CGM	Continuous glucose monitoring
CHD	Coronary heart disease
CM	Cutaneous melanoma
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular diseases
DASH	Dietary Approaches to stop hypertension
DM	Diabetes mellitus
IARC	International Agency for Research in Cancer
LDL	Low density lipoprotein
MET	Metabolic Equivalent
NCDs	Non-communicable diseases
PA	Physical activity
T2DM	Type 2 diabetes mellitus
UV	Ultraviolet
WCRF	World Cancer Research Fund
WHO	World Health Organisation
YLL	Years of life lost

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1 INTRODUCTION

Non-communicable diseases (NCDs) are the main cause of death and morbidity worldwide, and have important social and economic effects. They represent a challenge for healthcare professionals and public health institutions. The four main recognised NCDs are cardiovascular diseases, chronic respiratory diseases, cancer and diabetes.

The aim of the present report is to summarise the evidence on modifiable and non-modifiable risk factors of NCDs, relevant, as well as the health-related outcomes associated with these risk factors. This will be used to set the base and prioritise the variables to be included in the WARIFA solution for the estimation of personalised risk, as well as for the development of tailor-made recommendations.

2 INTERNATIONAL HEALTH PROGRAMMES

In this section, we will summarise the most updated information on NCDs, published by the World Health Organisation (WHO) and the European Union, including risk factors and prevention, as well as programmes for improving the global burden of disease.

The main objectives of the section will be:

- To identify modifiable risk factors, amenable to intervention;

- To summarise the prevention strategies, proposed by the different guidelines.

2.1 WHO

NCDs lead to premature death, which is, to a certain degree, preventable. To improve prevention, the WHO approved the "World Action Plan for the prevention and control of NCDs 2013-2020" [1]. This action plan establishes a road map of health policies with 6 objectives for 2025 which include giving prevention of NCDs high priority at national, regional, and global level, improving national capacity to do so, reducing modifiable risk factors by creating healthy environments, focusing on person-centred care with universal health coverage, as well as improving research and monitoring of NCDs (see Figure 1).

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Figure 1 Objectives for 2025 according to WHO's World Action Plan for the prevention and control of NCDs 2013-2020 [1].

The Action Plan itself comprises 9 global voluntary targets for the improvement of NCDs (see Figure 2), and includes a reduction in the prevalence of NCDs themselves, as well as aims associated to reductions in the risk factors leading to these conditions (primary prevention) or their complications (tertiary prevention). Several overarching principles must be taken into consideration in this action plan, many of them closely related to the philosophy of WARIFA, such as promoting the empowerment of people and using evidence-based strategies, with an equity-focussed approach.

In the context of WARIFA, special attention should be paid to objective 3 (see Figure 1), focussed on the reduction of modifiable risk factors for NCDs and underlying social determinants through the creation of health-promoting environments. Indeed, 63% of deaths worldwide in 2008 were due to NCDs, mainly cardiovascular diseases (48% of NCDs), cancer (21%), chronic respiratory diseases (12%) and diabetes (3,5%). These conditions share 4 behavioural risk factors, namely tobacco, alcohol, an unhealthy diet, and physical inactivity.

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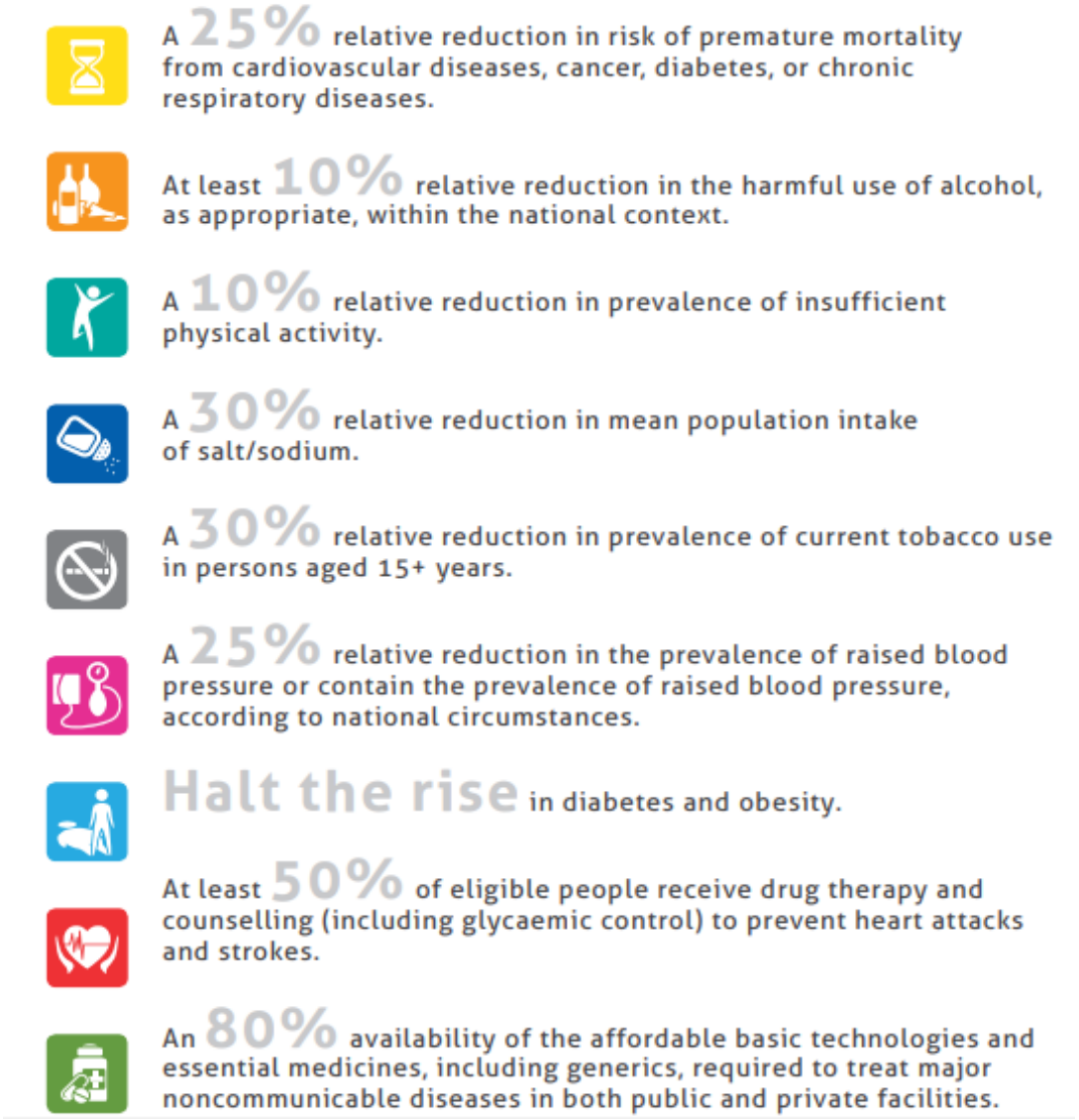

Figure 2 Voluntary global targets of WHO's World Action Plan for the prevention and control of NCDs 2013-2020 [1].

A series of indicators are established in the action plan, as well as a set of policy options and cost-effective interventions, for each of the voluntary global targets. The following list is applicable to WARIFA:

- **Tobacco use**: warn people of the dangers of tobacco and tobacco smoke through effective health warnings, surveillance and support to quit.
- **Alcohol**: strengthen awareness of alcohol-attributable burden; provide surveillance, prevention and treatment interventions for those at risk of or affected by alcohol use disorders and associated conditions.
- **Physical inactivity and unhealthy diet**: increase consumption of fruits and vegetables; replace saturated and trans fats with unsaturated fats; reduce salt intake; implement surveillance and public awareness programmes on healthy eating and physical activity; implement the WHO Global Strategy on diet, physical activity and health.

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Additional WHO guidelines are referred to:

- WHO Framework Convention on Tobacco Control, where articles 12 (*Education, communication, training and public awareness*) and 14 (*Demand reduction measures concerning tobacco dependence and cessation*) are especially relevant to WARIFA [2].
- Global strategy to reduce the harmful use of alcohol, with references to awareness and education [3].
- Global strategy on diet, physical activity and health [4].
- The WHO Package of Essential Noncommunicable (PEN) disease interventions for primary health care also includes management recommendations for the main NCDs, as well as specific actions on life-style interventions (see Figure 3) [5].

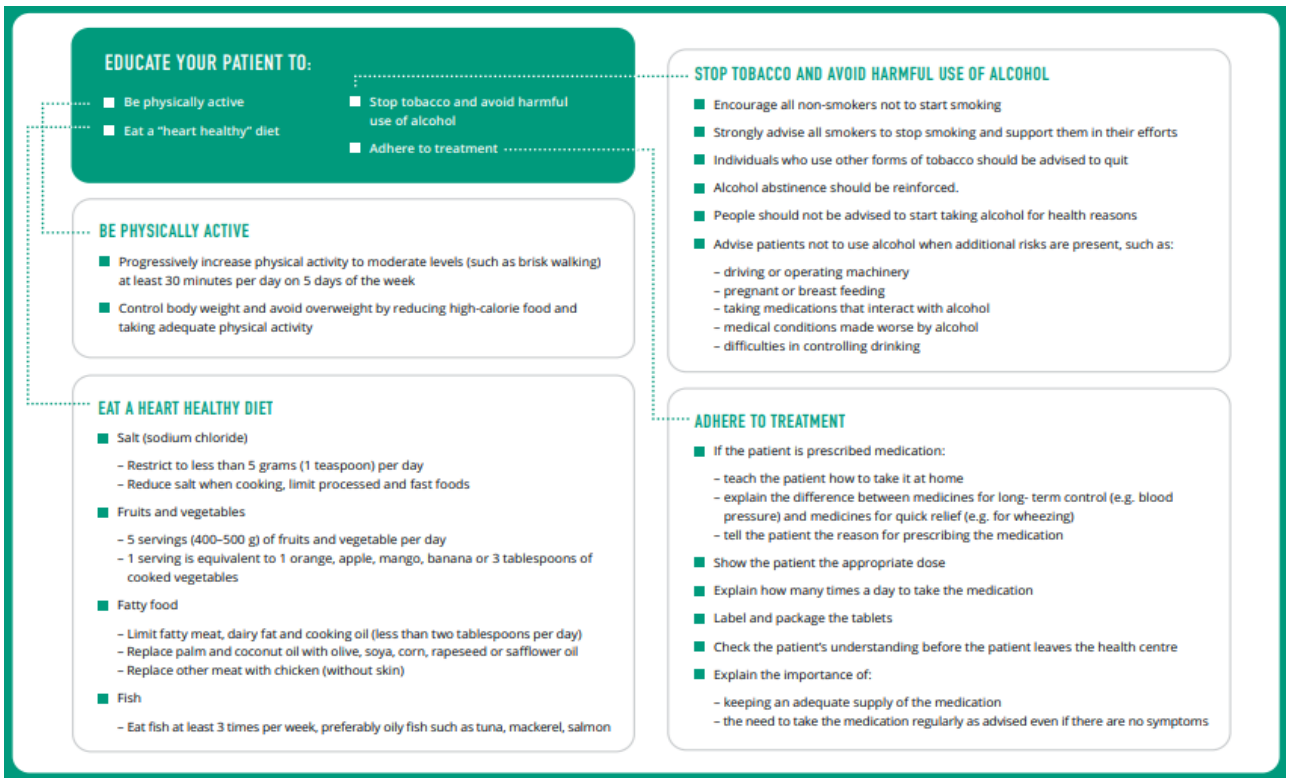

Figure 3 Life-style recommendations included in the WHO Package of essential non-communicable disease interventions for primary health care [5].

A healthy diet includes [6]:

- A balanced energy intake, to maintain a healthy weight.
- Total fat below 30% of total energy intake, with saturated fats <10% and trans fats <1%, with a goal of eliminating the latter from industrial production. Unsaturated fats are preferred.
- Free sugar intake should be below 10% (5% for additional health benefits) of total calorie intake.
- Daily salt intake <5g (<2g sodium), to prevent hypertension, heart disease and stroke.

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- At least 400g (5 portions) of fruit and vegetables per day (potatoes, sweet potatoes and other starchy roots not included).
- Legumes, nuts and whole grains.

Table 1 summarises WHO's practical advice to enforce these recommendations.

Table 1 Practical advice for healthy eating (WHO).

Recommendation	Practical advice
400g fruit and vegetables	Include vegetables in all meals. Eat fresh fruit and raw vegetables as snacks. Eat fresh fruit and vegetables that are in season. Eat a variety of fruit and vegetables.
Saturated fats<10% of total calorie intake. Avoid industrially-produced trans fats	Steam or boil instead of frying food. Replace butter, lard and ghee (solid fats) with oils, such as rapeseed, sunflower,corn, … Eat skimmed dairy products and lean meats (eliminate all visible fat). Limit the consumption of baked and fried foods, as well as pre-packaged snacks (biscuits, crisps, cakes, pies, cookies,…).
Salt <5g/day	Limit the amount of salt-rich condiments when cooking (soya sauce, fish sauce, boullion,…). Limit the amount of salty snacks. Avoid having salt or salty sauces on the table. Choose products with lower sodium content.
Free sugars<10% of total calorie intake	Limit the consumption of sugary snacks, candies, sugar-sweetened beverages (i.e carbonated and non-carbonated soft drinks, juices, energy and sports drinks, ready-to-drink tea and coffee, flavoured milk drinks,…). Eat fresh fruit and raw vegetables as snacks.

More recently, the 2030 Agenda for Sustainable Development was published [7]. It updates the long-term NCD goals and targets from the WHO Global NCD Action Plan 2013-2020.

Where the Global Action plan 2013-2020 aims, by 2025:

- To reduce overall premature mortality from NCDs by 25%, using a 4 x 4 strategy.
- Four main risk factors - tobacco use, physical inactivity, unhealthy diet and the harmful use of alcohol.
- Four main diseases - cardiovascular diseases, cancers, chronic respiratory diseases and diabetes

The Agenda for Sustainable Development aims, by 2030:

- To reduce overall premature mortality from NCDs by 33% and promote mental health and well-being, using a 5 x 5 strategy
- Five main risk factors - tobacco use, physical inactivity, unhealthy diet, the harmful use of alcohol and air pollution.
- Five main diseases - cardiovascular diseases, cancers, chronic respiratory diseases, diabetes, and mental disorders

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2.1.1 WHO European Region

Cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes are commonly grouped as the main NCDs due to their shared risk factors (tobacco use, unhealthy diet, lack of physical exercise and harmful consumption of alcohol). These four NCDs, are the world's and also Europe's biggest killers and they also make a substantial contribution to the global disease burden [7–11]. Over 85% of all deaths and 75% of all diseases in Europe are attributable to NCDs [12]. More than half a million people under the age of 65 die of NCDs in the EU each year [13]. While progress is made on reducing premature mortality from NCDs [14], longer lives do not necessarily translate into healthy lives.

In 2016, the WHO published the Action plan for the prevention and control of non-communicable diseases in the WHO European region 2016-2025 [15].

"*Taking account of new evidence, existing commitments and progress of Member States, the Action plan focuses on priority action areas and interventions for the next 10 years in order to achieve regional and global targets to reduce premature mortality, reduce the disease burden, improve the quality of life and make healthy life expectancy more equitable*".

Since cardiovascular diseases are the main cause of premature death in Europe, special emphasis is put on tobacco control, reduction in the consumption of salt, saturated and *trans* fatty acids, hypertension control and alcohol control. Furthermore, environmental exposure is recognized as a risk factor for several NCDs, and clean air is put forward as a goal. In addition, other conditions leading to disability, such as sarcopenia and osteoporosis, are also recognized, and health promotion in this area is encouraged. Finally, early detection and effective treatment of major NCDs is promoted.

In 2019, the report "Towards an EU strategic framework for the prevention of non-communicable diseases (NCDs)" was published. This document focuses on the main NCDs as the 21st century's biggest health threat in EU. One of the suggested deliverables under action 4 in this document is an EU-wide system for health data collection and information sharing containing registries for key NCD indicators [16].

2.2 EUROPEAN COMMISSION

In line with WHO's efforts, "The European Commission is committed to supporting EU countries in their efforts to reach the nine voluntary targets [17] of the United Nations and the World Health Organisation (WHO) by 2025, as well as Sustainable Development Goal 3.4, which aims to reduce premature mortality from non-communicable diseases by one third, and promote mental health and well-being by 2030", according to its portal, [18] accessed on March 28th 2021.

The European Commission has a specific policy on cancer, [19] Europe's Beating Cancer Plan, which is structured around prevention, early detection, diagnosis and treatment, and improving quality of life of cancer patients and survivors.

"*Evidence shows that 40% of cancers are preventable if we implement what we know already. However, only 3% of health budgets is being currently spent on health promotion and disease prevention. Therefore, the scope for action is immense.*

Action on cancer prevention and healthy lifestyles also serves the fight against obesity and other non-communicable diseases such as cardiovascular disease and diabetes, as they share common risk factors."

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Indeed, the code against cancer [20] includes avoidance of tobacco, keeping a healthy weight, being physically active and reducing sitting time, following a healthy diet (with plenty of whole grains, fruits, vegetables and pulses; avoiding calorie-dense foods and sugary beverages and avoiding processed meat and limiting red meat and salt-rich foods), avoiding alcohol, limiting sun exposure and environmental exposure to other carcinogens.

WARIFA's objectives are very much aligned with this statement. Personalised risk estimations will be complemented with recommendations to improve health behaviours. In the following chapter, the main risk factors responsible for the global burden of NCDs in Europe will be summarized.

3 GLOBAL BURDEN OF DISEASE 2019

A comprehensive assessment of 369 health conditions (and their risk factors) was performed in 2019 in 204 countries/regions. Incidence, prevalence, mortality, years of life lost, years of life with disability and disability adjusted life years were recorded and compared over time. Since 1990, there has been a shift towards a higher proportion of burden caused by years of life with disability from NCDs. The top 10 diseases (affecting disability adjusted life years) for adults aged 50 to 74 in 2019 include 9 NCDs, namely ischaemic heart disease, stroke, chronic obstructive pulmonary disease, diabetes, lung cancer, chronic kidney disease, age-related hearing loss, low back pain and cirrhosis. In those above 75, the latter two are replaced by Alzheimer's disease [21].

The Global Burden of Disease 2019 endeavour also estimated attributable mortality, years of life lost, years of live with disability and disability adjusted life years for 87 risk factors and combinations of risk factors, both globally and regionally. Focusing on NCDs, in the last decade, a reduction in smoking and other unhealthy environmental exposures (household air pollution and lead) was observed, while there was an increased exposure to ambient particulate matter pollution, high fasting plasma glucose and high body mass index. The risk factors which accounted for more deaths globally in 2019 were high systolic blood pressure (19% of all deaths) and tobacco (15.4% of deaths) [8]. The top modifiable risk factors in adults also include high fasting plasma glucose, high body mass index, high LDL cholesterol, alcohol use, ambient particulate matter and low whole grain and high sodium intake. Figure 4 shows an example of the information provided. Risk factors for years of life with disability in women from high income countries (which includes most of Europe) has been selected. Figure 5 shows the equivalent for men.

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Leading risks 2019	Mean % change number of YLLs 2010-2019	Mean % change all-age YLL rate 2010-2019	Mean % change age-standardised YLL rate 2010-2019
1 Smoking	**3.4%**	**-2.1%**	**-11.8%**
2 High body-mass index	**17.9%**	**11.6%**	2.2%
3 High fasting plasma glucose	**20.9%**	**14.4%**	3.2%
4 High blood pressure	**11.4%**	**5.5%**	**-6%**
5 High LDL	**3.4%**	-2.1%	**-12.3%**
6 Kidney dysfunction	**16.1%**	**10%**	-1.6%
7 Alcohol use	4.1%	-1.5%	**-6.2%**
8 Drug use	**41.9%**	**34.4%**	**38%**
9 Ambient particulate matter	-4.9%	**-10%**	**-17.8%**
10 Low temperature	**6.5%**	0.8%	**-12.2%**
11 Low bone mineral density	**24.9%**	**18.3%**	**4.8%**
12 Low whole grains	**8%**	2.3%	**-7.8%**
13 High red meat	**11.5%**	**5.6%**	-3.7%
14 Low physical activity	**8.6%**	2.8%	-5.6%
15 Low birth weight	**-12.7%**	**-17.3%**	**-13.7%**
16 High processed meat	**11.1%**	**5.2%**	-4.3%
17 Second-hand smoke	**8.7%**	2.9%	**-5.2%**
18 Short gestation	**-12.5%**	**-17.2%**	**-13.6%**
19 Occupational ergonomic	**4.9%**	-0.7%	-0.8%
20 Low legumes	**4%**	-1.5%	**-12.1%**
21 High sodium			

Legend:
Environmental
Behavioural
Metabolic

Figure 4 Leading 20 risk factors for disability adjusted life years for women in high income countries. YLL: years of life lost (estimated as death counts multiplied by remaining life expectancy from a standard life table). The three columns show changes in years of life lost for each risk factor between 2010 and 2019 [8].

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Leading risks 2019	Mean % change number of YLLs 2010-2019	Mean % change all-age YLL rate 2010-2019	Mean % change age-standardised YLL rate 2010-2019
1 Smoking	1.4%	**-4.8%**	**-16.1%**
2 High blood pressure	**12.4%**	**5.6%**	**-7.7%**
3 High fasting plasma glucose	**24.2%**	**16.6%**	1.7%
4 High body-mass index	**19.7%**	**12.4%**	1.7%
5 Alcohol use	**4.5%**	-1.8%	**-7.7%**
6 High LDL	**3.8%**	-2.6%	**-12.8%**
7 Drug use	**43.1%**	**34.4%**	**38.3%**
8 Kidney dysfunction	**20.1%**	**12.8%**	**-3.1%**
9 Ambient particulate matter	-2.2%	**-8.2%**	**-17.5%**
10 Low whole grains	**9.4%**	2.7%	**-8.9%**
11 Low temperature	**13%**	**6.1%**	**-13.3%**
12 High red meat	**12.8%**	**6%**	-5.1%
13 High sodium	7%	0.5%	**-12%**
14 Low legumes	**5.4%**	-1%	**-12.4%**
15 Occupational asbestos	5.6%	-0.9%	**-17.1%**
16 High processed meat	**10.9%**	**4.2%**	**-7.4%**
17 Second-hand smoke	**6.9%**	0.4%	**-9.8%**
18 Occupational injury	0.5%	-5.6%	-4.4%
19 Low fruit	4.1%	-2.3%	**-12.6%**
20 Low bone mineral density	**22.1%**	**14.7%**	-0.7%
21 Low birth weight			
22 Short gestation			

Legend:
Environmental
Behavioural
Metabolic

Figure 5 Leading 20 risk factors for disability adjusted life years for men in high income countries. YLL: years of life lost (estimated as death counts multiplied by remaining life expectancy from a standard life table). The three columns show changes in years of life lost for each risk factor between 2010 and 2019 [8].

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3.1 DIET

According to the Global Burden of Disease report, dietary factors were responsible for 7.9 million deaths worldwide among adults in 2019, and accounted for 6-10% of disability adjusted life years in Europe [22].

Indeed, 15 dietary risks are identified:

1. Diet low in fruits
2. Diet Low in vegetables
3. Diet low in legumes
4. Diet low in whole grains
5. Diet low in nuts and seeds
6. Diet low in milk
7. Diet high in red meat
8. Diet high in processed meat
9. Diet high in sugarsweetened beverages
10. Diet low in fiber
11. Diet low in calcium
12. Diet low in seafood omega 3fatty acids
13. Diet low in polyunsaturated fatty acids
14. Diet high in trans fatty acids
15. Diet high in sodium

Information on the weight of each one can be found in specific reports [22].

3.2 ALCOHOL

Alcohol consumption is defined by the Global Burden of Disease 2019 report by the ingestion of at least one alcoholic beverage in the past year and daily consumption is calculated as grams of alcohol. Alcohol remains the 10th cause of death globally since 1990, and is currently the 9th risk factor for disability adjusted life years (1st in males aged 15-49). It was responsible for 2.44 million deaths in 2019. It is an especially prevalent risk factor in Europe.

3.3 TOBACCO

According to the Global Burden of Disease 2019 specific report on tobacco (which includes tobacco smoking, chewing tobacco use and second-hand smoke exposure), "*Globally, tobacco accounted for 8·71 million (95% UI 8·12–9·31) deaths and was the second-leading Level 2 risk factor for deaths in 2019. Among all ages, tobacco accounted for 21·4% (20·5–22·3) of male deaths and 8·3% (7·7–8·9) of female deaths in 2019*". Tobacco is a major cause for disability adjusted life years associated to all the top NCDs, namely cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes (see Figure 6).

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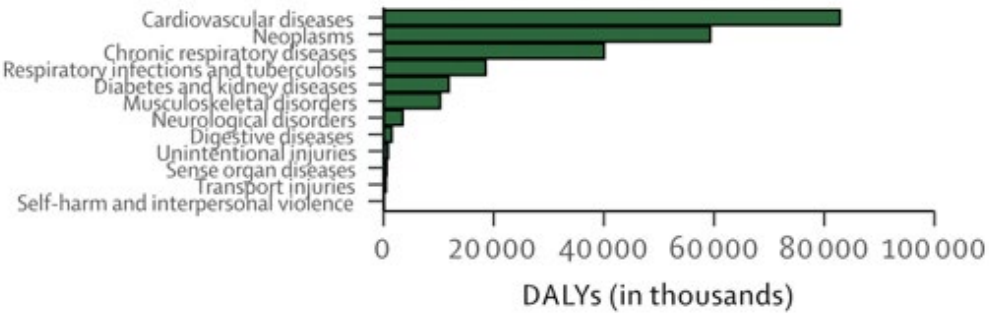

Figure 6 Global disability adjusted life years attributable to tobacco, in both sexes combined.

3.3.1 Electronic cigarettes

Although this form of tobacco use is not included in the Global Burden of Disease 2019 report, it is worth mentioning, given its increasing prevalence, as well as its proven harm. The European Association of Preventive Cardiology recently issued a position statement summarising that the prevalence of e-cigarette smoking is increasing, particularly in the young, and evidence suggests that this will increase the likelihood of conventional smoking. Some studies have found e-cigarettes to have harmful cardiovascular effects, but more studies in particular on long-term effects of e-cigarettes on cardiovascular outcomes and respiratory disease are needed. Currently, there is a lack of robust longitudinal data on the impact of e-cigarettes on smoking cessation, and more research is warranted [23]. This is also in line with a statement from WHO [23].

3.4 Physical Activity

In the Global Burden of Disease report, physical activity was measured in total metabolic equivalents (METs). Low physical activity was defined as a total weekly average (including at work, home, transport-related, and recreational) below 3000-4500 MET minutes (equivalent to 6-10 times the minimum recommended 150 minutes of moderate activity/week). It was ranked 18th in attributable disability adjusted life years in 2019, accounting for 198.4 age-standardised disability adjusted life years (95% UI 108·2–360·3) per 100 000 and 11.1 age-standardised deaths (5·7–19·5) per 100 000, globally (see Figure 7).

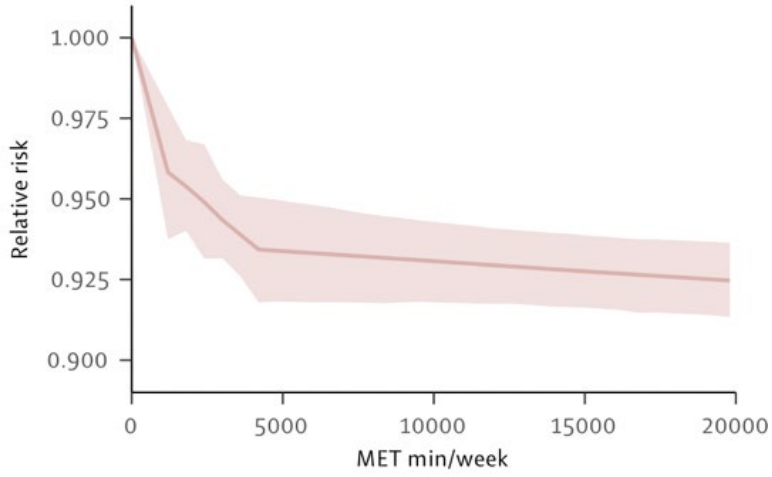

Figure 7 All-cause mortality risk according to level of physical activity globally, in both sexes combined.

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4 OTHER PUBLICATIONS ON RISK FACTORS OF NCD

Searches were performed in PubMed, limited to systematic reviews (with or without meta-analysis) and randomised clinical trials published since 2016, for each of the NCDs and on mortality.

4.1 MORTALITY

The search of the terms NCD and mortality, led to several systematic reviews and meta-analyses (see Table 2). Most of the evidence originates from studies performed in high-income countries and white ethnicity, which limits its generalizability, although it probably can be applied to Europe as a whole. Adherence to **healthy dietary patterns,** such as the Mediterranean, DASH, and the Nordic dietary patterns, was associated with similar reductions in mortality risk. Larger benefits could be obtained if people adopt **healthy lifestyles** at an **early age** and are followed for a **long time**. **Avoiding smoking** should be prioritised when we make lifestyle-related recommendations or policies to prevent premature death. The **greatest difference in mortality rates occurs among inactive compared to minimally active individuals,** and prescription of low-dose physical activity increases the probability of adherence. Finally, a low occupational position was associated with an increased mortality risk. Indeed, **socioeconomic circumstances,** in addition to other risk factors, should be targeted by local and global health strategies to reduce mortality.

4.2 DIABETES

4.2.1 Type 2 diabetes

Type 2 diabetes is a common disease associated with reduced life expectancy and considerable morbidity. It is often associated with other NCDs, and causes a high number of hospitalizations and a significant economic impact. About 50% of all people with diabetes worldwide are not diagnosed, and complications may be present already in up to half of the people with newly diagnosed diabetes. The prevalence of the disease ranges from 5% to 20% of the adult population, with a higher incidence in Oceania, the Caribbean, South Asia, the Middle East, Latin America, and Central Asia.

The effect of lifestyle intervention on the prevention and delay of type 2 diabetes in high-risk adults was successfully demonstrated in the Diabetes Prevention Program and its outcome follow-up study. In the general population, systematic reviews of longitudinal studies have shown association of physical activity and lower risk of incident obesity with reduced risk of diabetes and coronary heart disease (see Table 2). Furthermore, systematic reviews and meta-analyses agree that a healthy lifestyle not only **reduces the risk of diabetes up to 78%**, but also reduces all-cause mortality, cardiovascular mortality, cancer mortality and incident cardiovascular disease among diabetic individuals. These healthy lifestyles have a dose-dependent effect, regarding both intensity and duration of the intervention.

A randomised, controlled trial in patients with prediabetes showed short term benefit in anthropometric characteristics and lipid profile in the group randomized to metformin + physical activity + healthy diet + family intervention (with monthly lifestyle enhancement program for 6 months), vs individual intervention but with a high rate of drop out was observed in both groups, suggesting that perhaps face-to-face visits are not the best way to implement these healthy habits in people who do not feel sick (see Table 2).

Some of the studies include non-classical healthy lifestyle components, such as air pollution, noise and sleep disorders or sleep duration.

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Table 2 NCDs, associated risk factors, references and (where available) respective databases.

DISEASE	Risk Factor for developing disease	Measurable Parameter	Quantitative contribution of the risk (if known)	Modifiable	Reference and type of study	Reference database
Global burden of disease	87 risk factors, 369 diseases	Behavioural and metabolic risk factors.		yes	[21][8]	http://ghdx.healthdata.org/gbd-2019/code [24]
T2DM	Combined lifestyle factors	Smoking; alcohol, Physical activity (PA); Diet; body fat; Blood Pressure; Blood lipids, Blood glucose; others (watching television; sleep disorders, sleep duration).	- Healthiest lifestyle was associated with 75% -78% lower risk of incident type 2 diabetes; 56% lower risk of all-cause mortality; 49% of CVD mortality; 31% of cancer mortality; 52% of incident CVD - In dose-response analyses, the adherence to every additional healthy lifestyle factor was associated with a reduced relative risk of 32% for T2D and 21% for mortality.	yes	**Systematic review and meta-analysis** [25][26]	
T2DM in overweight prediabetic surviving participants of the original DPP study	Physical activity (PA)	Physical activity (METs).	- 6% decrease in diabetes incidence per 6 MET-h/week increase in time-dependent PA for the entire cohort over an average of 12 years. - The effect was greater (12% decrease) among participants less active at baseline (<7.5 MET-h/week). - Significant remain after adjusting for weight change.	yes	**Clinical trial** [27]	
T2DM	Non-genetic risk factors	Biomarkers, medical conditions, and dietary, lifestyle, environmental and psychosocial factors.	**Highly significant:** - Obesity: Metabolically unhealthy obese 10-fold risk; metabolically healthy obese 4.5-fold risk. - Gestational diabetes: seven-fold increase of risk. - Metabolic syndrome. **Convincing:** - Preterm birth. **Highly suggestive relationship**: - Processed meat - Total and leisure-time physical activity, lower educational status.	yes	**Systematic review of meta-analyses** [28]	

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			- Air pollution: (PM10 and NO2). **Suggestive:** - Sugar-sweetened beverages.			
T2DM	Environmental factors	Air pollution, food environment, physical activity resources, walkability, and roadway proximity.	**Moderate evidence:** - Higher levels of walkability and green space were associated with lower T2DM risk, while increased levels of noise and air pollution were associated with greater risk.	yes	**Systematic review** [29]	AirBase (European air quality database)
New onset obesity, CHD, diabetes, and hypertension	Physical activity		**Association between:** - Higher PA and lower risk of incident obesity (27-48%). - Higher levels or amount of PA and a decreased risk of incident CHD (27-56%). - Increasing PA levels and a decreased risk of incident diabetes (19-74%). - No consistent association between PA and incident hypertension.	yes	**Systematic review** [30]	
All-cause mortality; CVD mortality, T2DM; Cancer; Stroke; Myocardial infarction	*Adherence to the Nordisk Diet:* Consumption of fruits, vegetables, whole grains, fish, rapeseed oil, low-fat dairy products and low consumption of processed meat and alcohol.	Mostly Food Frequency Questionnaire. 4-day food records.	- Highest compared to the lowest category of adherence to the ND was associated with a 22% lower risk of all-cause mortality and CVD mortality; 20% lower risk of Miocardial infarction; 14% lower risk of cancer mortality; 12% lower risk of stroke and 10% lower risk of Diabetes. - Results consistent with those of other healthy dietary patterns such as Dietary Approaches to Stop Hypertension (DASH) dietary pattern; Healthy Eating Index and Alternative Healthy Eating Index, and the Mediterranean dietary pattern.	yes	**Systematic review and meta-analysis of prospective cohort studies** [31]	
All-cause mortality; CVD mortality, CHD mortality; stroke mortality	*Combined lifestyle factors:* - Cigarette smoking, alcohol - Consumption, physical activity, diet and overweight/ - Obesity; sleep	- Simple score (which gave equal weight to each lifestyle factor). - LS7 Score. - World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) score.	- The pooled HR (hazard ratio) comparing participants with the healthiest versus the least-healthy lifestyles for all-cause mortality was 0.45; 0.42 for total CVD mortality, 0.40 for CHD mortality and 0.38 for stroke mortality. - Association stronger in studies with smoking included in the score.	yes	**Systematic review and meta-analysis of prospective cohort studies** [32]	

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	- Duration/quality; blood pressure, blood lipid level, blood glucose level.					
Mortality in adults with NCDs	Physical activity. MET-h/week: - Inactive to high. - None, irregularly; regularly.	Questionnaire/ Interview.	- For every 10 MET-h increase of physical activity per week, the summary hazard ratio (SHR) decreased by 22% in people with breast cancer, by 12% in people with IHD and by 30% in people with COPD. The mortality rates in people with T2D reduced by 4% for every 10 MET-h/week. - Very low certainty of evidence for COPD, and low certainty of evidence for breast cancer, IHD, and T2D. - Greatest difference in mortality rates occurs among inactive compared to minimally active individuals. - Greatest difference in mortality rates occurs among inactive compared to minimally active individuals.	yes	**Systematic review and meta-analysis of prospective observational studies** [33]	
Premature Mortality	25 × 25 risk factors (alcohol, insufficient physical activity, current tobacco use, raised blood pressure, intake of salt or sodium, diabetes, and obesity).	Self-reported; physical examination; Lab results.	- Low socioeconomic status was associated with 2·1 Years of life lost between ages 40 and 85 years. - The corresponding years of life lost were 0·5 for high alcohol intake; 0·7 for obesity; 3·9 for diabetes; 1·6 for hypertension; 2·4 for physical inactivity and 4·8 for current smoking in men and women combined. - The 25 × 25 risk factors were generally more strongly associated with cardiovascular disease mortality than with cancer and with mortality of other causes	Yes (some)	**Multicohort study and meta-analysis** [34]	

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4.2.2 Type 1 diabetes

There are currently no established preventive recommendations for type 1 diabetes, given the inconsistent evidence in this area [35]. However, the lives of people living with the disease can be improved by reducing their short- and long-term complications and by reducing their everyday diabetes-related burden. Although type 1 diabetes-related mortality and disability have improved in the last two decades [36], most reports do not take the challenges of selfcare into account. In order to keep glucose concentrations as close as possible to their target (and reduce the HbA1c, which has proved to be closely related to chronic diabetes complications [37]), people with type 1 diabetes need to administer subcutaneous insulin through multiple (generally 4-6 per day) injections or by means of a pump and make decisions each time a new dose is required. Present glucose concentrations, previous and planned physical activity, carbohydrate (and, to a smaller degree, also protein and fat) content in the diet are taken into account for insulin dose adjustments and the potential need for extra snacks.

Recent progress in the incorporation of technology in the treatment of type 1 diabetes also poses a challenge [38]. The availability and integration of insulin pumps and continuous glucose monitoring (CGM) have recently redefined type 1 diabetes therapy. Insulin pumps allow for more physiological insulin administration and dosage fine-tuning with meals and exercise. CGM consists of the interstitial measurement of glucose and allows to have results every few minutes. The amount of information related to glucose concentrations has skyrocketed, and allows for real-time decision making, albeit with adequate training. In clinical practice, new terms have emerged, related to the more continuous nature of the data obtained. Reports now include time in/above/below range (amount of time a given person is within/above/below glucose targets for a given period), average glucose concentrations and measures of variability (standard deviation or coefficient of variation [39]).

The integration of pumps and CGMs with predictive software, has allowed for some degree of automation of insulin delivery, with frequent adjustments to keep glucose concentrations within a target range. The implications on quality of life are mixed as all these new devices require patient education and training and can be perceived as intrusive by some, while allowing lower glucose variability, slightly better glycaemic control, and fewer short-term adverse events [40].

Patient reported outcomes have gained importance over the past decade. Quality of life, functional capacity, and mental health outcomes (such as depression, anxiety, or diabetes related distress) are linked to glycaemic control, glycaemic variability, and diabetes complications both in the short and in the long term (with lower quality evidence for the latter).

A search was performed in PubMed, Google Scholar and Tripdatabase using the terms “type 1 diabetes” (as population), “smoking”, “alcohol”, “sedentary”, “exercise”, “sex”, “ethnicity”, “diet”, “fibre” (as interventions/risk factors), “mortality”, “glycaemic control”, “glycaemic variability”, “distress” and “diabetes complications” (as outcomes) for the last 5 years, including randomized clinical trials, systematic reviews, and meta-analyses. Language was limited to English and Spanish. The findings of the search are summarized in Table 3.

Briefly, lack of physical activity, smoking, alcohol consumption and dietary composition all play a role in long-term prognosis. Physical activity over 20-60 minutes daily has shown improvements in HbA1c, body mass index and lipids. Smoking is associated with higher HbA1c, a worse lipid profile, higher blood pressure and albuminuria. Mediterranean, low carb and high fibre diets have all shown promising improvements (vs high carb diets) in weight management, hypoglycaemia events, HbA1c and glycaemic variability, although evidence is low for most of these outcomes and long-term safety of some of the interventions is still to be proved.

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Table 3 Risk factors and outcomes in people with type 1 diabetes (T1D).

Risk factor	Disease for which it is relevant	Negative outcome of the risk factor*	Measurable parameter of the risk factor	Quantitative contribution to risk (if known)	Modifiable yes/no	Reference	Existing database that collects that parameter
Hyperglycaemia (intensive treatment vs standard care; DCCT/EDIC)	T1D	Cardiovascular disease; stroke, myocardial infarction, or cardiovascular death. New albuminuria, worsening of albuminuria, non-fatal myocardial infarction.	Glycaemia; HbA1c% Glycaemia; HbA1c%	Cardiovascular disease 30% (95% IC 7,48) Stroke, myocardial infarction, or cardiovascular death 32% (95% IC -3,56)	Yes	**Randomized controlled trial** [37] **Systematic Review** [41] **Review** [42]	
Physical inactivity	T1D	Higher HbA1c%, BMI and triglycerides.	Physical activity at least >20-60 min/d, aerobic or strengthening or both, for at least 2-39 weeks.	HbA1c -0.52% (95% IC -0.97,-0.07) BMI -0.41 (IC95% -0.7,-0.12) Triglycerides -0.7 (95% IC -1.25, -0.14)	Yes	**Systematic review, Meta-analysis** [43][44][45] **Randomized Controlled Trial** [46] **Systematic Review** [47]	
Smoking	T1D	Hyperglycaemia, triglycerides, HDL and total cholesterol, Macroalbuminuria, diastolic blood pressure.	Smoking status (non vs passive vs active).	HbA1c 7.9 +/- 1.3% smokers vs 7.3+/- 1.1% non-smokers. HDL 1.53+/-0.45 smokers vs 1.68+/-0.51 non smokers MacroAlbum 9.8% smokers vs 4.8% non-smokers	Yes	**Systematic Review** [48] **Observational Study** [49][50][51]	
Alcohol Low evidence	T1D	Hypoglycaemia Ketosis	Weekly consumption?	Hypoglycaemia risk Higher B-hydroxybutyrate	Yes	**Pilot Study** [52]	

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High Carb Diet versus… **- Low carb (<45%)** **-Mediterranean diet** **- High fibre intake (high heterogeneity)**	T1D	HbA1c Hypoglycaemia Glycaemic variability Weight No diff with low-C Mortality, A1c, variability, HOMA-IR, lipids, weight.	Dietary composition	No evidence Weak evidence favours low-carb Lower with Low-C Loss with Low-C, gain with H-C A1c -2.0 mm/	Yes	**Randomized clinical trial** [53] **Systematic review** [54] **Randomizer Controlled Trial** [55] **Randomized trial** [56] **Meta-analysis** [57]	
Sex	T1D	End-stage renal disease	Male/Female		No	**Meta-analysis** [58]	
Ethnic group	T1D	Mortality, A1c, HDL, neuropathy, microalbuminuria, systolic BP.	South Asian vs Europeans vs Africans vs Malay / Chinese		No	**Systematic review** [59]	
Continuous glucose monitoring	T1D	HbA1c	Continuous glucose monitoring vs capillary blood glucose measurements	Lower HbA1c in CGM group Lower incidence of hypoglycaemia in CMG Better neonatal outcomes in pregnant women with CGM	Yes	**Randomized controlled trial** Population: teens [60] **Randomized controlled trial** Population: > 60 years [61] **Randomized controlled trial** Population: adults with multiple insulin injections [62] **Randomized controlled trial** Population: pregnancy [63]	

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"Automatic" insulin delivery	T1D	Time in range	"Automatic" insulin delivery vs insulin pump + continuous glucose monitoring	Time in range 12.6% higher for artificial pancreas	Yes	**Systematic review and meta-analysis** [40]	
Continuous subcutaneous insulin infusion	T1D	HbA1c, hypoglycaemia	Insulin pump vs multiple daily injections	Mild improvement in HbA1c in previously non controlled T1D on injections	Yes	**Meta-analysis** [64]	
Hypoglycaemia	T1D	Cardiac arrhythmia Quality of life	Hypoglycaemic episodes	QT increase 0.64 units at hypo vs euglycemia	Yes	**Meta-analysis** [65][66]	
Severe hypoglycemia, fear of hypoglycemia, neuropathy	T1D	Severe hypoglycaemia	Episodes of severe hypoglycaemia		Yes	**Randomized CT**. Population: type1 + impaired awareness [67]	
A1c, exercise, and daytime hypoglycemia	T1D	Nocturnal hypoglycaemia	Episodes of nocturnal hypoglycemia		Yes	**Randomized CT** [68]	
Glycaemic variability	T1D	Severe hypo Microvascular complications Micro and macrovascular complications	Within day SD of BG (short term) Within-day, no evidence HbA1c variability (long term)	1.1-fold increased risk of first hypoglycaemia per 1 mmol/l increase in SD Renal disease risk ratio 1.6, cardiovascular events 1.98, retinopathy 2.11	Yes Yes	**Randomized CT** [69] **Randomized CT** [70] **Meta-analysis** [71]	
Patient reported outcomes	Diabetes	Functional capacity Mortality Quality of life	Well-being, Self-management, Diabetes control		yes	[72] [73] [74] [75] [76] [77]	
Time in range	Diabetes	Quality of life Complications	Time in range			[66] [78] [79]	

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4.3 CARDIOVASCULAR DISEASES

CVDs are the number 1 cause of death globally, representing 31% of all global deaths. It is estimated that 17.9 million people dying annually from CVDs, out of which 85% of deaths are due to ischemic heart disease and stroke [80]. In Europe 1.68 million deaths resulted in 2016 from CVD, equivalent to 37.1 % of all deaths in EU-27. The CVD mortality burden is unequally distributed in Europe, with CVD deaths accounting for up to 60-66% of all deaths in Eastern Europe, but for 23% of all deaths in Northern and Western European countries. The EU-27's standardised death rate for CVD was 370 deaths per 100 000 inhabitants in 2016, 1.4 times higher in men as in women. Again, mortality varied widely in Europe, with 7-fold differences between the highest mortality rate in Bulgaria and the lowest rate in France.

The main risk factors for CVD include hypertension, hyperglycaemia, hyperlipidaemia, and overweight, that are strongly modulated by behavioural risk factors including tobacco use, harmful levels of alcohol consumption, unhealthy diets with high intakes of fats, sugars and salt and low physical activity. The WHO estimates that at least 80% of all heart disease, stroke and diabetes could be prevented if these four main risk factors for NCDs were addressed [80,81].

Close to half of patients with myocardial infarction and one-third of those who die from sudden cardiac death have no known coronary artery disease [82], so primary prevention of CVD would have an important impact on CVD mortality reduction.

Seven metrics of ideal cardiovascular health are defined: no smoking, healthy diet, sufficient physical activity, optimal body weight, and ideal levels of blood pressure, blood sugar and cholesterol [80,82,83] definition of ideal and optimal included in guidelines [84–86] (see Box 1).

Box 1. Risk factors goals for CVD prevention

Definitions – Risk factors goals [84,85]

Smoking No exposure to tobacco in any form.

Diet Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish [85] nuts, lean animal protein, with minimal intake of trans fats, processed meats and refined carbohydrates, including sweetened beverages [84].

Physical activity

At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof [83–85].

Body weight BMI 20–25 kg/m2. Waist circumference <94 cm (men) or <80 cm (women)

Blood pressure <140/90 mmHg

Lipids if LDLc is the primary target **Very high-risk: <1.8 mmol/L (<70 mg/dL),** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)d **High-risk: <2.6mmol/L (<100 mg/dL)**, or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) **Low to moderate risk: <3.0 mmol/L (<115 mg/dL).**

HDL-C No target; >1.0 mmol/L (>40mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.

Triglycerides No target; <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

Diabetes HbA1c <7%. (<53 mmol/mol)

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To achieve these goals the current evidence-based guidelines recommend a multi-direction approach encompassing options that range from pharmacotherapeutic interventions (lipid-lowering, blood pressure-lowering and anti-platelet medication) to interventions directed to behaviour change to achieve healthy lifestyle goals (smoking cessation, healthy diet, physical activity and optimal body weight) [84–90]. The choice of primary prevention interventions is recommended to be tailored according to the estimated level of individual risk- with the individuals at highest end of risk level spectrum being offered highest intensity interventions including pharmacotherapy, and the individuals at the lower end of the risk level spectrum being considered for lifestyle change behavioural interventions.

Several tools for risk assessment have been developed and are recommended worldwide for risk assessment, such as the Pooled Cohort Studies Equations or SCORE algorithm with its regional and local adaptations [84,85,91] The risk factors for CVD used for risk assessment worldwide include age, sex, systolic blood pressure, cholesterol concentrations, body mass index and presence [84,85,89,91] Additional enhancers of risk such as socio-economic status and support, family history of premature CVD, metabolic syndrome, central obesity, paraclinical evidence of atherosclerotic disease are recommended to be taken into consideration.

In addition, while the individual net benefit from primary prevention interventions is highest in the individuals at high-risk, the adoption of a healthy lifestyle by all individuals including those with low or no-CVD risk has most impact on CVD morbidity and mortality at population level, as most deaths in a community come from those at lower levels of risk, because they are more numerous compared with high-risk individuals [84,85] Resources should be focused on modifying behaviours in the general population to promote a healthy lifestyle [82,84,85,88].

4.3.1 CVD Prevention: focus on modifiable factors

There is an extensive body of evidence, enhanced by recent systematic reviews and meta-analysis (see Table 4) supporting the fact that the change in lifestyle factors towards achieving the optimal goals in healthy diet, physical activity, smoking cessation, and weight loss are effective in decreasing the risk of CVD and CVD morbidity and mortality.

However, the most effective interventions to motivate people to make and maintain those lifestyle changes, remain subject of research and discussion, as the gap between knowledge about healthy lifestyle and implementation of healthy lifestyle is well documented [90,92–94].

Behavioural counselling interventions are confirmed to result in improvements in healthy behaviours and small but potentially important improvements in intermediate outcomes, including reductions in blood pressure and low-density lipoprotein cholesterol levels and improvements in measures of adiposity [86,93] Behavioural counselling is hence recommended across the current valid best practice guidelines [82,84–86,88].

Interventions consisting in face to face, one-to one behavioural counselling towards healthy lifestyle changes appear more effective that group counselling interventions, and in person counselling, individually or in groups appears more effective than general education interventions like web-based or in print materials. In addition, the multifactorial approach seems to be the most effective. The evidence suggests that an intervention tailored to reduce multiple risk factors at the same time (like e.g., physical activity and diet) could be more effective than an intervention targeting only a single risk [92,95–97]. The benefits appear higher for primary prevention, and for moderately high-risk groups, and highest for the combination of diet and physical activity directed interventions [92].

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Patient-centred approach within multidisciplinary teams including physicians, nurses, care coordinators, pharmacists, social workers, and other allied health professionals are recommended for the preventive care of CVD in patients with CVD risk factors, for which multifactorial, higher intensity behavioural intervention is recommended [84–86,93] . The combination of educational interventions, motivational strategies, identification of individual barriers, and social and family support is deemed necessary to achieve CVD prevention goals and to maintain the healthy behaviours [92,97].

The new digital technologies have the potential to help implement and maintain healthy lifestyle changes. Web-based intervention for primary prevention have shown some benefit in improving CVD risk factors like systolic blood pressure, weigh, and LDL cholesterol, but their effects appear modest, improved by in-person interventions, and limited in time [98]. Mobile-health based interventions appear to be effective mainly for weight-loss, but so far, the evidence on their role in CVD prevention is low, due to the limited number and quality of the studies, and the small effects that were measured [99].

Table 4 Overview of systematic reviews and meta-analysis, 2016-2020 on the role of lifestyle interventions on lowering CVD risk factors, mortality/morbidity

Disease	Lifestyle factor	References
CVD	Diet ▪ Marine Omega-3 Supplementation ▪ Food Groups ▪ Mediterranean Diet and Other Dietary Patterns ▪ Portfolio Dietary Pattern ▪ Dietary Omega-6 Fatty Acids ▪ Dietary Saturated and Polyunsaturated Fat ▪ Fruit and Vegetable Intake ▪ Intake of Dietary Fibre ▪ Folic Acid Supplementation ▪ Dietary Magnesium Intake ▪ Vitamin D, Marine n-3 Fatty Acids ▪ Psychological Methodologies in promoting a Mediterranean Style Diet	[100–112]
	Diet and physical activity	[86,92,97]
	Physical activity	[113–116]
	Overweight/obesity	[96,117]
	Multifactorial	[97,98,118,119]
	Smoking	[120]
	Sleep	[81]

4.4 CHRONIC RESPIRATORY DISEASES

Chronic respiratory diseases comprise many different diseases. The most prevalent is chronic obstructive pulmonary disease (COPD) which is a major public health problem. COPD accounts for 55% of chronic respiratory disease and can cause significant reduced quality of life, disability, morbidity, hospitalizations, and premature death. It is a progressive life-threatening lung disease and is an important contributor to NCDs. The first signs of COPD are chronic cough and sputum in the morning as well as breathlessness after physical exertion. In serious cases, breathing problems may also occur at rest. About 174 million people were affected with COPD in 2015 [121]. The prevalence of COPD globally in 2017 was 3.9% [122]. In central and Eastern Europe and central Asia the prevalence of COPD was 6.1%. There were 3 914 196 deaths due to chronic respiratory diseases in 2017 globally. In 2016, there were 339 000 deaths in the EU resulting from diseases of the

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respiratory system, equivalent to 7.5 % of all deaths [123]. In total, chronic respiratory diseases accounted for 51.2 deaths per 100 000 individuals in 2017, which accounted for 7.0% of total all-cause deaths globally. Indeed, chronic respiratory diseases were the third leading cause of death in 2017, just behind cardiovascular diseases (31.8% of all deaths) and cancer (17.1%). COPD was the most common cause of chronic respiratory disease-attributable deaths, at 41.9 deaths per 100 000 individuals. More than 90% of COPD-related deaths occur in low- and middle-income countries.

The majority of cases of COPD are preventable. The most important risk factors for chronic respiratory diseases and in particular COPD are tobacco and air pollution.

4.4.1 Tobacco

Smoking is the main cause of chronic respiratory disease and explains two out of three [121,122] Tobacco smoking is associated with morbidity and mortality from non-communicable respiratory diseases, including about 600 000 people who are estimated to die every year from the effects of second-hand smoke [124]. Avoiding the use of tobacco and quitting smoking is the most important preventive measure to reduce COPD.

4.4.2 Air pollution and household air pollution

Air pollution is the biggest environmental cause of death worldwide and household air pollution accounts for a large part. Air pollution is the second leading cause of deaths from NCDs after tobacco-smoking [125]. Respiratory morbidity from pollution relates to products of incomplete combustion of biomass that produces for example carbon monoxide and particulate matter. Exposure reduction initiatives must focus on cook-stove interventions such as cleaner fuel, or better ventilation [124]. Worldwide 43% of COPD were attributable to ambient and household air pollution in 2016. In the WHO European Region, 6% of COPD were attributable to ambient and household air pollution in 2012 [125].

4.4.3 Other risk factors

Working environment with dusts, fumes and chemicals increases risk of chronic respiratory diseases. Genetic factors, poor nutrition, low physical activity, asthma, frequent childhood respiratory infections, poverty play a role as risk factors. Although much of the burden of COPD is preventable, this disease has received less attention than other NCDs [124].

4.5 CANCER

In 2018, the World Cancer Research Fund (WCRF) issued its recommendations for cancer prevention [126]. Two more recent reports from the International Agency for Research in Cancer (IARC) [9] and WHO [127] have synthesised measures that are recognized to limit the burden of cancer. Among noncommunicable diseases, cancer has emerged as a particularly important health concern. Cancer is the first or second leading cause of premature mortality (i.e., deaths at ages 30–69 years) in 134 of 183 countries. Specifically, cancer has surpassed cardiovascular diseases as the leading cause of death in countries with high or very high Human Development Index. In 2018, worldwide 1 in 8 men and 1 in 10 women were likely to develop cancer during their lifetimes [9].

Europeans represent about one-tenth of the global population, yet one in four of all cancer diagnoses occur in this region. In 2018, cancers of the female breast (13%), colorectum (13%), lung (12%), and prostate (12%) were the most common cancers on the continent, and combined they represented almost half of the overall cancer burden [128].

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Many of the known risk factors for cancer can be prevented. Tobacco use, unhealthy diet, excess body weight, physical inactivity, and alcohol consumption account for the majority of cancer deaths [9,127], according to the Cancer Atlas [128] and the recently published "Europe's Beating Cancer Plan" [129].

4.5.1 A Cancer Plan for Europe

In February 2021, the European Commission finalized the "Europe's Beating Cancer Plan". About 40% of cancer cases are preventable: effective cancer prevention strategies can prevent illness, save lives, and reduce suffering. The plan aims, first and foremost, to prevent cancer, and to ensure cancer patients, survivors, their families and carers can enjoy a high quality of life [129]. Lives lost to cancer in the EU are predicted to increase by more than 24% by 2035 [130] making cancer the leading cause of death in the EU. The Cancer plan for Europe aims to prevent this from happening [129].

Tobacco use.

Tobacco use is the leading preventable cause of cancer worldwide. Cigarettes have been determined to cause at least 20 different types or subtypes of cancer. Other forms of tobacco use are of growing importance worldwide but have been less studied than cigarettes. The IARC Monographs [131] and the United States Surgeon General [132] have established causal relationships with at least 20 types of cancer, including cancers of the lung, oral cavity, nasal cavity and accessory sinuses, nasopharynx, oropharynx, hypopharynx, larynx, oesophagus (adenocarcinoma and squamous cell carcinoma), stomach, pancreas, colorectum, liver, kidney (body and pelvis), ureter, bladder, cervix, and ovary (mucinous), and acute myeloid leukaemia. This list is conservative, because it does not include breast cancer or advanced prostate cancer, two sites for which the evidence for causality has been labelled suggestive but not conclusive. Exposure to second-hand smoke has been determined to cause lung cancer, while associations with other cancer types are less clear. Smokeless tobacco causes cancers of the oral cavity, oesophagus, and pancreas [9].

Alcohol consumption.

Alcohol consumption has been found to be causally associated with the development of cancers of the oral cavity, oropharynx, hypopharynx, larynx, oesophagus (squamous cell carcinoma), colon, rectum, liver and intra- hepatic bile duct and female breast. The burden of cancers caused by alcohol consumption might be decreased through (i) individual-level and societal-level interventions that reduce alcohol consumption, and (ii) measures that target those risk factors that interact with alcohol consumption to increase the risk of cancer or that directly affect the risk of alcohol-related cancers [9].

Diet and nutrition. Understanding which factors are critical.

Probably most important are the influences of diet on adiposity, a major risk factor for many cancer types. Avoidance of sugar-sweetened beverages and replacement of refined carbohydrates with whole-grain alternatives is particularly important. Limiting consumption of red meat and processed meat, especially the latter, may decrease risk of colorectal cancer. Generous consumption of fruits and vegetables has less impact on cancer risk than was thought earlier, but some benefits exist. An overall healthy dietary pattern that emphasizes abundant intake of fruits and vegetables, whole grains rather than refined grains, and low intake of red meat and processed meat, sugar-sweetened beverages, and salt will reduce risk of cancer, as well as of cardiovascular disease, diabetes, and overall mortality [9].

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Physical activity, sedentary behaviour, and obesity. Established and emerging modifiable risk factors

Strong epidemiological evidence exists that being physically active reduces the risk of cancers of the bladder, breast, colon, endometrium, kidney, oesophagus, and stomach. Emerging evidence suggests that sedentary behaviour is associated with an increased risk of cancers of the breast, colon, endometrium, and lung. Strong evidence exists for an association between obesity and increased risk of cancers of the postmenopausal breast, colorectum, endometrium, ovary, kidney, liver, gall bladder, stomach, oesophagus, and pancreas, and moderate evidence exists for an association with cancers of the mouth, pharynx, larynx, prostate (advanced), and male breast, and diffuse large B-cell lymphoma. The population attributable fractions associated with physical inactivity, sedentary behaviour and obesity are estimated to range, collectively, from 20% to 40% for all cancers associated with these risk factors [9].

Obesity

The incidence of obesity-related cancers is critically affected by dietary composition, physical activity, and sedentary practices. In population studies of cancer, the predominant measures used are BMI, obtained by dividing the body weight (in kilograms) by the square of the height (in metres), and waist circumference. There is now considerable epidemiological evidence supporting an association between overweight and obesity and cancer risk, specifically cancers of the oesophagus (adenocarcinoma), gastric cardias, colon and rectum, liver, gall bladder, pancreas, breast (in postmenopausal women), endometrium, ovary, kidney (renal cell carcinoma), thyroid, meningioma, and multiple myeloma. The recommendations of the WCRF/AICR report [133] for healthy weight are to keep weight within the healthy range of BMI for adults, which is 18.5–24.9 kg/m^2, and to avoid weight gain in adult life.

4.5.2 Melanoma

Skin cancer is by far the most common type of cancer representing a major public health burden [134,135]. The landscape of cutaneous melanoma (CM), the most lethal form of skin cancer, has changed dramatically in recent decades: it is one of the most rapidly increasing cancers, with a clear upward trend in Europe, and a major public health challenge in white populations [136]. The greatest burden from melanoma falls on New Zealand, Australia and Europe [137]. The **opportunity to conquer melanoma is prevention** through reduction in ultraviolet (UV) radiation exposure, the **main risk factor** for skin cancer [138]. More than 85% of melanoma cases in Europe are attributed to sun exposure [139–142], and 6-9% are attributed to indoor tanning [143,144].

The entire UV spectrum is carcinogenic to humans [139]. **Sun exposure** is complex and classified as *ambient* (place of living)*, recreational* (short, intense exposure through recreational activities), *everyday exposure* (regular, low-medium level exposure of daily living/occupation) and *sunburn* (marker of severe acute UVB exposure) [145].

Sunscreen use is recommended as the third line of sun protection, after clothing and shade, but is the most popular method of sun protection [146]. Effectiveness of **sunscreen use** to reduce UV-induced skin damage has been proven in experimental studies but evidence of effectiveness in melanoma prevention in human populations is not conclusive [147]. The only one randomized controlled trial of sunscreen use to prevent skin cancer showed reduced CM risk in the intervention

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group, in sunny Australia with high awareness of sun-related melanoma risk [148], while observational studies **yield contradictory results, consistent with the challenges of controlling for innate confounding by indication** [147]. Two recent meta-analyses did not find consistent protective effects of sunscreen use in observational studies [147,149]. Sun protection factor ≥ 30 is important, but it should not be the only defence against the sun. **Best protection is achieved from the combined** use of **shade, clothing**, a **hat** with a wide brim, and **sunglasses**, as well as sunscreen on the uncovered skin surfaces, and current practice guidelines concur in recommending this multi-component approach. Public health recommendations should place emphasis on the proper use of sunscreen (for sun protection, not as excuse to prolong time in the sun), in adequate quantity [147], and in conjunction with other means of sun protection**.**

Erythema-weighted UV radiation from indoor tanning devices is generally higher than from natural sun, with large variations between devices, and UVA irradiance is much higher than from natural sun [150]. Vulnerability to the harmful effects of indoor tanning is greater at a younger age, and melanoma risk increase with increasing cumulative number of tanning sessions [151]. The use of **indoor tanning** devices was classified as carcinogenic in 2009 [152]. There is no safe limit for exposure to UV radiation from indoor tanning devices [153].

Melanoma incidence is higher in persons with fair skin, blond/red hair, freckles, many nevi, atypical nevi, and who burn easily and (almost) never get a tan [145], as well as in individuals with personal or familial history of melanoma. **Pigmentary characteristics** cannot be changed, except some prevention of nevi through sun protection [154].

Age and sex are important modulators of melanoma risk, as melanoma incidence and mortality increase with age, and men over 50 years have highest melanoma incidence, in thick melanoma incidence and melanoma mortality [145].

Avoiding excessive sun exposure is not in conflict with the fact that the sun is our most important source of vitamin D. The body needs small amounts of UV to make vitamin D, and adequate amounts of vitamin D should be obtained from a healthy diet [155]. Daily, reasonable use of broad-spectrum sunscreens with high UVA protection in optimal amount, will not negatively impact vitamin D status in healthy people [156,157]. In the same time consistent photoprotection, for people with skin cancer risk, that includes high protection sunscreens use together with photoprotective clothing and sun avoidance behaviour will likely cause vitamin D insufficiency. This insufficiency can be easily redressed, however, by diet and oral supplementation.

Behavioural interventions have been shown to be effective in increasing sun-protection behaviour, but there is limited evidence on their effects on reducing sunburns and on improving skin cancer outcomes [158].

5 DIETARY FACTORS

Specific literature searches were performed for dietary factors, using the following strategies in PubMed:

("Noncommunicable Diseases/prevention and control"[Mesh]) AND ("Nutrition Therapy"[Mesh] OR "Nutrition Policy"[Mesh] OR "Diet, Food, and Nutrition"[Mesh] OR "Diet, Healthy"[Mesh])

("Noncommunicable Diseases/prevention and control"[Mesh]) AND ("Diet"[Mesh] OR "Diet Therapy"[Mesh] OR "Diet, Healthy"[Mesh] OR "Diet, Food, and Nutrition"[Mesh])

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("Noncommunicable Diseases/prevention and control"[Mesh]) AND ("Risk Factors"[Mesh] OR "Cardiometabolic Risk Factors"[Mesh] OR "Heart Disease Risk Factors"[Mesh])

Time of publication was limited to 2015 and thereafter. Systematic reviews (with or without meta-analysis) and randomised controlled trials were selected. Studies focussed on dietary patterns (rather than specific modifications) or which included supplements were excluded. Regarding outcomes, studies focussing on less established risk markers, such as inflammatory markers, were also excluded.

A total of 7840 titles were identified, of which 65 articles were preselected and 22 were finally included, based on the quality of the evidence and their relevance for the WARIFA project (see Table 5). Although body mass index and overweight/obesity are properly not a “dietary risk factor”, they were included due to their association with increased caloric intake.

Among the preselected (and excluded) studies, several assessed dietary patterns which already have strong evidence of benefit, or less proven dietary patterns, such as fasting, anti-inflammatory, or anti-oxidative diets.

Recent publications support international recommendations on increasing the intake of fruits, vegetables, and whole grains, as well as reducing the intake of sugar-sweetened beverages. Furthermore, they add information on processed or highly processed foods as unhealthy choices, adding to established recommendations regarding avoidance of trans fatty acids and their replacement with unsaturated fats.

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Table 5 Dietary risk factors and NCD-related outcomes

DISEASE	Risk Factor for developing disease	Measurable Parameter	Quantitative contribution of the risk (if known)	Modifiable	Reference and type of study	Reference database
NCDs	Consumption of ultra-processed food (poorer dietary quality)	Diet Weight/ BMI: Overweight/obesity Body fat % Abdominal obesity Blood Pressure, blood glucose. Mortality	**The average intake** of ultra-processed food across these 28 studies was 37% of total calories. **All-cause mortality in adults.** Four studies were included in a meta-analysis, which showed that higher consumption of ultra-processed food significantly increased risk of all-cause mortality compared with lower consumption in adults. **Ultra-processed food was also associated with a higher risk of type 2 diabetes** (hazard ratio for 10% increase in proportion of ultra-processed food).	yes	**Systematic review and meta-analysis** [159]	https://world.openfoodfacts.org/nova [160]
NCDs Preventive	**Combined factors:** **Interventions that promote health.**	Dietary patterns, Physical activity, tobacco use, excess alcohol intake, medication adherence, cancer screening, and immunization status	Preventive interventions that favourably impact mortality and morbidity among individuals aged 50 years and older. Preventive recommendations to promote longevity	yes	**Systematic review** [161]	
NCDs **Overweight and obesity**	**Sugar intake** **Weight gain**	Sugar intake Weight (overweight an obesity) Blood triglycerides Diabetes, Insulin resistance, cardiovascular disease.	Accordingly, the new French recommendations set an upper limit of 100 g total sugar/day but reiterate that fruit and vegetable intakes are to be promoted.	yes	**Systematic review** [162]	
NCDs **Burden of various chronic diseases (cancer, hypertension,**	**Diet:** Unhealthy dietary pattern	Low fruit and vegetables intakes	**Mortality and disease incidence.** Eating 400 g/day F/V to promote good health has long been a global priority and actively advocated by national and international health organizations.	yes	**Systematic review and meta-analyses** [163]	

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CVD, CHD, T2 DM)						
NCDs **Obesity, T2DM, hypertension and all-cause mortality.**	**Diet:** sugar sweetened beverages **Obesity** **T2DM** **Hypertension**	Consumption of sugar sweetened beverages (SSB) and artificial sweetened beverages (ASB) BMI Waist circumstance T2DM Hypertension All-cause mortality	Summary relative risks (RRs) and 95% confidence intervals (CIs) were estimated for the dose-response association. Restricted cubic splines were used to evaluate linear/non-linear relations. We included 39 articles in the meta-analysis. **For each 250-mL/d increase in SSB and ASB intake, the risk increased by 12%** (RR = 1.12, 95% CI 1.05-1.19, I^2 = 67.7%) **and 21%** (RR = 1.21, 95% CI 1.09-1.35, I^2 = 47.2%) **for obesity**, **19%** (RR = 1.19, 95% CI 1.13-1.25, I^2 = 82.4%) **and 15%** (RR = 1.15, 95% CI 1.05-1.26, I^2 = 92.6%) **for T2DM**, **10%** (RR = 1.10, 95% CI 1.06-1.14, I^2 = 58.4%) **and 8%** (RR = 1.08, 95% CI 1.06-1.10, I^2 = 24.3%) **for hypertension**, **and 4%** (RR = 1.04, 95% CI 1.01-1.07, I^2 = 58.0%) **and 6%** (RR = 1.06, 95% CI 1.02-1.10, I^2 = 80.8%) **for all-cause mortality**. **Increased consumption of SSBs and ASBs is associated with risk of obesity, T2DM, hypertension, and all-cause mortality.**	yes	**Meta-analysis** [164]	
NCDs **(obesity and prediction NCDs)**	Obesity	Waist height (WHtR)	**Waist to height ratio (WHtR).** As a predictor of body fat. Of the 16 studies included in the review, ten concluded that WHtR is a valid anthropometric measure to diagnose obesity in elderly persons and that **this measure is associated with non-communicable diseases, which makes it recommended to predict such diseases.** (cardiovascular disease and cardiovascular risk factors, diabetes, metabolic syndrome, abdominal obesity.)	yes	**Systematic review** [165]	
NCDs	Overweight/obesity	Weight BMI Waist circumstance	By analysing the body weight, was found a decrease in the mean weight (-3,52k), and the Confidence Interval (95%) ranged from -5.26 to -1,79. These effects were also found in BMI, with a mean reduction of -1.09kg/$m^{2,}$, Confidence Interval (95%) from -2.03 to -0.14. For WC, the mean reduction was -2.46cm, and for the Confidence Interval (95%) from -4.28 to 0.64.	yes	**Systematic review and meta-analysis** [166]	
NCDs	Fibre intake Body weight Systolic blood pressure Cholesterol Glycated haemoglobin	Incidence, mortality, and risk factors for coronary heart disease, diabetes 2, and colorectal cancer.	Findings from prospective studies and clinical trials associated with relatively high intakes of dietary fibre and whole grains were complementary, and striking dose-response evidence indicates that the relationships to several non-communicable diseases could be causal. Those higher intakes of total dietary fibre are associated with a 15-31% reduction in the risk of specified critical outcomes. Dietary fibre: intakes in the range of 25-29d daily are adequate, while the dose-response data suggest that amounts greater than 30 g per day confer additional benefits.	yes	**Systematic review and meta-analysis** [167]	

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	Fasting glucose Etc.					
CVD	**Diet** (dietary total fat, fatty acids intake and risk cardiovascular disease)	**Intake: total fat, fatty acids.** (TFA, MUFA, SFA, PUFA)	**Higher TFA intake is associated with greater risk of CVDs in a dose-response fashion.** By comparing the highest vs. the lowest categories of fat or fatty acids intake, we found that higher dietary trans fatty acids (TFA) intake was associated with increased risk of CVDs [RR:1.14]. However, no association was observed between total fat, monounsaturated fatty acids (MUFA), saturated fatty acids (SFA), and polyunsaturated fatty acids (PUFA), and risk of CVDs. Subgroup analysis found a cardio-protective effect of PUFA in the studies that has been followed up more than 10 years [0.95, I^2 = 62.4%]. Dose-response analysis suggested that the risk of CVDs increased 16% [1.16] for an increment of 2% energy/day of TFA intake.	yes	**Meta-analysis of cohort studies** [168]	
CVD	**Diet portfolio** A plant-based dietary pattern as a protective factor against cardiovascular disease.	Cholesterol, lipids (LDL) and other cardiometabolic risk factors. Intake: nuts, plant protein soy, beans, fibre, fruit, vegetable and food enriched with sterols.	**The combination of a portfolio dietary pattern and NCEP Step II diet significantly reduced the primary outcome LDL-C** by ~17% (MD, −0.73 mmol/L, [95% CI, −0.89 to −0.56 mmol/L]) as well as non-high-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, triglycerides, systolic and diastolic blood pressure, C-reactive protein, and estimated 10-year coronary heart disease (CHD) risk, compared with an NCEP Step 2 diet alone ($p < 0.05$). There was no effect on high-density lipoprotein cholesterol or body weight. The certainty of the evidence was high for LDL-cholesterol and most lipid outcomes and moderate for all others outcomes.	yes	**Systematic review and meta-analysis of controlled trials** [103]	
CVD and cancer	**Diet:** vegetarian and vegan	Incidence and mortality: Disease cardiovascular, cerebrovascular, and different types of cancer	Association between vegetarian, vegan diets, risk factors for chronic diseases, risk of all-cause mortality, incidence, and mortality from cardio-cerebrovascular diseases, total cancer, and specific type of cancer (colorectal, breast, prostate, and lung). The overall analysis among cross-sectional studies reported significant reduced levels of body mass index, total cholesterol, LDL-cholesterol, and glucose levels in vegetarians and vegans versus omnivores. With regard to prospective cohort studies, the analysis showed a significant reduced risk of incidence and/or mortality from ischemic heart disease (RR 0.75; 95% CI, 0.68 to 0.82) and incidence of total cancer but not of total cardiovascular and cerebrovascular diseases, all-cause mortality and mortality from cancer	yes	**Systematic review with meta-analysis of observational studies** [169]	

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CVD and cancer	**Diet:** Intake of whole grains	Consumption of whole grains and specific types of grains. Risk of Cardiovascular disease, cancer and **All-cause mortality**	The summary relative risk per 90g/day increase in whole grain intake (90g is equivalent to three servings- for example, two slices of bread and one bowl of cereal or one and half pieces of pita bread made from whole grains) was 0.81 (95% confidence interval 0.75 to 0.87, n=7 studies) for coronary heart disease, 0.88 for stroke, and 0.78 for cardiovascular disease, with similar results when studies were stratified by whether the outcome was incidence or mortality. The relative risk for mortality were 0.85 infectious diseases, 1.15 for diseases of the nervous system disease, and 0.78 for all non-cardiovascular, non-cancer causes. Reductions in risk were observed up to an intake of 210-225g/day for most of the outcomes. Intakes of specific types of whole grains including whole grain bread, whole grain breakfast cereals, and added bran, as well as total bread and total breakfast cereals were also associated with reduced risks of cardiovascular disease and/or all-cause mortality, but there was little evidence of an association with refined grains, white rice, total rice, or total grains.	yes	**Systematic review and meta-analysis of prospective studies** [170]	
CVD	**Dietary cholesterol** (risk of cardiovascular disease)	Cholesterol and saturated fat content in food. Blood cholesterol and LDL	**Dietary and blood cholesterol. Lipids** The available evidence suggests that within the context of eating patterns, replacing saturated fat with unsaturated fat is expected to produce greater reductions in LDL cholesterol concentrations than reducing dietary cholesterol alone.	yes	**Systematic review** [171]	
CVD (cardiovascular disease, cancer and mortality)	**Diet:** Fruit and vegetable intake	Intake of fruit and vegetables All-cause mortality.	For fruits and vegetables combined, the summary RR per 200g/day was 0.92 for coronary heart disease, 0.84 for stroke, 0.92 for cardiovascular disease, 0.97 for total cancer and 0.90 for all-cause mortality. Reductions in risk were observed up to 800g/day for all outcomes except cancer (600g/day). Inverse associations were observed between the intake of apples and pears, citrus fruits, green leafy vegetables, cruciferous vegetables and salads and cardiovascular disease and all-cause mortality.	yes	**Systematic review and meta-analysis of prospective studies** [106]	
CVD and cancer	**Diet:** Fruit and vegetable intake	Intake of fruit and vegetables	After assessing the strength, the direction, and the consistence of the associations, we **concluded that the strongest evidence related to fruit and vegetable consumption is a probable reduced risk of CVD** and age-related cataract (for vegetable only). Among other possible associations**, higher consumption of fruit and vegetable was related with lower risk of colon cancer, depression, and pancreatic diseases,** while vegetable only was possibly further associated with **decreased risk of rectal cancer, stroke** (total)	yes	**Systematic review of observational studies** [172]	

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			and hip fracture. However, the latter associations lacked information on potential confounding factors, making evidence slightly weaker than for CVD.			
T2DM	**Diet and T2DM**	**Intake of food groups.** Whole grains, refined grains, vegetables, fruits, nuts, Legumes, eggs, dairy, fish, red meat, processed meat, sugar sweetened beverages.	Six of the 12 food-groups showed a significant relation with risk of T2D, three of them a decrease of risk with increasing consumption (whole grains, fruits, and dairy), and three an increase of risk with increasing consumption (red meat, processed meat and SSB) in the linear dose-response meta-analysis. **Optimal consumption of risk-decreasing foods resulted in a 42% reduction, and consumption of risk-increasing foods was associated with a threefold T2D risk, compared to non-consumption**.	yes	**Systematic review and meta-analysis of prospective studies** [173]	
T2DM	Diet and diabetes	Diet quality indices (HEI) Healthy dietary pattern Vegetarian diet DASH Mediterranean diet Low Carbohydrate diet **Intakes:** Food groups Beverages Alcoholic beverages Macronutrients Micronutrients	Quality of evidence was rated high for an inverse association for type 2 diabetes incidence with intake of whole grains (every 30 g/day, led to adjusted summary hazard ratio 0.87) and cereal fibre (every 10 g/day, HR 0.75), as well as for moderate intake of total alcohol (12-24 g/day vs no consumption, HR 0.75). Quality of evidence was also high for the increased incidence of type 2 diabetes with higher intake of red meat (100 g/day, HR 1.17), processed meat (50 g/day, HR 1.37), bacon (two slices/day, HR 2.07), and sugar sweetened beverages (one serving/day, HR 1.26).	yes	**Systematic reviews with meta-analyses of prospective observational studies** [174]	
T2DM	Diet Weight Physical activity Glucose	Weight reduction Optimal Diet Physical activity Oral glucose tolerance test (OGTT	The overall risk reduction of T2D by lifestyle interventions was 0.53 (95% CI). Most of the trials aimed to reduce weight, increase physical activity, and apply a diet relatively low in saturated fat and high in fibre. The PREDIMED trial that did not meet eligibility criteria for inclusion in the meta-analysis was used in the final assessment of diet quality. **We conclude that T2D is preventable by changing lifestyle and the risk reduction is sustained for many years after the active intervention (high certainty of evidence).** Healthy dietary changes based on the current recommendations and the Mediterranean dietary pattern can be recommended for the long-term prevention of diabetes.	yes	**Systematic review and meta-analysis** [175]	
T2DM	Diet Weight	Diet Mediterranean or low-fat diets.	The Mediterranean diet is able to reduce the incidence of diabetes by 19–23%. A significant reduction of type 2 diabetes has been found to be associated with greater consumption of healthy dietary patterns, including	yes	**Systematic review with**	

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		Glycosylated Haemoglobin Cholesterol levels Overweight/ obesity	the Mediterranean diet, the DASH, the AHEI and various a posteriori defined prudent/healthy dietary patterns. All the protective dietary patterns, including the vegetarian diet, since they are mostly plant-based and include a high consumption of whole-grain foods, fruit, and vegetables. In the PREDIMED trial, 3541 patients without diabetes at high cardiovascular risk were randomly assigned to education on either a low-fat diet or to one of two Mediterranean diets, supplemented with either free virgin olive oil (1 L/week) or nuts (30 g/day). After a 4.1-year follow-up, participants assigned to the two Mediterranean diets without calorie restriction had a 40% (significant) and 18% (non-significant) reduction, respectively, in the risk of diabetes compared with a low-fat control diet.		**meta-analyses** [176]	
T2DM	Diet	Vegetarian Diet and its variants (Diabetes risk). Prevalence or incidence of diabetes	A vegetarian diet was inversely associated with diabetes incidence/prevalence (OR 0.73, 95% CI: 0.61, 0.87). The duration of adherence to a vegetarian diet should also be considered. The beneficial health effects of a vegetarian diet on chronic diseases are often related to the duration of adherence to the diet.	yes	**Systematic review and meta-analysis of observational studies** [177]	
T2DM	Diet Physical activity	Diet Physical activity Weight Blood glucose	Compared with usual care, diet and physical activity promotion programs reduced type 2 diabetes incidence (risk ratio [RR], 0.59 (95% CI), decreased body weight (net change, −2.2% [CI, −2.9% to −1.4%]) (24 studies) and fasting blood glucose level (net change, −0.12 mmol/L [−2.2 mg/dL] [CI, −0.20 to −0.05 mmol/L {−3.6 to −0.9 mg/dL}]) (17 studies), and improved other cardiometabolic risk factors.	yes	**Systematic review** [178]	
COPD (Chronic Obstructive Pulmonary disease)	Diet (dietary patterns)	Healthy prudent Unhealthy western style Consumption: vegetables and fruit, cured meat, fibre	Decrease in the risk of COPD in the highest compared with the lowest category of **healthy dietary pattern.** There was evidence of an increased risk of COPD in the highest compared with the lowest category of **"western-style" dietary pattern**	yes	**Meta-analysis** [179]	

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5.1 CANCER

A thorough review on how different aspects of diet, as well as body weight and physical activity, might be linked to cancer has recently been performed by the World Cancer Research Fund, and the following, evidence-based recommendations for cancer prevention are made [126]:

- Be a healthy weight.
- Be physically active.
- Eat a diet rich in wholegrains, vegetables, fruit and beans.
- Limit consumption of fast foods and other processed foods high in fat, starches or sugars.
- Limit consumption of red and processed meat.
- Limit consumption of sugar sweetened drinks.
- Limit alcohol consumption.
- For mothers: breastfeed your baby, if you can.
- Do not use supplements for cancer prevention.

6 INTERVENTIONS DURING AND AFTER PREGNANCY

Pregnancy represents a window into future cardiovascular risk, exemplified by gestational diabetes and pre-eclampsia. Furthermore, intrauterine milieu is associated with lifetime risk of NCDs in the offspring. Thus, high-risk women can be identified and targeted at a time when their motivation for self-care is high, for their own, but especially for their child's sake.

6.1 DURING PREGNANCY

A search was performed in PubMed, using the terms "pregnancy" and "physical activity", limiting results to those published in 2016 and later, and only including randomized controlled trials, systematic reviews, and meta-analyses. The search yielded 418 results. Due to the abundance of studies, the selection was limited to meta-analyses of randomized controlled trials for most of the outcomes (gestational weight gain, risk of gestational diabetes, risk of hypertensive disorders in pregnancy), but also included randomized controlled trials for longer-term outcomes in the mother and offspring. Studies in women with established pre-gestational or gestational diabetes were excluded.

The most consistent evidence for the effects of physical activity during pregnancy was that supporting the reduction in gestational weight gain (between **0.7 and 1.6 Kg less** than in the control group, according to several meta-analyses) and a 15 to 42% reduction in the risk of developing gestational diabetes (see Table 6). Gestational diabetes, in its turn, predicts the future risk of maternal type 2 diabetes, and is associated with obesity and diabetes in the offspring. Two sessions of 50-60 minutes or 3 sessions of 30-45 minutes each during pregnancy already have positive effects.

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Table 6 Effects of physical activity during pregnancy on maternal health outcomes related to NCDs.

DISEASE	Risk Factor for developing disease	Measurable Parameter	Quantitative contribution of the risk (if known)	Modifiable	Reference and type of study	Reference database
Maternal future risk of diabetes and CVD	Physical activity during pregnancy	Gestational weight gain Risk of gestational diabetes (glucose)	Thirteen RCTs (N=1439). Physical exercise reduced gestational weight gain (mean difference = -1.14 kg, 95% CI = [-1.67 to -0.62], P < 0.0001) and the risk of gestational diabetes (RR = 0.71, 95% CI = [0.57-0.89], P = 0.004) in overweight and obese pregnant women. There were no significant differences in other outcomes such as gestational hypertension (RR=0.63 [0.38-1.05]), preeclampsia, caesarean delivery, birthweight, large for gestational age, small for gestational age, macrosomia, and preterm birth.	yes	**Meta-analysis of RCT** [180]	
Maternal future cardiovascular risk	Physical activity during pregnancy	Risk of hypertensive disorders of pregnancy (blood pressure)	Seventeen RCT (N=5075). Women who were randomized in early pregnancy to aerobic exercise for about **30-60 min two to seven times per week** had a lower incidence of gestational hypertensive disorders (5.9% vs. 8.5%; relative risk 0.70, 95% confidence interval 0.53-0.83; seven studies, 2517 participants), specifically a lower incidence of gestational hypertension (2.5% vs. 4.6%; relative risk 0.54, 95% confidence interval 0.40-0.74; 16 studies, 4641 participants) compared with controls. The incidence of preeclampsia (2.3% vs. 2.8%; relative risk 0.79, 95% confidence interval 0.45-1.38; six studies, 2230 participants) was similar in both groups. The incidence of caesarean delivery was decreased by 16% in the exercise group.	yes	**Meta-analysis of RCT** [181]	
Maternal future risk of diabetes and CVD	Physical activity during pregnancy	Risk of gestational diabetes (glucose) Risk of hypertensive disorders of pregnancy (blood pressure) Physical activity (MET-min/week)	'Moderate' to 'high'-quality evidence from randomised controlled trials revealed that exercise-only interventions, but not exercise+cointerventions, reduced odds of gestational diabetes (n=6934; OR 0.62, 95% CI 0.52 to 0.75), gestational hypertension (n=5316; OR 0.61, 95% CI 0.43 to 0.85) and pre-eclampsia (n=3322; OR 0.59, 95% CI 0.37 to 0.9) compared with no exercise. To achieve at least a **25% reduction** in the odds of developing these disorders, pregnant women need to accumulate at least **600 MET-min/week** of moderate-intensity exercise (e.g., 140 min of brisk walking, water aerobics, stationary cycling or resistance training)	yes	**Meta-analysis of RCT** [182]	
Maternal future risk of diabetes and CVD	Physical activity during pregnancy	Risk of gestational diabetes (glucose)	Six RCTs (N=2164). Exercise intervention was associated with significantly decreased incidence of gestational diabetes mellitus (Std. mean difference = 0.59; 95%CI = 0.39-.88; p = .01)	yes	**Meta-analysis of RCT** [183]	

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Maternal future risk of diabetes and CVD	Physical activity and diet before and during pregnancy	Risk of gestational diabetes (glucose) Dietary patterns Physical activity (min/week of leisure time physical activity)	N= 30,871 pregnant women. Diets such as Mediterranean Diet, Dietary Approaches to Stop Hypertension diet and Alternate Healthy Eating Index diet were associated with 15–38% reduced relative risk of gestational diabetes. Frequent consumption of potato, meat/processed meats, and protein (% energy) derived from animal sources was associated with an increased risk. Compared to no physical activity, any pre-pregnancy or early pregnancy physical activity was associated with 30% and 21% reduced odds of gestational diabetes, respectively. Engaging in **>90 min/week** of leisure time physical activity before pregnancy was associated with **46% decreased** odds of gestational diabetes.	yes	**Meta-analysis** [184]	
Maternal future risk of diabetes and CVD	Physical activity during pregnancy	Risk of gestational diabetes (glucose) Gestational weight gain	Eight RCTs (N=2981). Exercise during pregnancy was shown to decrease the occurrence of gestational diabetes [RR = 0.58, 95% CI (0.37, 0.90), P = 0.01 and RR = 0.60, 95% CI (0.36, 0.98), P = 0.04 based on different diagnosis criteria, respectively] in normal-weight women. Exercise during pregnancy can also decrease gestational weight gain [MD = - 1.61, 95% CI (- 1.99, - 1.22), P<0.01], and had no significant effects on gestational age at birth [MD = - 0.55, 95% CI (- 1.57, 0.47), P = 0.29] or birth weight [MD = - 18.70, 95% CI (- 52.49, 15.08), P = 0.28]	yes	**Meta-analysis of RCT** [185]	
Maternal and offspring future risk of diabetes and CVD	Physical activity initiated in second trimester of pregnancy	Blood pressure Weight, height, body mass index Body composition (% body fat)	84 women were randomised to intervention or usual activity, with follow-up data available for 61 mother-child pairs (38 exercisers) at 1 year and 57 (33 exercisers) at 7 years. At 1 year, there were no observed differences in measured outcomes between mothers and offspring in the two groups. At the 7-year follow-up, mothers were mostly similar, except that exercisers had lower systolic blood pressure (-6.2 mmHg; p = 0.049). However, offspring of mothers who exercised during pregnancy had increased total body fat (+3.2%; p = 0.034).	yes	**RCT, follow-up at 1 and 7 years** [186]	
Maternal future risk of diabetes and CVD	Physical activity and diet during pregnancy	Blood pressure Risk of gestational diabetes (glucose) Gestational weight gain	23 RCTs (N=8918) that compared combined diet and exercise interventions with no intervention (standard care). There was a possible reduced risk of gestational diabetes in the diet and exercise intervention group (average risk ratio (RR) 0.85, 95% confidence interval (CI) 0.71 to 1.01; 6633 women; 19 RCTs; $Tau^2 = 0.05$; $I^2 = 42\%$; P = 0.07; moderate-quality evidence). There was also a possible reduced risk of caesarean section (RR 0.95, 95% CI 0.88 to 1.02; 6089 women; 14 RCTs; moderate-quality evidence). No clear differences were seen between groups for pre-eclampsia (RR 0.98, 95% CI 0.79 to 1.22; 5366 participants; 8 RCTs; low-quality evidence), pregnancy-induced hypertension and/or hypertension (average RR 0.78, 95% CI 0.47 to 1.27; 3073 participants; 6 RCTs; $Tau^2 = 0.19$; $I^2 = 62\%$; very low-quality evidence), perinatal mortality (RR 0.82, 95% CI 0.42 to 1.63; 3757 participants; 2 RCTs; low-quality evidence) or large-for-gestational age (RR 0.93, 95% CI 0.81 to 1.07; 5353 participants; 11 RCTs; low-quality evidence). There was	yes	**Meta-analysis of RCTs** [187]	

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			evidence of less gestational weight gain in the diet and exercise intervention group (mean difference (MD) -0.89 kg, 95% CI -1.39 to -0.40; 5052 women; 16 RCTs; Tau^2 = 0.37; I^2 = 43%; moderate-quality evidence).			
Maternal future risk of diabetes and CVD	Physical activity during pregnancy	Risk of gestational diabetes (glucose) Gestational weight gain Risk of hypertensive disorders of pregnancy (blood pressure)	Individual participant data from 36 RCTs (N=12 526). Less weight gain occurred in the intervention group than control group (mean difference -0.70 kg, 95% confidence interval -0.92 to -0.48 kg, I^2=14.1%; 33 studies, 9320 women). No evidence was found of differential intervention effects across subgroups. There was strong evidence that interventions reduced the odds of caesarean section (0.91, 0.83 to 0.99, I^2=0%; 32 studies, 11 410 women), but not for other individual complications.	yes	**Meta-analysis of individual participants in RCTs** [188]	
Maternal future risk of diabetes and CVD	Physical activity during pregnancy	Risk of gestational diabetes (glucose)	Eleven RCTs (N= 1467). Physical activity reduced the risk of gestational diabetes, but only when it was delivered in the healthcare facility (RR 0.53; 95% CI 0.38-0.74). The overall effect of physical activity interventions regardless of location of the intervention was RR 0.69 (95% CI 0.51 - 0.94).	yes	**Meta-analysis of RCT** [189]	
Maternal future risk of diabetes and CVD	Physical activity and diet during pregnancy	Risk of gestational diabetes (glucose) Gestational weight gain	Forty-seven RCTs (N=15 745). Diet and exercise during pregnancy were preventive of gestational diabetes (RR 0.77, 95% CI 0.69-0.87). Four key aspects were identified to improve the preventive effect: targeting the high-risk population; an early initiation of the intervention; the correct intensity and frequency of exercise; and gestational weight gain management. Although 24 RCTs targeted women who were overweight or obese, body mass index failed to predict the effectiveness of an intervention. Interventions are most effective in high-incidence populations rather than simply in women who are overweight or obese. Furthermore, exercise of **moderate intensity for 50-60 minutes twice a week** could lead to an approximately **24% reduction** in gestational diabetes.	yes	**Meta-analysis of RCTs** [190]	
Maternal future risk of CVD	Physical activity and diet during pregnancy	Gestational weight gain Risk of pre-eclampsia or hypertensive disorders of pregnancy (blood pressure)	Twenty-three RCTs (N=7236), 11 (N=5023 participants) investigating the effect of diet and 3 (N=387) investigating the effect of exercise on risk of pre-eclampsia, 14 (N=4345) investigating the effect of diet, five (N=884) investigating the effect of exercise and one (N=304) investigating the effect of diet and exercise on risk of hypertensive disorders. In women randomized to diet and/or exercise, compared to expectant management, there was no significant difference in the risk of pre-eclampsia (RR 1.01, 95% CI 0.80-1.27; *p* = .96) or hypertensive disorders of pregnancy (RR 0.87, 95% CI 0.70-1.06; *p* = .17). In the intervention group, compared	yes	**Meta-analysis of RCTs** [191]	

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			to expectant management, gestational weight gain was significantly lower (-1.47 kg, 95% CI -1.97 to -0.97; *p* < .00001)			
Maternal future risk of diabetes and CVD	Physical activity and/or diet during/after pregnancy	Post-partum weight	Eighteen RCTs (N=2559):3 pregnancy only, 12 postpartum only and 3 pregnancy and postpartum. Intervention duration varied from 10 weeks to 10 months and included diet only (n = 5) or diet and physical activity (n = 13). Seven postpartum only interventions reported significant improvements in postpartum weight when compared to the control group. Most were short and intensive, lasting 10-16 weeks. One pregnancy only and one pregnancy and postpartum intervention reported reduced post-partum weight at 6 months. Nine trials did not report an effect of the intervention on postpartum weight.	yes	**Systematic review of RCTs** [192]	
Maternal future risk of diabetes and CVD	Physical activity during pregnancy	Gestational weight gain	23 RCTs (N=4462). In pregnant women with physical exercise, there was less weight gain [weighted mean difference (WMD) -1.02, 95% CI -1.35 to -0.70; P < .01; I = 48.4%]. Women appeared to benefit more for gestational weight control for exercise frequency of **3 times per week** (WMD -1.22, 95% CI -1.55 to -0.90; I = 40.3%) and exercise **duration of 30 to 45 minutes** each time (WMD -1.32, 95% CI -1.79 to -0.85; I = 1.5%).	yes	**Meta-analysis of RCTs** [193]	

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6.2 BREASTFEEDING

WHO recommends exclusive breastfeeding for the first 6 months, followed by the progressive introduction of complementary food while still breastfed until 2 years or beyond. However, almost two thirds of infants are not exclusively breastfed for the recommended 6 months, and this has not improved in twenty years [194].

"Breastmilk is the ideal food for infants. It is safe, clean and contains antibodies which help protect against many common childhood illnesses. Breastmilk provides all the energy and nutrients that the infant needs for the first months of life, and it continues to provide up to half or more of a child's nutritional needs during the second half of the first year, and up to one third during the second year of life.

Breastfed children perform better on intelligence tests, are less likely to be overweight or obese and less prone to diabetes later in life. Women who breastfeed also have a reduced risk of breast and ovarian cancers.

Inappropriate marketing of breast-milk substitutes continues to undermine efforts to improve breastfeeding rates and duration worldwide".

The more recent literature review on the effects of breastfeeding yielded evidence of benefits for the mother (see Table 7) and the child (see Table 8), supporting previous statements by WHO. Benefits for maternal health include a reduction in the risk of ovarian, endometrial, and thyroid cancer, as well as a reduced risk of diabetes, hypertension, and the metabolic syndrome. Although short duration breastfeeding (1 month) already seems to have a positive effect on maternal health, there is evidence supporting a dose-response effect for up to 9 months' breastfeeding (see Table 7).

Regarding the health of the offspring, apart from the proved benefits of breastfeeding on communicable diseases, evidence also supports an association between lactation and NCD-risk. There is evidence suggesting an inverse association between breastfeeding and the child's risk of overweight and obesity and type 1 diabetes. The association with type 2 diabetes is less evident.

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Table 7 Breastfeeding and maternal NCD-related outcomes.

DISEASE	Risk Factor for developing disease	Measurable Parameter	Quantitative contribution of the risk (if known)	Modifiable	Reference and type of study	Reference database
General Health **Preventive**	Breastfeeding	Intensity and duration of breastfeeding Pain Engorgement Inflammation (mastitis) Quantity of breast milk	Different types of breast massage were reported as effective in reducing immediate pain for the participants. There was considerable heterogeneity of study outcome measures, and the use of unvalidated tools in many of the studies led to the inability to pool the results. However, all included studies reported a reduction in pain regardless of the breast massage were helpful in reducing immediate pain and resolving symptoms.	Yes	**Systematic Review** [195]	
CVD	Breastfeeding Cardiovascular disease Hypertension Overweight/ Obesity Diabetes mellitus type 2 Metabolic syndrome	Intensity and duration of breastfeeding Prevalence, incidence, and mortality BMI, waist circumference Hyperlipidaemia	Metabolic syndrome (n = 10), hypertension (n = 7), subclinical cardiovascular disease (n = 2), prevalence/incidence of cardiovascular disease (n = 3) and cardiovascular disease mortality (n = 2). Overall, 19 studies (10 cross-sectional/retrospective, 9 prospective) reported significant protective effects of breastfeeding, nine studies (3 cross-sectional/retrospective, 5 prospective, 1 cluster randomized controlled trial) reported non-significant findings and none reported detrimental effects of breastfeeding.	Yes	**Systematic Review** [196]	
CVD	Breastfeeding Hypertension	Intensity and duration of breastfeeding Prevalence, incidence Blood pressure, blood lipids.	Nineteen studies were included. Of the four studies with short-term follow-up, 50% showed a protective association. The fifteen studies with longer-term follow-up were stratified by outcome. Sixty-seven percent of the studies that evaluated for elevated blood pressure and 100% of the studies evaluating for an outcome of hypertension showed a protective association. The minimum duration of lactation associated with a benefit was 1 month	Yes	**Systematic Review** [197]	
CVD	Breastfeeding Metabolic Syndrome	Intensity and duration of breastfeeding	Despite data scarcity, the results suggest that lactation may have a preventive role in metabolic syndrome development as two prospective studies and five cross-sectional studies revealed an association between duration of lactation and metabolic syndrome indicating that lactation	Yes	**Systematic Review and meta-analysis**	

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	Overweight/ Obesity Hypertension Gestational Diabetes	BMI, waist circumference Blood pressure, blood lipids, cholesterol, blood glucose Incidence, prevalence Metabolic syndrome	improves metabolic health, where especially the longer duration of lactation may have a protective effect. Prolonged lactation may be associated with a healthier metabolic profile and body composition, especially lipid levels and waist to hip ratio.		[198]	
Cancer (ovarian)	Breastfeeding	Intensity and duration of breastfeeding **Other relevant variables**: age at diagnosis/interview, self-reported race, total duration of oral contraceptive use, parity, history of endometriosis, BMI in young adulthood and family history of ovarian cancer. Parity Total breastfeeding duration	Breastfeeding was associated with a 24% lower risk of invasive ovarian cancer. Independently of parity, ever having breastfed was associated with reduction in risk of all invasive ovarian cancers, particularly high-grade serous and endometrioid cancers. For a single breastfeeding episode, mean breastfeeding duration of 1 to 3 months was associated with 18% lower risk and breastfeeding 12 or more months was associated with a 34% lower risk. More recent breastfeeding was associated with a reduction in risk that persisted for decades. Thirty-two studies had parity categories of 1, 2, and ≥3. The summary RRs for ovarian cancer were 0.72 (95% CI, 0.65 to 0.79), 0.57 (95% CI, 0.49 to 0.65), and 0.46 (95% CI, 0.41 to 0.52), respectively. Small to moderate heterogeneity was observed for one birth (p<0.01; Q=59.46; I^2=47.9%). Fifteen studies had breastfeeding categories of <6 months, 6-12 months, and >13 months. The summary RRs were 0.79 (95% CI, 0.72 to 0.87), 0.72 (95% CI, 0.64 to 0.81), and 0.67 (95% CI, 0.56 to 0.79), respectively. Only small heterogeneity was observed for <6 months of breastfeeding (p=0.17; Q=18.79, I^2=25.5%). Compared to nulliparous women with no history of breastfeeding, the joint effects of two births and <6 months of breastfeeding resulted in a 0.5-fold reduced risk for ovarian cancer.	Yes	**Meta-analysis** [199] **Systematic review and meta-analysis** [200]	
Cancer (endometrial)	Breastfeeding	Duration of breastfeeding BMI (height, weight) Parity	Three prospective and 11 case-control studies were included in this meta-analysis. The pooled estimates for ever compared with never breastfeeding and the longest duration of breastfeeding compared with the shortest were 0.91 [95% confidence interval (CI): 0.75-1.09] and 0.76 (95% CI: 0.59-0.98). The risk of endometrial cancer decreased by 7% for every 6-month increase in the duration of breastfeeding (relative risk: 0.93; 95% CI: 0.88-0.97). This study provides evidence that ever	Yes	**Meta-analysis** [201][202]	

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		Oral contraceptive use	breastfeeding, particularly a longer duration of breastfeeding, is associated with a lower risk of endometrial cancer. Ever breastfeeding was associated with an 11% reduction in risk of endometrial cancer (pooled OR 0.89, 95% CI 0.81-0.98). Longer average duration of breastfeeding per child was associated with lower risk of endometrial cancer, although there appeared to be some levelling of this effect beyond 6-9 months. The association with ever breastfeeding was not explained by greater parity and did not vary notably by body mass index or histologic subtype (grouped as endometrioid and mucinous compared with serous and clear cell).			
Cancer (thyroid)	Breastfeeding	Intensity and duration of breastfeeding Have breastfed/ Have not breastfed. Parity	There was an inverse association between ever breastfeeding and risk of thyroid cancer (RR = 0.91, 95% CI 0.83-0.99), with minor heterogeneity (I(2) = 10.1%). The dose-response analysis revealed a significant linear relationship between the duration of breastfeeding and risk of thyroid cancer. The summary RR for an increment of 1 month of breastfeeding with risk of thyroid cancer was 0.983 (95% CI 0.98-0.99). When focusing on cohort studies, a more prominent linear dose-response relationship was detected, with the combined RR for every increment of 1 month of breastfeeding to be 0.965 (95% CI 0.96-0.97).	Yes	**Meta-analysis** [203]	
Diabetes and Hypertension	Breastfeeding	Breastfeeding duration Blood pressure Blood glucose	Breastfeeding for more than 12 months was associated with a relative risk reduction of 30% for diabetes and a relative risk reduction of 13% for hypertension	Yes	**Systematic Review and meta-analysis** [204]	

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Table 8 Breastfeeding and offspring NCD-related outcomes.

DISEASE	Risk Factor for developing disease	Measurable Parameter	Quantitative contribution of the risk (if known)	Modifiable	Reference and type of study	Reference database
NCDs	Breastfeeding Overweight/Obesity Metabolic syndrome	Duration of exclusive breastfeeding Transition from breast milk to complementary food Weight, height, BMI. Diet intake, energy intake. Eating behaviours Cholesterol, LDL, HDL, triglycerides, blood lipids, Blood pressure, glucose.	Data showed lower odds of picky eating behaviour when exclusively breastfed until age 4–5 months compared to exclusively breastfed for 0–1 month. In the crude analysis only, exclusively breastfed until age 6–10 months was associated with a higher daily intake of vegetables. This study suggests that exclusive breastfeeding duration seems to influence pickiness and may contribute to facilitate the consumption of more vegetables in later childhood in obesity prone normal weight children. It was demonstrated that breastfeeding promoted growth without body composition alteration and without increased insulin resistance in children with exclusive breastfeeding, when compared to children receiving a higher calorie formula, except for one article that observed an increase in fat mass in exclusively breastfed children. Breastfeeding stimulation in these populations seems to be a way of preventing the health problems associated with the high risk of chronic non communicable diseases and obesity. A consistent association of breastfeeding with a modest reduction in the risk of later overweight and obesity in childhood and adulthood was found (the odds decreased by 13% based on high-quality studies), but residual confounding cannot be excluded. Lowering the protein content of infant formula is a promising intervention to reduce the risk of later overweight and obesity in children. There is no consistent evidence of an association of the age of introducing complementary foods	Yes	**Randomized Controlled Trial** [205] **Systematic review** [206][207]	
Diabetes	Breastfeeding	Breastfeeding Glucose Insulin resistance	Observational evidence suggests that never versus ever feeding human milk (limited evidence) and shorter versus longer durations of any (moderate evidence) and exclusive (limited evidence) human milk feeding are associated with higher type 1 diabetes risk. Insufficient evidence examined type 2 diabetes. Limited evidence suggests than the durations of any and exclusive human milk feeding are not associated		**Systematic review** [208]	

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			with intermediate outcomes (e.g., fasting glucose, insulin resistance) during childhood. Limited to moderate evidence suggest that feeding less or no human milk is associates with higher risk of type 1 diabetes in offspring. Limited evidence suggests no associations between the durations of any and exclusive human milk feeding and intermediate diabetes outcomes in children.			

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7 SUMMARY AND CONCLUSIONS

This literature review supports the importance of a healthy lifestyle in the prevention of NCDs. As WHO recommends, our efforts should focus on **avoiding tobacco and alcohol, increasing physical activity, and eating a healthy diet**, as well as avoiding **ultraviolet radiation exposure** and **ambient pollution**.

Specific dietary recommendations should include reducing salt, sugar-sweetened beverages, red and processed meat, and highly processed food in general and increasing whole grains, fruits, vegetables, and legumes, as well as promoting breastfeeding, which has health benefits both for the mother and for the child.

For people with type 1 diabetes, summarising, interpreting and making decisions based on data from different sources can be challenging. Using artificial intelligence to support these decisions could potentially improve glucose control and health-related quality of life.

Our next challenge will be to design an mHealth tool, with the appropriate recommendations, that is engaging enough for the end-users to adopt and at the same time has a positive impact on the users' health-related behaviour.

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