FRESHER

FORESIGHT AND MODELLING FOR EUROPEAN HEALTH POLICY AND REGULATION

D 2.1
Umbrella Review on major NCDs

Report Information

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PREFACE

This document contains the report of activities conducted within Task 1 of WP2, that is an Umbrella review of the existent literature to identify social, behavioural, and biologic determinants of relevant chronic conditions.

An umbrella review is designed to compile evidence from multiple systematic reviews or meta-analyses into one accessible and usable document. This approach is appropriate when there is already quite abundant systematic evidence on the determinants of chronic diseases.

The steps involved in this process are:

1) description of inclusion and exclusion criteria
2) comprehensive search for relevant studies
3) collection of data from the relevant studies; if necessary, by seeking additional information from the authors of included reviews or from the primary studies included in the reviews
4) critical assessment of limitations using predefined explicit criteria
5) evaluation of the quality of the evidence for each outcome
6) syntheses of results across included studies for each outcome.

This report provides an overview of the existing meta-analyses and systematic reviews focusing on the following chronic conditions:

- cardiovascular diseases (cerebrovascular)
- cardiovascular diseases (conorary)
- cancers
- diabetes
- chronic lung disease
- depression
- musculoskeletal diseases
- chronic neurologic disorders

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INTRODUCTION TO THE FRESHER PROJECT

FRESHER is a collaborative research project that aims to detect emerging health scenarios to test and assess future policy options to tackle the burden of chronic non-communicable diseases (NCDs) in Europe. As one of the largest threats to public health globally, the exponential growth of NCDs in Europe has a serious negative impact on human development, reduces productivity, contributes to impoverishment and creates a significant burden on health systems. Therefore, one of the main goals of FRESHER is to identify core determinants that could be targeted to lessen the impact of NCDs. We focus on a set of chronic diseases which currently constitute the bulk of the mortality rate in Europe: cardiovascular diseases, cancers, diabetes, chronic lung disease, depression, musculoskeletal diseases, and neurologic disorders.

Rather than just extrapolating past health trends, the project consortium will use a variety of foresight techniques that account for the interdependencies of structural long term trends in demographic factors, gender relations, technological, economic, environmental, and societal factors for European countries. Supported by a mapping of determinants of NCDs in Europe, the developed model will capture the complex set of inter-relationships between individuals' history of engagement in risk-taking behaviors, exposure to environmental risks and the resulting distribution of health, social and economic consequences across sex and social groups. All of these efforts will be combined to elaborate and produce inputs for the empirically-based dynamic micro-simulation tool capable of quantifying current and future health and economic impacts of risk factors as well as potential new policies and policy combinations.

HORIZON SCANNING AND FORESIGHT

Recent health related Foresights and Forecasts show widespread use of visions, scenarios and forecasts with demographic shifts, rising healthcare costs, and emerging technologies playing a predominant role in these analyses. Scenarios are ubiquitous in health Foresights and Forecasts. Many combine statistical forecasting with perceived trends to develop future scenarios that could form the basis for discussions on future policy formulations and options. Many also commence from a view normatively determined on previous trends and expectations to foresight and forecast future requirements in research, policy development, resources prioritization and interactive stakeholder engagement. Visions, scenarios, forecasts are preoccupied with issues of demographic trends, rising healthcare costs in order to finance those shifts, the inadequacies of healthcare structures in high and low income countries in delivering

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services often through lack of skilled personnel combined with the serendipitous effects of climate change, the widening epidemiology of chronic and infectious diseases and perceived changes in social attitudes to caring in communities.

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1 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND DIABETES

1.1 BACKGROUND

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased.

Diabetes mellitus is a global health concern; an estimated 347 million people worldwide are affected, and in 2008 diabetes accounted for 3 million deaths. The incidence of diabetes is projected to increase by more than 50% in the next decade because of rapid increases in the prevalence of obesity and physical inactivity (1).

The World Health Organization estimates that, from the year 2000 to the year 2030, the number of people with diabetes will increase from 170 millions to 500 millions; As a result, diabetes is predicted to become the seventh leading cause of death in the world by 2030 (2).

The American Diabetes Association (ADA) estimates that prevalence of diabetes will increase from 7 to 14.5 % by the year 2031 in USA. These estimates also speak of the epidemics of obesity as the main risk factor for type 2diabetes. It is estimated that 79 million Americans aged 20 or older have prediabetes, with 25 % of them progressing to type 2 diabetes in 3–5 years, with similar figures in European countries (3).

The burden of diabetes as a major cause of premature illness and death is mostly caused by the associated increased risk of cardiovascular disease. Widely quoted estimates from WHO suggest that the cardiovascular risk in people with diabetes is two to three times higher than in those without the disease, and that cardiovascular diseases cause between 50% and 80% of deaths in people with diabetes. However, these estimates are based on the assumption that diabetes confers the same degree of risk in women as in men, which is unlikely to be correct in view of the accruing evidence that women and men experience the disease differently (4).

Diabetes is a condition primarily defined by the level of hyperglycaemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced

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life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life (5).

The American Diabetes association (aDa) estimated the national costs of diabetes in the USA for 2012 to be $ 132 billion, increasing to $ 192 billion in 2020 (6-7).

Alcohol

Several studies show that moderate alcohol consumption, compared with abstaining and heavy drinking, is related to a reduced risk of type 2 diabetes. Although the risk is reduced with moderate alcohol consumption in both men and women, the association may differ for men and women. In a meta-analysis, consumption of 24 g alcohol/day reduced the risk of type 2 diabetes by 40% among women, whereas consumption of 22 g alcohol/day reduced the risk by 13% among men. The association of alcohol consumption with type 2 diabetes may be explained by increased insulin sensitivity, anti-inflammatory effects, or effects of adiponectin. Several intervention studies have examined the effect of moderate alcohol consumption on these potential underlying pathways.

Unhealthy diet

The transition from a traditional diet toward a diet composed of more industrialized, refined, and energy-dense foods (i.e., Western diet) has led to the well-known worldwide epidemics of obesity and type 2 diabetes (i.e., the so-called “nutritional transition”). The causes of these two chronic metabolic diseases may be related to the consumption of an unbalanced diet over many years. In addition, both diseases may be risk factors for other diet-related chronic diseases (DRCDs), including cardiovascular diseases (CVD), cancers, digestive diseases, mental illnesses, sarcopenia, and some skeletal, kidney, and liver diseases. The scientific literature shows that diets rich in unrefined and/or minimally processed plant-based foods (i.e., rich in micronutrients and fiber and low in saturated fat)and/or seafoods (e.g., the Prudent, Mediterranean, and Okinawa diets) are protective against the development of risk factors for several chronic diseases, notably cancers, CVD, obesity, and type 2 diabetes. On the contrary, the consumption of hypercaloric and hyperlipidemic diets with a high glycemic index and which are rich in saturated fatty acids but low in fibers associated with physical inactivity may promote the manifestation and lack of control of

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diabetes.

Several reviews have presented evidence syntheses on associations between sugar-sweetened beverage (SSB) consumption and metabolic syndrome/type 2 diabetes, weight, and cardiovascular disease. In a meta-analysis of 11 prospective cohort studies, the highest quantile of SSB consumption (one to two servings/day) was associated with a statistically significant increased risk of developing type 2 diabetes (risk ratio (RR) = 1.26, 95% confidence interval (CI): 1.12–1.41) and metabolic syndrome (RR = 1.20, 95% CI: 1.02–1.42) in adults. Vartanian et al. found associations between SSB consumption and increased energy intake and body weight, lower intake of calcium and other nutrients, and increased risk of medical problems such as type 2 diabetes, hypocalcemia, dental caries, and elevated blood pressure.

Overweight/obesity

Obesity is a well-established risk factor for type 2diabetes. Although histological characteristics of adiposity play a direct role, much of the increased risk for diabetes among the obese is thought to stem from the underlying cardio-metabolic abnormalities associated with excess fat, such as islet beta-cell dysfunction, insulin resistance, hyperglycaemia and high chronic systemic inflammation. Other contributing factors may include higher levels of visceral fat, an energy-dense/nutrient poor diet including excessive sugar intake, and physical inactivity along with genetic, ethnic and socioeconomic susceptibilities. It remains unclear if obese adults who are metabolically healthy also face an increased risk for type 2 diabetes over time.

The prevalence of obesity gradually increases from 20 years to 60 years of age, and a large percentage of T2DM develops from 45 years to 64 years of age. These data suggest that body weight (BW) gain in adulthood has an important role in the development of T2DM in middle-to-late adulthood. While the relationship between body mass index (BMI) and the risk of T2DM has been quantified in previous meta-analyses, the quantitative relationship between BW gain and risk of T2DM remains to be solved because of the variability in study design, such as gender, ethnicity and the period when BW gain occurred.

However, different strategies have shown effectiveness in prevention of new cases of type 2 diabetes in obese subjects, be it lifestyle modification, use of anti-diabetic drugs, antihypertensive drugs, weight loss-promoting drugs and lipid lowering drugs or bariatric surgery. A few meta-analyses, published 2005-2008, have confirmed the validity of these strategies, considered

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separately and not only in obese subjects.

Physical inactivity

Recommendations for type 2 diabetes prevention include maintaining a healthy weight, consuming a healthy diet, and participation in exercise. Most type 2 diabetes prevention programs have recommended aerobic (cardio-respiratory) activities with strong evidence supporting this approach. Large scale prevention studies such as the Diabetes Prevention Program (DPP) reported reductions in type 2 diabetes incidence of up to 58% and improvements in risk factors such as weight and insulin sensitivity. More recently, resistance training (RT) has been included in guidelines for type 2 diabetes based on evidence established over the last decade, which demonstrates benefits from RT including improved fasting plasma glucose(FPG), glycosylated haemoglobin (HbA1C), insulin sensitivity and the maintenance of fat free mass during energy restriction for weight loss.

The American College of Sports Medicine presents a strong body of evidence supporting the inclusion of physical activity and exercise in the treatment and management of diabetes in adults and youth. Together, physical activity and lifestyle modifications can effectively reduce the development of and/or slow the progression of Insulin Resistance.

1.2 METHODS

Objective. The goal of this paper is to synthetize the evidences on the determinants of type 2 diabetes mellitus, undertaking a review of systematic reviews and meta-analysis published from 2005 to 2015. We focused on behaviour determinants: alcohol, physical exercise, diet, overweitht/obesity, job strain. We selected studies that reported data on type 2 diabetes mellitus.

Inclusion and exclusion criteria. We included only systematic reviews and meta-analysis with information about the association between the considered determinants and type 2 diabetes mellitus and with quantitative data (RR, OR, HR, ect.). We excluded papers on the effect of treatment on risk reduction.

Database search. We performed a systematic literature search in PubMed and limited our search to human populations and articles published in English from 2005 to 2015, using the following search terms:

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"Diabetes Mellitus"[Mesh] AND (“Exercise” [Mesh] OR "Diet, Carbohydrate-Restricted"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Overweight"[Mesh]) AND "Meta-Analysis"[Publication Type] AND ("2005/01/01"[PDAT]: "2015/12/31"[PDAT]).

The electronic search produced 211 titles and abstracts. After reading these records, we selected 35 studies, according to our eligibility criteria and excluded 176 which were not pertinent. After reading the full-texts we excluded 8 reviews: 2 because they were protocols currently underway, 3 were not systematic reviews, 1 was the same study published in another journal(included), 1 assessed type 1 diabetes as outcome, and 1 because it assessed the effect of treatment on risk reduction. Therefore, a final set of 27 selected studies are fully taken into account in this review. Figure 1 shows the diagram of the paper selection process following PRISMA.

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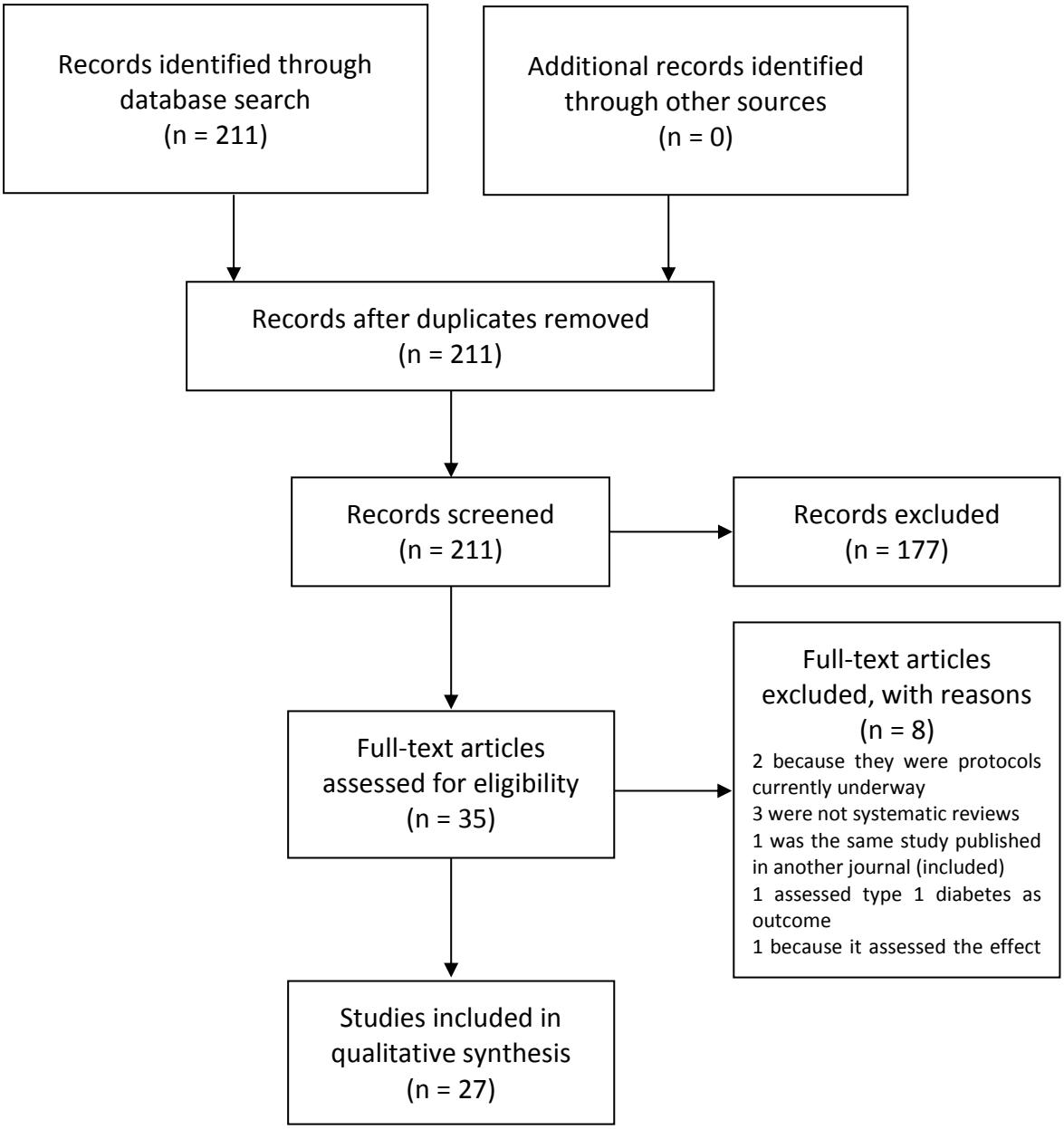
FIGURE 1.
Flow diagram of paper selection process



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1.3 RESULTS

Alcohol

The risk of Diabetes related to alcohol consumption was evaluated in 3 reviews (8-10).

The first review (8) included 25 Cohort studies (follow-up time of up to 20 years) and was conducted searching for reports published from 1 January 1980 to 31 January 2008. The aim of this review was to clarify the relationship between alcohol consumption and type 2 diabetes. The majority of studies concern men, but some included women. Nine studies were not included in the meta-analyses since the authors analysed alcohol consumption continuously or dichotomised, did not provide confidence intervals or analysed men and women together.

The alcohol consumption includes the influence of high versus moderate alcohol consumption, different susceptibilities for men and women and the magnitude of any protective effect of alcohol consumption. Moderate alcohol intake, corresponding to about 5–30 g of alcohol per day and high alcohol consumption corresponding to about 30 g of alcohol per day or more.

Moderate alcohol intake, corresponding to about 5–30 g of alcohol per day, was associated with a reduced risk of type 2 diabetes in the order of 30% (relative risk [RR]meta=0.72, 95% CI=0.67–0.77) compared to low consumption or abstention. There are few studies in women, but available data seem to indicate that moderate alcohol consumption is equally beneficial in women as in men (RRmeta in women=0.68, 95% CI=0. 61–0.75). Most of these studies were based on Caucasians, but the results were consistent across other ethnic groups such as Japanes, African-Americans and Nauruans. Moderate consumers of alcohol have a reduced risk compared to low consumers and to abstainers. Thus it does not seem likely that inclusion of people who did not drink because of disease or previous high alcohol consumption as reference can explain a protective effect in moderate consumers.

The relationship between high alcohol consumption (corresponding to about 30 g of alcohol per day or more) and type 2 diabetes is inconsistent across studies. In all studies except two, high consumers have an increased risk of type 2 diabetes compared to moderate consumers, but whether they have an increased risk compared to low consumers or abstainers is less clear. This was suggestedin two studies but not confirmed by others.

In women an increased risk of diabetes has been found in subgroups of high consumers such as

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lean women, (RR=2.8, 95% CI=1.1–7.3), and women with high consumption of spirits (RR=2.5, 95% CI=1.0–6.2).

The second review (9) took under consideration 20 prospective and case-control studies dealing with diabetes as outcome. In particular, this approach allowed to examine the relationship between alcohol consumption and the risk of type 2 diabetes among women and men by conducting a meta-analysis that uses a flexible modeling approach and that, for the first time, uses lifetime abstention as the reference category. The databases were searched for reports published from 1 January 1980 to 31 January 2008.

Alcohol consumption was converted to grams per day. For studies that reported ranges of alcohol consumption for the categories, the midpoint was used. When the highest category was open ended, three-quarters the width of the previous interval was added to the lower limit.

For both sexes, the relationship was U shaped. For women, the protective effect was greatest at the 24 g/day level, with a risk reduction of 40% compared with lifetime abstainers (95% CI 0.52–0.69). Alcohol consumption remained protective until just under 50 g/day. For men, the protective effect of alcohol consumption was greatest at 22 g/day, with the risk of diabetes being 0.87 times that of lifetime abstainers (95% CI 0.76 –1.00), and remained protective until consumption of 60 g/day. Thus, for both women and men, the protective effect of alcohol consumption on incident type 2 diabetes was greatest with the consumption of about two drinks per day. Similarly, for both men and women, higher levels of consumption (above 50 g/day for women and 60 g/day for men) were no longer protective but actually increased the risk for diabetes.

The third review (10) 14 intervention studies were included in a meta-analysis of six glycemic end points. Relevant studies were selected on the basis of the following inclusion criteria: trials with an alcohol intervention, relevant outcome measures as previously described and intervention period of at least 2 weeks. They excluded studies of individuals with (a history of) alcoholism or heavy drinkers (individuals consuming ≥ 60 g alcohol for at least 1 day per week) and animal studies. No publication date or status restrictions were imposed.

The exposure of interest was (moderate) alcohol consumption and the primary outcome measure, insulin sensitivity. All estimates of insulin sensitivity were included, which were indices from direct measures (e.g., hyperinsulinemic-euglycemic glucose clamp [HEGC]) and indirect measures of insulin sensitivity (e.g., the frequently sampled intravenous glucose tolerance test [FSIVGTT] and

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oral glucose tolerance test [OGTT]). HOMA of insulin resistance (HOMA-IR) was also included, which is based on fasting insulin and glucose levels and, therefore, primarily reflects hepatic insulin resistance. Other relevant outcome measures taken into account were fasting insulin, fasting glucose, and hemoglobin A1c (HbA1c). HbA1c reflects average plasma glucose levels over the past 8–12 weeks and is therefore used as a measure of glycemic status.

The main findings were that alcohol consumption did not influence estimated insulin sensitivity (standardized mean difference [SMD] 0.08 [20.09 to 0.24]) or fasting glucose (SMD 0.07 [-0.11 to 0.24]) but reduced HbA1c (SMD -0.62 [-1.01 to-0.23]) and fasting insulin concentrations (SMD -0.19 [-0.35 to -0.02]) compared with the control condition. Alcohol consumption among women reduced fasting insulin (SMD -0.23 [-0.41 to -0.04]) and tended to improve insulin sensitivity (SMD 0.16 [2-0.04 to 0.37]) but not among men. Results were similar after excluding-studies with high alcohol dosages (>40 g/day) and were not influenced by dosage-and duration of the intervention.

Job strain

The risk of Diabetes related to Job strain was evaluated in 1 review (11).

As the status of psychosocial stress at work as a risk factor for type 2 diabetes is unclear because existing evidence is based on small studies and is subject to confounding by lifestyle factors, such as obesity and physical inactivity, this review (11) examined whether stress at work, defined as "job strain" is associated with incident type 2 diabetes independent of lifestyle factors.

The authors extracted individual-level data for 124,808 diabetes-free adults from 13 European (from Finland, France, Denmark, Sweden, and the U.K.) cohort studies participating in Individual-Participant-Data meta-analysis of Working populations (IPD-Work) Consortium. They measured job strain with baseline questionnaires. Incident type 2 diabetes at follow-up was ascertained using national health registers, clinical screening, and self-reports. Data were analyzed for each study using Cox regression and pooled the study-specific estimates in fixed-effect meta-analyses.

During the mean follow-up of 10.3 years, a total of 3,703 incident type 2 diabetes cases were ascertained. Job strain was associated with increased risk of type 2 diabetes onset across the entire follow-up. After adjustment for age, sex, and SES, the hazard ratio (HR) for job strain compared with no job strain was 1.15 (95% CI 1.06–1.25). Job strain was independently associated with new onset of type 2 diabetes. In a model adjusted for age, sex, SES, BMI category, physical activity, smoking, and alcohol consumption, the HR for job strain compared with no job strain was

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1.11 (1.00–1.23). After adjustment for age, sex, SES, lifestyle factors, and self-reported or clinically measured biological risk markers, such as hypertension or blood lipid values, the HR was 1.12 (0.99–1.26).

The sensitivity analyses showed that the association between job strain and type 2 diabetes was not explained by working hours. After additional adjustment forworking hours, the HRwas 1.15 (95% CI 1.03–1.29). As expected, all lifestyle risk factors (obesity, physical inactivity, smoking, and heavy alcohol consumption) were associated with an increased diabetes risk. The strongest associations were seen for obesity. Job strain was associated with a similar excess risk of type 2 diabetes in both participants exposed and unexposed to lifestyle risk factors.

No difference in the association between job strain and incident type 2 diabetes was observed for men and women (age-, sex-, and SES-adjusted HRs 1.19 [95% CI 1.06–1.34] and 1.13 [1.00–1.28], respectively). The association was also similar among employees younger than 50 years (1.13 [0.99–1.28]; incident cases 1,685, n = 80,798, 13 studies) and those 50 years or older (1.16 [1.04–1.31]; incident cases 2,018, n = 44,010, 13 studies).

Overweight and Obesity

Seven different reviews (12-18) investigate the role of obesity and overweight as risk factors for type 2 diabetes.

The first review (12) included 32 studies and it was focused on the associations of diabetes incidence and general and central obesity indicators. In particular the role of body mass index, waist circumference and waist/hip ratio was investigated. Additionally, the authors explored if the associations differed by age. The pooled relative risks for incident diabetes were 1.87 (95% CI, 1.67 - 2.10), 1.87 (95% CI, 1.58 - 2.20), and 1.88 (95% CI, 1.61 - 2.19) per standard deviation of body mass index (BMI), waist circumference (WC), and waist/hip ratio, respectively, demonstrating that these three obesity indicators have similar associations with incident diabetes. Heterogeneity was present for all obesity indicators: $I^2 > 0.90$. In studies where the mean age was less than 50 years, RR-WHR (2.1; 95% CI, 1.7 - 2. 6) was higher than RR-BMI (1.7; 95% CI, 1.4 - 2.0) and RR-WC (1.6; 95 % CI, 1.4 - 1.9). For studies where the mean age was greater than or equal to 50 years, RR-WHR (1.7; 95% CI, 1.5 - 2.0) was weaker than RR-BMI (2.0; 95% CI, 1.7 - 2.3) and RR-WC (2.0; 95% CI, 1.6 - 2.7).

The second review (13) deal with the incidence of co-morbidities related to obesity and

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overweight defined by BMI. The definition for overweight was having a BMI greater than or equal to 25 kg/m2 and below 30 kg/m^2. The definition for obesity was having a BMI greater than or equal to 30 kg/m^2. According to the World Health Organization (WHO), the definition for abdominally overweight or obesity is a WC of greater than or equal to 80 cm and 88 cm, respectively, for females, and 94 cm and 102 cm, respectively, for males. The authors selected only prospective cohort study of the general population of a Western country (Europe or North America, Australia or New Zealand). Nine studies met the inclusion criteria and were included in the meta-analysis. Elevated BMI and WC were significantly associated with type II diabetes in men and women. The pooled IRRs [95% CI] across categories of BMI were 2.40 [2.12–2.72] and 6.74 [5.55–8.19] in men while the corresponding IRRs in women were 3.92 [3.10–4.97] and 12.41 [9.03– 17.06]. The association between increased WC and type II diabetes was similar but weaker in comparison with BMI. Only two studies were included in men. The pooled IRRs [95% CI] across categories of WC were 2.36 [1.76–3.15] and 5.67 [4.46–7.20] in men and the pooled RR-Ps [95% CI] based on the same two studies were 2.27 [1.67–3.10] and 5.13 [3.81–6.90], respectively. The pooled IRRs [95% CI] across categories of WC were 3.40 [2.42–4.78] and 11.10 [8.23– 14.96] in women.

The review by Asnawi et al (14) investigated the relationship between obesity or overweight, classified according to categories of body mass index (BMI), and the risk of developing type 2 diabetes by combining the available relative risks derived from 18 prospective cohort studies. Overweight was defined as BMI 25–29.99 kg/m^2 or closest to this category (including BMI 23.4–29.5 kg/m^2 or BMI 24.7–29.2 kg/m^2) and obesity was defined as BMI 30 kg/m^2 or other BMI category closest to this range (including BMI 29.2 or and BMI 29.5). The overall pooled results showed that the relative risk of diabetes for obese persons compared with those with normal weight was 7.19 (95% CI: 5.74 - 9.00) and for overweight was 2.99 (95% CI: 2.42 - 3.72). The relative risk of diabetes for women with obesity was eight times higher compared to women with normal weight, while men with obesity had a risk six times higher compared to men with normal weight.

The review by Kodama et al (15) aimed to summarize the risk of development of type 2 diabetes related to each anthropometric obesity indicator, including waist-to-height ratio (WHtR), and to compare the strength of the association among the obesity indicators. This review included 15

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cohort studies (120,102 participants). The exposure variables were BMI, waist circumference (WC), and waist-to-hip ratio (WHR), waist-to-height ratio (WHtR). Overall, the incremental diabetes risk was 1.62 (95% CI, 1.48 - 1.78) for RR-WHtR, 1.55 (95% CI, 1.43 - 1.69) for RR-BMI, 1.63 (95% CI, 1.49 - 1.79) for RR-WC, and 1.52 (95% CI, 1.40 - 1.66) for RR-WHR. This meta-analysis indicated that WHtR and WC were more strongly associated with the development of diabetes than was BMI or WHR. WHtR or WC has been more strongly correlated with intra-abdominal visceral fat than has BMI or WHR. The accumulation of visceral fat stores affects insulin metabolism by releasing free fatty acids. Free fatty acids reduce the hepatic clearance of insulin, which could lead to insulin resistance and hyperinsulinemia. This metaanalysis has confirmed the consistency between findings at the tissue- and whole-body levels.

A review by Neves Ribeiro D (16) aimed to critically assess studies that evaluated the effect of oilseed consumption on appetite and on the glycemic control. Although oilseeds are high-calorie foods, their consumption has been inversely related to the BMI. The studies demonstrate methodological differences regarding the way of the oilseed ingestion: liquid (oil) or solid (muffins), added to a food or meal, making it difficult to carry out more detailed comparisons of the results. A meta-analysis wasn't carried on, but the selected studies shows a DM2T risk reduction by 20%-30% when such food is consumed more times a week (compared to those who almost never consumed these foods). The results of the epidemiological studies are not conclusive about the effect of oilseeds in the prevention of type 2 diabetes.

The objective of the review by Kodama S. (17) was to synthesize existing prospective evidence on the risk of incident type 2 diabetes preceded by body weight (BW) gain in the general population. Systematic literature searches retrieved 15 eligible cohort studies. This meta-analysis quantified the risk of type 2 diabetes mellitus (T2DM) preceded by body weight (BW) gain in the general population. Systematic literature searches retrieved 15 eligible studies. The BW gain was divided into early weight-gain, which was defined as BW gain from early adulthood (18–24 years of age) to cohort entry (≥25 years of age), and late weight-gain, which was defined as BW gain from cohort entry. The pooled relative risk (RR; 95% confidence interval [CI]) of T2DM for an increment of BW gain standardized into a 5-point increment in the body mass index (BMI) was 3.07 (2.49–2.79) for early weight-gain and 2.12 (1.74–2.58) for late weight-gain. The meta-analysis suggested that BW gain was a quantifiable predictor of T2DM, as well as current obesity in adults. Particularly, BW

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gain in early rather than middle-to-late adulthood played an important role in developing T2DM.

Finally, another review (18) on this topic selected 7 cohort studies. Estimates from meta-analysis showed a pooled adjusted relative risk (RR) for incident type 2 diabetes of 4.03 (95% confidence interval = 2.66–6.09) in healthy obese (BMI > 30) adults and 8.93 (6.86–11.62) in metabolically unhealthy obese compared with healthy normal-weight (BMI < 25) adults. Although there was between-study heterogeneity in the size of effects (I2 = 49.8%; P = 0.03), RR for healthy obesity exceeded one in every study, indicating a consistently increased risk across study populations.

Diet and Physical activity

The effects of diet and physical attivity on type 2 diabetes was evaluated in 10 reviews.

In the fhe first review (19) the authors'aim was to identify rigorous, clinically relevant research studies that provide high-quality evidence that therapeutic fasting regimens are clinically beneficial to humans.

Fasting includes caloric restriction and total caloric desistance (i.e., intermittent fasting, alternate-day fasting, routine periodic fasting, or intermittent energy restriction), that are methods of energy deprivation.

Only two observational clinical events studies have examined fasting and major adverse clinical outcomes in humans. In the first study (20) fasting was associated with a lower odds of diabetes (NS after correction for multiple comparisons). The other study (21), using the same fasting survey question, was conducted among 200 patients from 2007 to 2008. This study evaluated a new set of cardiac patients for the primary outcome of diabetes, which was not significantly associated with fasting (after multiple-comparisons correction) in the first study and, thus, required additional evaluation as the primary hypothesis test. The second study found that patients who fasted routinely had lower odds of diabetes (adjusted OR: 0.40; 95% CI: 0.16, 0.99; P = 0.044). The meta-analysis result was OR = 0.57.

In another review (22) were collected in a pooled/meta-analyses and systematic reviews in orther to obtain an overview of the associations between diet-related chronic disease (DRCDs) (n = 10) and food and beverage groups (n = 17) and to establish new directions for future research needs.

Among the DRCDs diabetes was taken under consideration. Food groups and beverages were selected on the basis of their study frequency in the literature and their representativeness within the diets of Westernized countries and included the following: tea (from the Camellia sinensis

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genus of the Theaceae family only), coffee (excluding decaffeinated coffee), milk, wine (red, rosé, and white wines were considered), sweetened beverages, fruits and vegetables, vegetables, fruits, whole-grain cereals, refined cereals, legumes, nuts and seeds, dairy products, eggs, red and processedmeats, poultry, and fish.

A total of 304 PMASRs were analyzed for the 170 associations studied.

Based on meta-analyses only, the highest levels of coffee (0.96) and tea (0.84) consumption may significantly reduce the risks of type 2 diabetes.

The highest level of consumption of sweetened beverages tends to have deleterious effects for type 2 diabetes (1.26).

The highest level of fruit and vegetable consumption tends to be either protective against or not associated with diabetes risk (0.93-1.00).

Based on meta-analyses only, the highest level of wholegrain cereal consumption may significantly reduce the risks of type 2 diabetes (0.92-0.93).

As to refined cereals the most striking results were associated with white rice: a maximum increase of + 40% for risk of type 2 diabetes (1.40).

Meta-analysis showed that high legume consumption was associated with significant reductions in pooled blood glucose and insulin of −0.82 and −0.49 pmol/L, respectively, for a 1- to 16-week period.

Two systematic reviews (a total of 6 interventional studies) reported a reduction in levels of blood biomarkers of deregulated glucose metabolism, i.e., HbA1C, glucose, and insulin with the highest consumption of nuts and seeds.

Based on meta-analyses only, the highest levels of dairy products consumption compared with lowest/no consumption may significantly reduce the risk of type 2 diabetes (0.82–0.92).

Based on meta-analyses only, the highest levels of egg consumption may significantly increase the risks of type 2 diabetes (1.68).

Based on meta-analyses only, with regard to redmeat, the highest intakes are associated with significantly higher risks of type 2 diabetes (1.21–1.29). With regard to processed meat, the highest intakes are associated with significantly higher risks of type 2 diabetes (1.41–1.55).

The highest fish consumption tends to be not associated with type 2 diabetes (0.99-1.15).

Diet in the prevention of type 2 diabetes mellitus is taken into account in a Cochrane review (23),

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whose aim was to assess the exinting evidence to establish what kind of dietary advice is effective in preventing development of type 2 diabetes mellitus in adults.

Two trials which randomised 358 people to dietary treatment and control groups were identified. Longest duration of follow-up was six years.

In the trial lead by Pan (24) participants were randomized by clinic to one of four groups: diet only, diet plus exercise, exercise only and control. For the purpose of this review, only the diet and control groups were eligible for comparison. Participants with a body mass index (BMI) less than 25kg/m² were prescribed a diet containing 25 to 30kcal/kg body weight which consisted of 55% to 65% carbohydrate, 10% to 15% protein and 25% to 30% fat. These participants were asked to consume more vegetables, limit their alcohol consumption, and reduce their intake of simple sugars. Individuals with a BMI greater than 25kg/m² were encouraged to reduce their calorie intake in order to promote weight loss of 0.5 to 1.0 kg per month until they reached a target BMI of 23 kg/m². The incidence of type 2 diabetes in the control group was 67.7% (95%confidence interval (CI) 59.8% to 75.2%) and in the diet group 43.8% (95% CI 35.5% to 54.7%). Overall, the dietary intervention group had a 33% reduction in the incidence of diabetes after six years ($P < 0.03$). Defined by WHO criteria (WHO 1985), the incidence of diabetes was 15.7/100 person-years (95% CI 12.7% to 18.7%) for the control group, and 10.0/100 (95% CI 7.5% to 12.5%) person-years in the diet group which was significantly different ($P < 0.05$). As dietary treatment and advice differed for participants of BMI less than 25kg/m² (lean) and participants with a BMI greater than 25kg/m² (overweight), some analyseswere done to compare the two sub-groups. Incidence rates of diabetes in the control group of overweight participants were higher than incidence in the lean participants control group (17.2 versus 13.3/100 person years [$P < 0.05$]). In the lean participants, the incidence of developing diabetes was not significantly changed by the dietary intervention.

In the Oslo Diet and Exercise Study (25) the diet intervention was individualised and provided individually for each participant with their spouse. The dietary counselling encouraged a decrease in the total caloric intake, included increased intake of fish and fish products and a reduced total and saturated fat intake. In addition, participants were advised to increase their intake of vegetables and fibre-rich complex carbohydrate products and a decrease their intake of sugar. The authors found significant ($P<0.05$) reductions in insulin resistance, fasting insulin (pmol/L), fasting C-peptide (pmol/L), fasting proinsulin (pmol/L), fasting blood glucose (mmol/L), BMI (kg/m²), mBP

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(mmHg) and fasting triglycerides (mmol/L), and a significant increase in fasting HDL cholesterol (mmol/L) and PAI-1 (U/ml) after 12 months of dietary intervention.

Data on mortality, morbidity, health-related quality of life, adverse effects, costs were not reported in either study.

Merlotti C. et al. (26) conducted a systematic review and meta-analysis to evaluate the effectiveness of different strategies in prevention of T2DM. Studies were grouped into 15 different strategies, independently of the original aim of the studies (ad-hoc interventions or post-hoc analysis), and of the nature of studies (randomized or not-andomized trials, observational studies). Eight RCT and 3 NRCT assessed diet+physical activity; 7 RCT and 2 NRCT assessed physical activity or education. These strategies considered in meta-analysis reduced the risk of T2DM, obtaining the following results: diet+physical activity OR 0.43 (CI 0.35-0.52); diets OR 0.44; physical activity or education OR 0.53.

Lifestyle is taken under consideration in one review (27), where the authors'aims were to systematically review and meta-analyze the evidence on multi-component (diet + aerobic exercise + resistance training) lifestyle interventions for type 2 diabetes prevention.

The collective sample size of the studies at baseline was 1050 participants. Median intervention length was 12 months (range 4–48 months) with a follow-up of 18 months (range 6.5 - 48 months). Participants were advised to perform aerobic exercise for an average of 5.0 ± 1.5 days.wk-1 (mean ± SD), with an average duration of 157.5 ± 44.4 min.wk-1 and to perform resistance training for an average of 2.3 ± 0.7 days.wk-1 for an average duration of 90.0 ± 24.5 min.wk-1. Five studies prescribed energy restriction for weight loss and seven studies prescribed a specific dietary macronutrient profile.

Type 2 diabetes incidence was only reported in two studies. The Finnish DPS reported that the cumulative incidence of T2DM after four years was 58% lower in the intervention group than controls. The SLIM study reported cumulative incidence for T2DM after three years of 18% (11/61) for intervention and 32% (19/60) for the controls (56% lower for the intervention compared to control).

The objective of Schellenberg's systematic review (28) was to assess the effects of comprehensive lifestyle interventions in the prevention of diabetes in adults who have been identified as having increased risk for type 2 diabetes (for example, those with the metabolic syndrome or

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prediabetes) and the prevention of diabetic complications (such as microvascular and macrovascular outcomes) in adults diagnosed with type 2 diabetes.

Twenty unique studies in 58 publications were included. Nine studies addressed patients at increased risk for type 2 diabetes.

The duration of the interventions ranged from 6 to 72 months, with follow-ups between 3 and 20 years. For all studies, the number of participants ranged from 39 to 3234.

Although all lifestyle interventions included diet and exercise components, additional components were diverse. Five studies included both individual and group counseling, 1 incorporated only group counseling, and 1 had only individual counseling. Other components included behavior modification, a smoking cessation program, regular telephone contact, individual goal setting, and cooking lessons. One study included medication (orlistat) as an intervention component. The comparison group received various interventions, including usual care by a family physician, educational materials or advice on diet or exercise, waitlist controls, food diaries, and annual diabetes education sessions.

Seven studies reported the development of type 2 diabetes from the end of intervention up to 10 years after it. At the end of intervention, there was an important difference in favor of the lifestyle intervention (RR, 0.35 [CI, 0.14 to 0.85]). The difference was maintained at up to 10 years of follow-up. The Da Qing Diabetes Prevention Trial (24) also reported a difference in the development of type 2 diabetes in favor of lifestyle interventions at both 6 and 20 years (HR, 0.49 [CI, 0.33 to 0.73] and 0.57 [CI, 0.41 to 0.81], respectively); however, these results combine several intervention groups, including a lifestyle intervention with both diet and exercise components, a diet-only intervention, and an exercise-only intervention. The strength of evidence was moderate for development of type 2 diabetes.

Orozco et al. (29) conducted a systematic review to assess the effects of exercise or exercise and diet for preventing type 2 diabetes mellitus.

They included eight trials that had an exercise plus diet (2241 participants) and a standard recommendation arm (2509 participants). Two studies had a diet only (167 participants) and exercise only arm (178 participants). All included publications focused their interventions on improving physical activity and encouraging weight loss. Two of them separated the intervention in four study arms: exercise only, diet only, exercise plus diet and control group. All publications

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included diet and exercise interventions in the same group. The exercise interventions differed largely between trials, from the advice to promote physical activity, to a few times weekly supervised exercise programmes, that differed in intensity. Most of the programmes included exercises like walking, jogging and cycling, with different intensities. The diet interventions were based mainly on caloric restriction, reduced fat intake and increased fibre intake.

All eight studies included an exercise and diet group, a standard recommendation or no intervention group. The total number of events was 339 of 1976 in the exercise plus diet groups and 616 of 2252 in the control groups. Pooling of the eight studies by means of random-effects meta-analysis revealed a risk ratio of 0.63 (95% CI 0.49 to 0.79). The test for heterogeneity indicated an I2-value of 55%. Therefore the analysis was repeated excluding the largest study which had a weight of 26% in the random-effects model and had a low risk of bias. The risk ratio in the random-effects model was then 0.69 (95% CI 0.55 to 0.87). Heterogeneity decreased to an I2 of 22%. No statistical significant effects on diabetes incidence were observed when comparing exercise only interventions either with standard recommendations or with diet only interventions.

Interventions aimed at increasing exercise combined with diet are able to decrease the incidence of type 2 diabetes mellitus in high risk groups (people with impaired glucose tolerance or the metabolic syndrome). There is a need for studies exploring exercise only interventions and studies exploring the effect of exercise and diet on quality of life, morbidity and mortality, with special focus on cardiovascular outcomes.

In a systematic review (30) the authors aimed to evaluate the efficacy of lifestyle education compared with conventional education for preventing type 2 diabetes in individuals at high risk by meta-analysis of randomized controlled trials, as assessed by incidence and a reduced level of plasma glucose 2 h after a 75-g oral glucose load (2-h plasma glucose).

Subjects with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and borderline were diagnosed to be at high risk for type 2 diabetes. Lifestyle (combined diet and exercise) or solely dietary education interventions were selected.

Overall, a 1-year lifestyle education intervention reduced 2-h plasma glucose by 0.84 mmol/l (95% CI 0.39 –1.29) compared with the control intervention. Concordant results were obtained by other models, i.e., a 0.80 mmol/l (0.58 –1.01) reduction was estimated by the fixed-effects model and a 0.84 mmol/l (0.39 –1.32) reduction by the Bayesian model. All of the overall estimates denoted a

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significant reduction of 2-h plasma glucose in the lifestyle education intervention groups compared with control groups. There was evidence of heterogeneity in this combined analysis. Overall estimates of 2-h plasma glucose were obtained according to the length of the study (1 year for five studies and 1 year [6 and 4.25 years] for two studies) and by the types of intervention (lifestyle education for six studies and solely dietary education for two studies.) Excluding studies that exceeded 1 year (two studies), the results still showed a significant reduction in 2-h plasma glucose, except those for the Bayesian model.

In the five studies in which the incidence was obtained the cumulative meta-analysis indicated significant effects in all cases. All of the results indicated that lifestyle education groups had a relatively lower incidence than control groups. The risk of incidence of type 2 diabetes in the lifestyle education intervention group was reduced by 50% (RR 0.55 [95% CI 0.44–0.69]) compared with the control intervention group by the random effects model. The results from other models were similar.

Hopper et al. (31), in their systematic review sought to determine whether interventions (including diet, exercise and pharmacological therapy), may prevent or delay the onset of overt diabetes and thus potentially reduce major cardiovascular (CV) events in pre-diabetic subjects (impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)).

Ten studies were selected. Duration of follow-up ranged from 2.8 to 6 years for the intervention arms, with mean intervention time of 3.75 years. Most trials had follow-up only for the time of the intervention, but three studies reported extended follow-ups of 10.6, 20 and 6.5 years. Interventions were divided into pharmacological and non-pharmacological. Diet and exercise interventions differed between the trials. The lifestyle interventions in the non-drug trials achieved greater weight loss than those in the drug trials.

Diabetes was delayed or prevented overall (RR 0.66, 0.55–0.80) by intervention versus control with a heterogeneity X^2 of 267.3 ($p<0.001$). Both non-drug and drug-based approaches reduced progression to overt diabetes. Non-drug approaches (n=3495, 0.52 95%CI 0.46–0.58) were superior ($p<0.05$) to drug-based approaches (n=20,872, 0.70, 0.58–0.85).

In one review (32) included in this report a meta-analysis of all prospective cohort studies was performed to determine the association between TV viewing and risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality.

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Of the 8 studies included, 4 reported results on type 2 diabetes (175 938 individuals; 6428 incident cases during 1.1 million person-years of followup). In the meta-analysis of the multivariable-adjusted estimates without adjustment for dietary variables, greater TV viewing time was associated with a higher risk of type 2 diabetes (pooled RR, 1.20 [95% CI, 1.14-1.27] per 2 hours of TV viewing time; P<0.001) and a linear dose-response relationship was observed; P=0.08 for nonlinear response; goodness-of-fit X^2 13=20.5, P=0.07). Further adjusting for dietary variables slightly attenuated the risk estimate but an increased risk of type 2 diabetes remained with greater TV viewing time (pooled RR, 1.18 [95% CI, 1.12-1.25] per 2 hours of TV viewing time; P<0.001). When individual studies were pooled with an additional adjustment for BMI or another obesity measure, the summary estimate was attenuated to 1.13 (95% CI, 1.08-1.18) per 2 hours of TV viewing time (P< 0.001).

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Summary of quantitative estimates

Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
Alcohol consumption	8	5–30 g of alcohol per day vs abstension	0.72 (0.67–0.77)		0.68 (0.61-0.75)
	8	high consumers= 30 g of alcohol per day or more vs abstension			2.8 (1.1-7.3) (lean women)
	8	high consumption of spirits			2.5 (1.0-6.2)
	9	24 g/day level vs lifetime abstainers			0.60 (0.52-0.69)
	9	22 g/day vs lifetime abstainers		0.87 (0.76–1.00)	
Job Strain	11	job strain vs no job strain (adjustment for age, sex, and SES)	1.15 (1.06-1.25)	1.19 (1.06–1.34)	1.13 (1.00–1.28)
	11	job strain vs no job strain (adjustment for age, sex, SES, BMI category, physical activity, smoking, and alcohol consumption)	1.11 (1.00-1.23)		
	11	job strain vs no job strain (adjustment for age, sex, SES, BMI category, physical activity, smoking, and alcohol consumption)	1.12 (0.99-1.26)		
Overweight or obesity	12	1-SD of BMI	1.87 (1.67-2.10)		
	12	1-SD of WC	1.87 (1.58-2.20)		
	12	1-SD of WHR	1.88 (1.61-2.19)		

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Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
	13	Overweight (25-30 Kg/m^2) vs Normal weight		2.40 (2.12-2.72)	3.92 (3.10-4.97)
	13	Obesity (>=30 Kg/m^2) vs Normal weight		6.74 (5.55-8.19)	12.41 (9.03-17.06)
	13	abdominally overweight (80-88 cm for females; 94-102 cm for males) vs Normal weight		2.36 (1.76-3.15)	3.40 (2.42-4.78)
	13	abdominally obesity (>=88 cm for females; >=102 cm for males) vs Normal weight		5.67 (4.46-7.20)	11.10 (8.23-14.96)
	14	Overweight (25-30 Kg/m^2 or closest) vs Normal	2.99 (2.42- 3.72)		
	14	Obesity (>=30 Kg/m^2) vs Normal weight	7.19 (5.74- 9.00)		
	17	body weight gain: yes vs no	3.07 (2.49-2.79) (early weight-gain)		
	17	body weight gain: yes vs no	2.12 (1.74-2.58) (late weight-gain)		
	18	healthy BMI > 30 vs healthy BMI < 25	4.03 (2.66-6.09)		
	18	Metabolically unhealthy BMI > 30 vs healthy BMI < 25	8.93 (6.86-11.62)		
Diet; physical activity;	19	Fasting vs no fasting	0.57 (p<0.05)		
	26	diet+physical activity vs control	0.43 (0.35-0.52)		

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Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
lifestyle interventions	28	lifestyle interventions (diet and exercise + additional components) vs other interventions (usual care by a family physician, educational materials or advice on diet or exercise, waitlist controls, food diaries, and annual diabetes education sessions)	0.35 (0.14-0.85)		
	29	exercise + diet vs standard recommendation	0.63 (0.49-0.79)		
	30	lifestyle education vs conventional education	0.55 (0.44-0.69)		
	31	Diet + exercise vs standard interventions	0.52 (0.46-0.58)		
	32	each 2 hours of TV viewing time	1.18 (1.12-1.25)		

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1.4 CONCLUSIONS

Alcohol

For the first review (8), the results of published studies on alcohol consumption and type 2 diabetes consistently indicate that moderate alcohol consumption reduces the risk of type 2 diabetes. The risk reduction is in the order of 30%. This is comparable to what has been reported for cardiovascular disease. The reduced risk is seen both in men and in women, although it should be noted that few studies investigated this issue in women. As to the effect of high alcohol intake on the risk of type 2 diabetes, it is difficult to draw any conclusions. The most consistent finding is that no beneficial effect can be attributed to high alcohol consumption. Whether high alcohol intake actually increases the risk of type 2 diabetes is unclear.

For the second review (9) the meta-analysis confirmed the U-shaped relationships between average amount of alcohol consumed per day and risk of incident type 2 diabetes among men and women, although a more protective effect of moderate consumption was found for women. For women, the protective effect at moderate consumption and hazardous effect at higher consumption were both statistically significant. For men, the protective effect was statistically significant, but for higher consumption the CI did not exclude the RR 1. Moreover, this analysis confirms previous research findings that moderate alcohol consumption is protective for type 2 diabetes in men and women.

In the third review (10), although the studies had small sample sizes and were of short duration, the current evidence suggests that moderate alcohol consumption may decrease fasting insulin and HbA1c concentrations among nondiabetic subjects. Alcohol consumption might improve insulin sensitivity among women but did not do so overall.

Job strain

In this pooled analysis of almost 125,000 European adults, job strain was associated with a 1.15-fold increased risk of incident type 2 diabetes, with no evidence of differences in the association by sex. Importantly, the excess risk of type 2 diabetes associated with job strain was similar in magnitude among participants with and without unhealthy lifestyle factors: obesity, physical inactivity, smoking, and heavy alcohol use.

Overweight and obesity

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A clear risk of developing type 2 diabetes associated with both overweight and obesity is confirmed by all the reviews that take these factors into account, regardless of which indicators are used to measure them. In fact, a strong associations of body mass index, waist circumference, waist/hip ratio and waist/height ratio with incident diabetes was found in the analyzed review. Moreover, the review by Kodama et al 2014 (17) showed that waist/height is a statistically but modestly better obesity indicator for prediction of future diabetes risk than is BMI or waist/hip. However, there is no evidence that waist/height is superior to waist circumference.

The review from Ribeiro et al (16) indicates the possible existence of an association between the consumption of oilseeds and the risk of developing diabetes, but they are not yet conclusive.

Bell J.A. et al (18) highlighted that metabolically healthy obese adults show a substantially increased risk of developing type 2 diabetes compared with metabolically healthy normal-weight adults and that healthy obesity is not a harmless condition.

As shown by Kodama et al (17) in their review in 2014, body weight gain in adulthood was a quantifiable predictor of T2DM as well as current obesity.

Diet and Phisical activity

Among the reviews examinated, only one assessed the effect of the diet in preventing development of type 2 diabetes mellitus in adults. The data which are available do suggest that there are benefits in following an energy-controlled diet with an increase in consumption of fresh fruit and vegetables, and a decrease in simple sugars intake.

One review assessed associations between diet-related chronic disease and food and beverage groups. Based on authors' meta-analysis of available data the highest levels of consumption of coffee, tea, wholegrain, and dairy products, may significantly reduce the risks of type 2 diabetes. On the contrary the highest level of consumption of sweetened beverages, rice, eggs, redmeat and processed meat is associated with significantly higher risks of type 2 diabetes.

One review examined the beneficial effect of therapeutic fasting regimens to humans. The studies included support the existence of a health benefit from fasting, even if clinical research studies of fasting with robust designs and high levels of clinical evidence are sparse in the literature. Therefore substantial further research in humans is needed before the use of fasting as a health intervention can be recommended.

Six reviews reveal the effectiveness of lifestyle intervention (mainly diet and physical exercise) in

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the prevention of T2DM. Moreover comprehensive lifestyle interventions effectively decrease the incidence of type 2 diabetes in high-risk patients.

One review assessed the association between TV viewing and risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality. Findings from this meta-analysis of prospective studies suggest that longer duration of TV viewing time is consistently associated with higher risk of type 2 diabetes. However the author conclude that further study is needed to determine whether reducing prolonged TV viewing can prevent chronic disease morbidity and mortality.

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2 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND CARDIOVASCULAR DISEASES (CVDS)-STROKE

2.1 BACKGROUND

Non-communicable diseases (NCDs) have become a primary health concern for most countries around the world. According to the World Health Organization (WHO) (1) NCDs are responsible for almost 38 million global deaths each year, accounting the 63% of annual global deaths.

Cardiovascular diseases account for most NCDs deaths, and is the leading cause of death globally. CVD incidence is predicted to increase steadily over the next few decades. Reports from the WHO (1) state that CVD account for about 17.5 million deaths annually, followed by cancers (8.2 million), respiratory diseases (4 million), and diabetes (1.5 million). These four groups share more or less the same risk factors (tobacco use, unhealthy diet, physical inactivity and the harmful use of alcohol).

According to the Global Burden of Disease estimates (2), 68% of the 751 million years living with disability (YLD) worldwide is attributable to NCDs. Stroke is reported as a leading cause of disability in LMICs (low- and middle-income country), second only to dementia. CVDs are responsible for 151 377 million DALYs, of which 46 591 million are due to cerebrovascular disease (3). The contribution of stroke to the global CVDs burden is 29% for males and 33% for females (3).

A large percentage of CVDs (and other NCDs) is preventable through the reduction of behavioural risk factors (tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol). Unhealthy behaviours lead to metabolic/physiological changes: raised blood pressure (hypertension); overweight/obesity; raised blood sugar (diabetes); and raised blood lipids (dyslipidaemia). These intermediate risk factors cause damage to coronary and cerebral blood vessels due to atherosclerosis, a process that develops over many years, starting in childhood and manifesting as heart attacks and strokes in people of middle age. Since the underlying pathological process that causes heart attacks and strokes is similar, common approaches that address behavioural risk factors and metabolic risk factors are effective for prevention of both conditions.

In terms of attributable deaths, the leading cardiovascular risk factor globally is raised blood pressure (to which 13% of global deaths is attributed), followed by tobacco use (9%), raised blood glucose (6%), physical inactivity (6%) and overweight and obesity (5%) (4).

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Recent research reports regarding the risk factors for stroke, include also unhealthy lifestyle habits such as unhealthy diet and the harmful use of alcohol, hyperlipidaemia and family history of diseases, among other traits (5).

These behavioural and metabolic risk factors often coexist in the same person and act synergistically to increase the individual's total risk of developing acute vascular events such as heart attacks and strokes. Strong scientific evidence demonstrates that reducing total cardiovascular risk results in the prevention of heart attacks and strokes.

Overweight/obesity

High body-mass index (BMI) is an important cardiovascular disease risk factor, and raised blood pressure, cholesterol, and glucose partly mediate its effects. Present behavioural interventions for weight management are only effective in the short term, most weight-loss drugs lack either sustained efficacy or an acceptable safety profile, and surgical methods are recommended only for very obese individuals. This situation has created concerns about a potentially massive world-wide increase in cardiovascular diseases as a result of increased BMI and prevalence of overweight and obesity in most countries. By contrast, effective clinical and public health interventions for blood pressure and cholesterol are available, as evidenced by large decreases in these measures in some countries despite rises in obesity. Therefore, an important clinical and public health question is to what extent can the adverse effects of high BMI be mitigated by targeting its metabolic mediators

Unhealthy diet

Unhealthy diets include increased intake of foods rich in total fat, saturated fat, n-6 polyunsaturated fatty acid (PUFA) and sugar, and decreased intake of dietary fibre, n-3 PUFA, fruits and vegetables.

Dietary guidelines recommend that saturated fats should be limited to <10% (5-6% for those who would benefit from lowering of LDL cholesterol), and trans fats to <1% of energy or as low as possible, primarily to reduce risk of ischemic heart disease and stroke.

Hypertension – Potassium Intake

Elevated blood pressure and hypertension are major risk factors for cardiovascular diseases, especially coronary heart disease, stroke, and heart failure, as well as renal failure.

Hypertension is an important modifiable risk factor for stroke. Several dietary factors can affect

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blood pressure and hence the risk of stroke. Well-established nutritional modifications that lower blood pressure are weight loss, reduced dietary intake of sodium chloride (salt), and moderation of alcohol consumption. Evidence also indicates that increased potassium intake may reduce blood pressure

Lower potassium consumption has been associated with elevated blood pressure, hypertension, and stroke, and higher levels of consumption could be protective against these conditions. Public health interventions aimed at increasing potassium intake from food are, therefore, potential cost effective measures for reducing the burden of morbidity and mortality from non-communicable diseases.

Smoke

Cigarette smoking has been shown to be an independent risk factor for both ischemic and haemorrhagic stroke in both men and women. Overall, smokers have an approximate doubling in the risk of incurring a stroke during their lifetime compared with never-smokers. Recent estimates indicate that ≈19% of the burden of stroke is because of current smoking. Yet, this estimate assumes that the effect of smoking is the same in women and men who smoke, which may not necessarily be a valid assumption. Some, but not all large-scale studies have suggested that, as with CHD, smoking has a greater relative effect on stroke risk in women compared with their male equivalents, especially among the heaviest smokers.

Physical Activity

Preventive measures, such as physical activity (PA), is recognized to reduce the risk of hypertension and coronary heart disease (CHD). Fewer studies, however, have investigated the relationship between PA and stroke outcomes, with conflicting and controversial conclusions. Whereas some of these studies reported an inverse association between PA and stroke outcomes, others showed no significant or demonstrated positive associations. Agnarsson et al., for example, showed intense PA to be protective in men over 40 years of age but not in younger men. To add to the controversy, other studies showed moderate or intense PA to be protective against stroke in men but not in women.

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Diabetes

Diabetes mellitus is an established risk factor for coronary heart disease and ischaemic stroke, but how much its effect varies by age, sex, or levels of conventional risk factors is uncertain. The extent to which diabetes is associated with fatal versus non-fatal myocardial infarction or ischaemic versus haemorrhagic stroke is also unknown. Furthermore, how much of the effect of diabetes on vascular risk can be accounted for by conventional vascular risk factors (eg, obesity, lipids, or blood pressure) is unresolved.

Alcohol

Alcohol is a commonly consumed beverage in many populations, and contributes both favourably and adversely to disease morbidity and mortality. A large number of cohort studies have showed that light-to moderate alcohol intake is associated with a decreased risk of cardiovascular disease and ischemic stroke. However, some studies suggest that an intake of even 2 drinks/day may increase the risk of important stroke risk factors like hypertension and atrial fibrillation. Furthermore, concerns have been raised regarding the accompanied risk of haemorrhagic stroke, which may be attributed to alcohol intake. The relationship between alcohol intake and an increased risk of haemorrhagic stroke was first revealed in an early Hawaiian cohort study. Moreover, later, in a US cohort, the risk of haemorrhagic stroke was found to be 259% higher in subjects with low alcohol intake (b15 g/day) and 370% higher in those with moderate alcohol intake (15–30 g/day). A collaborative analysis of 19 cohort studies and 16 case–control studies showed a 118% increase in the risk of haemorrhagic stroke with an alcohol intake of N60 g/day. However, conclusions were not consistent between studies, and the effects of alcohol intake on subsequent stroke morbidity and mortality are still limited and inconclusive.

2.2 METHODS

Objective. The goal of this paper is to synthetize the evidences on the determinants of cerebrovascular diseases, undertaking a review of systematic reviews and meta-analysis published from 2005 to 2015. We focused on biomedical and behaviours determinants: smoking, excise, diet, alcohol, overweitht, diabetes mellitus, hypertension and hyperlipidemia. As to cerebrovascular disease we selected studies which reported data on different kinds of stroke.

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Inclusion and exclusion criteria. We included only systematic reviews and meta-analysis with information about first events and with quantitative data (RR, OR, HR, ect.). We excluded papers on the effect of treatment on risk reduction.

Database search. We performed a systematic literature search in PubMed and limited our search to human populations and articles published in English from 2005 to 2015, using the following search terms:

"Stroke [Mesh] AND ("Smoking [Mesh] OR "Exercise [Mesh] OR "Diet, Sodium-Restricted" [Mesh] OR "Diet, Fat-Restricted [Mesh] OR "Diet, High-Fat" [Mesh] OR "Potassium, Dietary [Mesh] OR "Blood Pressure" [Mesh] OR "Diabetes Mellitus" [Mesh] OR "Hyperlipidaemia" [Mesh] AND "Meta-Analysis [Publication Type] AND ("2005/01/01" [PDAT] : "2015/12/31").

The electronic search produced 209 titles and abstracts. After reading these records, we selected 32 studies, according to our eligibility criteria and excluded 157 which were not pertinent, and 20 that dealt with the effect of treatment on risk reduction. After reading the full-texts we excluded 9 reviews: 4 because they included the same studies taken under consideration in other more recent reviews, 1 was a narrative review and did not report data on stroke events, 3 were not systematic reviews, 1 included only Asian studies, 1 assessed "bone mineral density" as risk factor, and 1 because it assessed the risk based on the value of an index comparing diastolic and systolic blood pressure. In addition, we reviewed the reference lists of obtained articles and added one review. Therefore a final set of 22 selected studies are fully taken into account in this review.
Figure 1 shows the diagram of the paper selection process following PRISMA (6).

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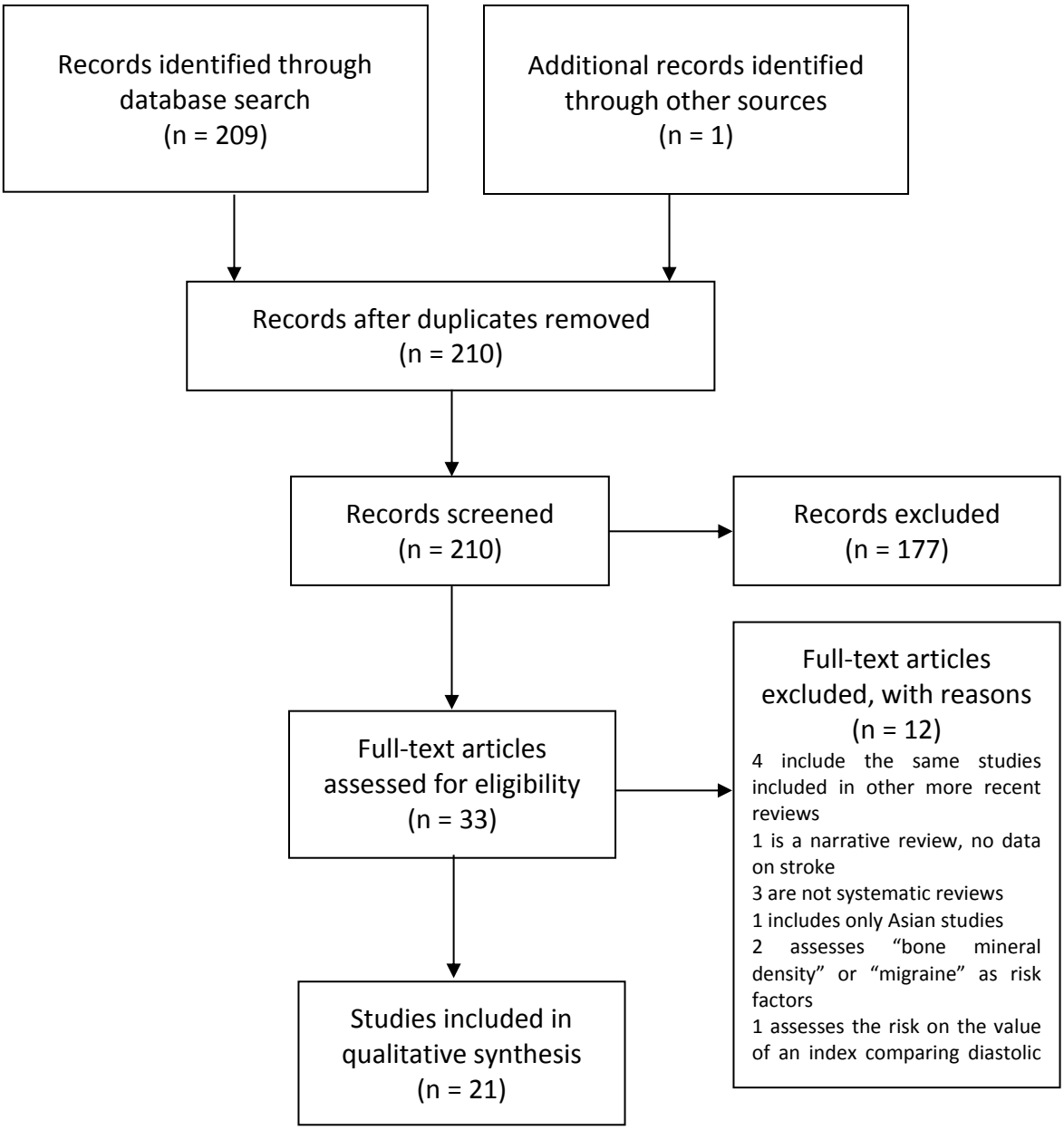
FIGURE 1.
Flow diagram of paper selection proces



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2.3 RESULTS

Potassium intake

Two reviews (7-8) explored the relationship between dietary potassium intake and the risk of stroke.

The first study (7) had the aim of evaluating the effect of increased potassium intake on cardiovascular risk factors and disease. The review included 22 randomized controlled trials and 11 cohort studies, the authors used GRADE to assess the quality of the body of evidence. Nine of the selected study dealt with the risk of stroke. The results of a meta-analysis conducted on nine cohort studies highlighted a protective effect of higher potassium intake (>155 mmol/day) on risk of incident stroke (risk ratio 0.76, 0.66 to 0.89) (moderate quality evidence). The risk of incident stroke was the least when the intake of potassium in the comparison group was 90-120 mmol/day (risk ratio 0.70, 0.56 to 0.88), although it was not significantly different from the result when the potassium intake was <90 mmol/day (0.82, 0.71 to 0.93). The same review explored the potential adverse effects in adults: it showed no significant adverse effect of increased potassium on total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, or triglyceride concentrations. Three studies measured renal function by serum creatinine, and the meta-analysis showed that increased potassium intake decreased serum creatinine by a non-significant 4.86 (−3.87 to 13.59) µmol/L.

The second study (8) focused on the risk of stroke. The main inclusion criteria were: original articles, prospective design and adult population. Twelve studies were included, for a total of 14 cohorts (overall 333,250 participants and 10,659 events); the meta-analysis of the selected studies showed an inverse and significant association between K intake and risk of stroke (Relative Risk: 0.80; 95% CI: 0.72-0.90). Sensitivity analysis showed that the risk of stroke did not vary substantially with the exclusion of any individual study. In addition, the dose response analysis showed that for every 1 g/day (25.6 mmol/day) increase in K intake there was a 10% reduction in stroke risk (RR: 0.90; 95% CI: 0.84-0.96).

Alcohol consumption

The risk of stroke related to alcohol consumption was evaluated in 4 reviews (9-12).

The first review (9) was conducted in 2010, the considered end-points were ischemic and

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hemorrhagic stroke morbidity and selected 9 studies.

The risk of hemorrhagic-stroke morbidity for men resulted in a monotonic relationship, almost linear on a logarithmized scale (RR = 2.52, 95% CI: 1.74-3.64; at 10 drinks per day vs lifetime abstainers). For women, the curve was J-shaped; there was a protective effect of moderate drinking up to 36 grams of pure alcohol or about 3 drinks a day. The minimum was reached at less than 1 drink per day (RR: 0.69, 95% CI: 0.54-0.89).

The risk of ischemic-stroke morbidity for both sexes resulted in a J-shaped curve as well. There was a protective effect up to 37 grams/day (about 3 drinks/day) among men and 46 grams/day (or about 4 drinks/day) among women observed. For 12 drinks/day, the risk of ischemic-stroke morbidity was highest at RR = 1.60 (95% CI: 1.38-1.86) among men and RR = 2.15 (95% CI: 1.62-2.86) among women.

The second review (10) took under consideration 12 studies dealing with stroke as outcome. The overall association of alcohol intake with stroke incidence was close to null. However, this null association seemed to obscure nearly significant but opposite associations with subtypes of incident stroke. Among the 12 studies on incident haemorrhagic stroke, the pooled relative risk for current alcohol drinkers compared with non-drinkers was 1.14 (95% confidence interval 0.97 to 1.34), whereas the eight studies on ischemic stroke showed a moderate reduction in the pooled relative risk of 0.92 (0.85 to 1.00). Analyses of the dose of alcohol consumed showed that 2.5–14.9 g alcohol (about ≤1 drink) per day was protective compared with no alcohol. The dose-response relation was consistent with U or J shaped curves, suggesting an increased risk among drinkers of greater amounts of alcohol. Specifically, those who consumed >60 g/day were at a significantly increased risk of incident stroke compared with abstainers (RR 1.62 (1.32 to 1.98)).

Twenty-two prospective cohort studies were included in the third selected systematic review and meta-analysis (5), four of these studies dealt with alcohol consumption and stroke. The review showed no significant association between alcohol consumption and stroke incidence (HR = 0.89; 95% CI 0.76 - 1.04), in Western population, whereas the risk was significant among Asian populations (HR = 1.28 95% CI 1.07 - 1.53).

The last meta-analysis (11) included 27 prospective studies reporting data on 1,425,513 individuals. Low alcohol intake (<15 g/day) was associated with a reduced risk of total stroke (RR, 0.85; 95% CI: 0.75–0.95), and ischemic stroke (RR, 0.81; 95% CI: 0.74–0.90), but it had no

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significant effect on haemorrhagic stroke (RR 0.96; 0.74-1.24). Moderate alcohol intake had little or no effect on the risks of total stroke (RR 1.01; 0.93-1.09), haemorrhagic stroke (RR 1.21; 0.85-1.73), and ischemic stroke (RR 0.89; 0.78-1.02). Heavy alcohol intake (>30 g/day) was associated with an increased risk of total stroke (RR, 1.20; 95% CI: 1.01–1.43), but it had no significant effect on haemorrhagic stroke (RR 1.29; 0.98-1.71), and ischemic stroke (RR 0.96; 0.77-1.19).

Body Mass Index (BMI)

Three different reviews (5, 12-13) deal with the risk of stoke for different categories of BMI.

The first review (12) was published in 2010, it included 25 prospective cohort studies, with 2,274,961 participants and 30,757 events and it focused on the risk of total, ischemic or hemorrhagic stroke. BMI exposure was stratified in normal-weight, overweight and obese subjects. The pooled RR of total stroke was 1.26 (95% CI, 1.07–1.48) for obese vs normal-weight subjects and it was 1.05 (95% CI, 0.93–1.17) in overweight vs normal-weight subjects. Authors report a significant heterogeneity between studies (>90%). As regards ischemic stroke, the estimates of pooled RR was 1.22 (95% CI, 1.05–1.41) for overweight and 1.64 (95% CI, 1.36 –1.99) for obesity, whereas RR for hemorrhagic stroke was 1.01 (95% CI, 0.88–1.17) and 1.24 (95% CI, 0.99 –1.54), respectively; in all these cases the heterogeneity between studies was significant. The relationship between excess body weight and risk of ischemic stroke was not significantly different in men (pooled RR, 1.21) and women (RR, 1.55). With regard to the populations' geographical origin, excess body weight seemed to be a better predictor of the risk of ischemic stroke in European and North American populations (pooled RR, 1.55) than in Asian populations (RR, 1.08).

The second review (5) included 22 prospective cohort studies and dealt with different risk factors. As regards the BMI, he combined results indicated that the risk of stroke was 0.96 (0.93-0.99) for a BMI of 18.5-21.9 kg/m^2 and 1.21 (0.99-1.48) for a BMI ≥ 25 kg/m^2. The statistical analyses of the final combined results were stratified by Western or Asian populations, the shown risks refers to western populations, no significant difference was observed between Western and Asian population as regard the risk of stroke related to BMI.

The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration group (13) in 2014 conducted a review and meta-analysis of 97 prospective cohorts with 1·8 million participants to evaluate the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke. After the adjustment for confounders, each 5 kg/m² higher BMI was associated with a HR

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of 1.18 (1.14–1.22) for stroke. Being overweight, compared with normal weight, was associated with an HR of 1.13 (1.08–1.18) for stroke after adjustment for confounders. Obesity had a significantly larger association: the confounder-adjusted HR of obesity versus normal weight was 1.47 (1.36–1.59) for stroke.

Smoking

The association between smoking habits and the risk of stroke has been analyzed by just one systematic review (14). The study systematically searched for prospective population-based cohort studies from 1966 to 2013. As the aim was to estimate the effect of smoking on stroke in women compared with men, only studies that presented sex-specific estimates of the relative risk of stroke comparing current smoking with nonsmoking and its associated variability were selected. Compared with nonsmoking, current smoking was associated with 83% (95% CI, 1.58–2.12) increased risk in women and 67% (95% CI, 1.49–1.88) increased risk in men. Compared with nonsmoking, current smoking was associated with an increased risk of ischemic stroke of 54% (95% CI, 1.21–1.96) in women and 53% (95% CI, 1.28–1.82) in men. The excess risk of former smoking versus never smoking was 17% (95% CI, 1.12–1.22) in women and 8% (95% CI, 1.03–1.13) in men.

Hypertension

The association between hypertension and the risk of stroke has been evaluated in 2 published reviews (15-16); two other studies (17-18) dealt with the risk related to prehypertension.

The first review (15) was published in 2006 and selected 8 cohort and 4 case-control studies which assessed hypertension and risk of total stroke. When hypertension was treat like a continuous variable, the pooled OR was 1.19 (95% CI 1.15–1.23) for each 10mmHg increase in systolic blood pressure (SBP). Based on ten studies assessing hypertension (as a dichotomous variable) and risk of ischemic or haemorrhagic stroke, the pooled OR for ischemic stroke was 1.96 (95% CI 1.66–2.30), while it was 3.11 (95% CI 2.39–4.05) for haemorrhagic stroke.

The second review (16) selected prospective study that examined the relationship between morning blood pressure surge (MBPS) and subsequent cardiovascular disease endpoints. Seventeen studies were suitable for data extraction and included in the analysis. Included studies were conducted in 14 different countries and examined a total of 33,154 patients with a mean age

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of 60 years. There was no evidence of an association between the MBPS, defined by a predetermined threshold, and stroke (HR = 1.26, 95% CI = 0.92–1.71). However, when the MBPS was analyzed as a continuous variable, a 10 mm Hg increase in the pre waking surge was associated with an increased risk of all stroke events (HR = 1.11, 95% CI = 1.03–1.20).

The other two reviews (17-18) evaluated the risk of stroke related to prehypertension (systolic blood pressure [SBP] 120–139 mm Hg or diastolic blood pressure [DBP] 80–89 mm Hg). The first one (17) included 13 articles derived from 12 prospective cohort studies. Prehypertension was associated with risk of stroke (RR 1.55, 95% CI 1.35–1.79). Seven studies further distinguished a low prehypertensive population (SBP 120–129 mm Hg or DBP 80–84 mm Hg) and a high prehypertensive population (SBP 130–139 mm Hg or DBP 85–89 mm Hg). Among persons with lower-range prehypertension, stroke risk was not significantly increased (RR 1.22, 0.95–1.57). However, for persons with higher values within the prehypertensive range, stroke risk was substantially increased (RR 1.79, 95% CI 1.49–2.16).

The second review on this topic (18) selected 19 prospected cohort studies that evaluated the association between prehypertentsion and the risk of stroke. The study highlighted an increased risk of stroke for subjects with prehypertentsion (RR 1.66; 95% CI 1.51-1.81) compared with optimal blood pressure (<120/80 mm/Hg). Even low-range prehypertension (120-129/80-84 mm/Hg) increased the risk of stroke (RR 1.44; 95% CI 1.27-1.63) and the risk was greater for high-range prehypertension (130-139/85-89 mm/Hg) (RR1.95; 95% CI 1.73-2.21).

DIET: Consumption of sugar-sweetened beverages, Intakes of saturated or trans fat, and Omega 3 supplementation

Three reviews (19-21) examined the effect of diet habits as consumption of sugar-sweetened beverages, intakes of saturated or trans fat on the risk of stroke, and Omega-3 supplementation.

Xi B et al. (19) performed a meta-analysis on prospective cohort studies investigating the associations between consumption of sugar-sweetened beverages (SSB) and the risk of hypertension, CHD and Stroke. There was no significant association between SSB consumption and total stroke (summary RR 1.06, 95% CI 0.97-1.15). This study suggested that a higher consumption of SSB is associated with higher risk of hypertension and CHD, but not with a higher risk of stroke.

One other recent review (20) studied the association between Intakes of saturated or trans fat and

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different health outcomes including ischemic stroke. Forty-one primary reports of prospective cohort studies about the associations between saturated fats and health outcomes were selected. The summary risk ratio for ischemic stroke was 1.02 (95% CI 0.90 to 1.15).

Regarding trans fats, 20 primary prospective cohort studies (published between 1996 and 2015) were selected and meta-analysis shows non association between trans fats intake and ischemic stroke: the summary risk ratio was 1.07 (95% CI 0.88 to 1.28).

The third review (21) performed a meta-analysis of 14 RCTs: Omega-3 supplementation has no effect on the incidence of stroke (OR, 1.21; 0.99 to 1.47).

Diabetes and Pre-diabetes

The risk of stroke associated with glucose metabolism dysfunctions has been evaluated in three reviews (22-24).

Peters SAE et al (22) published a systematic review and meta-analysis to estimate the relative effect of diabetes on stroke risk in women compared with men. A meta-analysis was conducted on data from 64 cohort studies. The pooled maximum-adjusted RR of stroke associated with diabetes was 2·28 (95% CI 1·93–2·69) in women and 1·83 (1·60–2·08) in men. Compared with men with diabetes, women with diabetes therefore had a greater risk of stroke. This sex differential was seen consistently across major predefined stroke, participant, and study subtypes.

The second review (23) assessed the effect of pre-diabetes or impaired fasting glucose on future risk of stroke. The final literature review included 15 prospective cohort studies, all studies excluded people with fasting glucose of 126 mg/dL or greater. In eight studies with information about fasting glucose 100 to 125 mg/dL, the random effects summary estimate did not show increased risk of stroke after adjustment for established cardiovascular risk factors (relative risk 1.08, 95% CI 0.94-1.23). In five studies with information about fasting glucose 110 to 125 mg/dL, the random effects summary estimate showed an increased risk of stroke after adjustment for established cardiovascular risk factors (relative risk 1.21, 1.02 to 1.44). In both cases some evidence of heterogeneity was found across studies (P for heterogeneity <0.0001). Other eight studies had information about impaired glucose tolerance (IGT - two hour values in the oral glucose tolerance test of 140-199 mg/dL two hour values in the oral glucose tolerance test of 140-199 mg/dL) or combination of pre-diabetes and IGT. The random effects summary estimate for these studies showed an increased risk of stroke after adjustment for established cardiovascular

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risk factors (relative risk 1.26, 1.10 to 1.43). No heterogeneity across studies was found. Three further studies provided information on participants with fasting glucose of 100 to 109 mg/dL and found no associated increased risk of stroke (relative risk 0.94, 0.73 to 1.20).

The third review (24) studied the risk of stroke or other CVD related to fasting insulin concentrations, as a continuous variable. Of the 22 identified studies, 7 reported results on stroke. Comparison of the highest with the lowest quantile of fasting insulin concentrations showed a pooled RR (95% CI) of 1.18 (0.87, 1.60). Each 50-pmol/L increment in fasting insulin was associated with a 25% increase in risk of hypertension and a 16% increase in risk of CHD but was not associated with risk of stroke [RR: 0.999 (0.99, 1.01)]. In the stratified analysis, the pooled risk of those in the highest quantile was 1.24 (0.88, 1.76) for ischemic stroke. Only one study reported results on haemorrhagic stroke. On the basis of 3 studies that reported results in men, a positive (RR: 1.67; 95% CI: 1.07, 2.60; high compared with low quantiles) and linear (RR: 1.20; 95% CI: 1.03, 1.40; per 50-pmol/L increment) association was identified between fasting insulin and risk of stroke.

Depression

Just one review (25) was performed with the aimed to determine the association between depression and risk of stroke. Seventeen cohort studies were selected for meta-analysis. Participants with depression, compared with those free of it, experienced a significant increased risk for development of stroke (combined RR, 1.34; 95% CI, 1.17–1.54). The associations between depression and stroke were similar between men (RR, 1.49; 95% CI, 1.28 –1.74; n=8) and women (RR, 1.35; 95% CI, 1.05–1.72; n=7).

Physical activity

The possible association between physical activity and stroke has been evaluated in one review (26) that concerns the question whether regular exercise can lower the risk of suffering or dying from a stroke, and, if so, whether ischemic or hemorrhagic strokes, or both, can be prevented by exercise. The review is based on 33 prospective cohort and 10 case-control studies. The meta-analysis shows that physical activity reduces the risk of all types of stroke (infarction, hemorrhage, and stroke of unspecified type) by 29% (RR = 0.71, 95% CI: 0.64–0.80). The RR for ischemic stroke is 0.75 (95% CI: 0.67–0.84), while the corresponding figures for cerebral hemorrhage is 0.67 (95%

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CI: 0.52–0.86).

The reduction of risk of total stroke is significant in both women and men (RR 0.71, 95% CI 0.58–0.88 in women; 0.72, 95% CI: 0.64–0.80 in men). It is only statistically significant for men regarding the risk of ischemic stroke (RR 0.73, 95% CI 0.65–0.83 in men; 0.76, 95% CI 0.56–1.02 in women) and haemorrhagic stroke (RR 0.60, 95% CI: 0.43–0.83 in men; 0.92, 95% CI 0.44–1.93 in women).

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Summary of quantitative estimates

Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
Potassium intake	7	>155mmol/day	0.76 (0.66 - 0.89)		
	8	average weighted difference: 1.5 g or 38.5 mmol/day	0.80 (0.72 - 0.90)		
	8	every 1 g/day (or 25.6 mmol/day) increase	0.90 (0.84 - 0.96)		
Alcohol consumption	9	10 drink/day vs lifetime abstainers		2.52 (1.74-3.64) (haemorrhagic stroke)	
	9	less than 1 drink per day vs lifetime abstainers			0.69 (0.54-0.89) (haemorrhagic stroke)
	9	12 drinks/day vs lifetime abstainers		1.60 (1.38-1.86) (ischemic stroke)	2.15 (1.62-2.86) (ischemic stroke)
	10	current alcohol drinkers vs non-drinkers	1.14 (0.97-1.34) (haemorrhagic stroke)		
	10	current alcohol drinkers vs non-drinkers	0.92 (0.85-1.00) (ischemic stroke)		
	10	>60 g/day vs non-drinkers	1.62 (1.32-1.98)		
	5	yes vs no	0.89 (0.76-1.04)		
	11	<15 g/day vs non-drinkers	0.85 (0.75–0.95)		
	11	<15 g/day vs non-drinkers	0.81 (0.74–0.90) (ischemic stroke)		
	11	<15 g/day vs non-drinkers	0.96 (0.74-1.24)		

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Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
			(haemorrhagic stroke)		
	11	15-30 g/day vs non-drinkers	1.01 (0.93-1.09)		
	11	15-30 g/day vs non-drinkers	1.21 (0.85-1.73) (haemorrhagic stroke)		
	11	15-30 g/day vs non-drinkers	0.89 (0.78-1.02) (ischemic stroke)		
	11	>30 g/day vs non-drinkers	1.20 (1.01–1.43)		
	11	>30 g/day vs non-drinkers	1.29 (0.98-1.71) (haemorrhagic stroke)		
	11	>30 g/day vs non-drinkers	0.96 (0.77-1.19) (ischemic stroke)		
BMI	12	overweight vs normal-weight	1.05 (0.93–1.17)		
	12	obese vs normal-weight	1.26 (1.07–1.48)		
	12	overweight vs normal-weight	1.22 (1.05–1.41) (ischemic stroke)		
	12	obese vs normal-weight	1.64 (1.36 –1.99) (ischemic stroke)		
	12	overweight vs normal-weight	1.01 (0.88 –1.17) (haemorrhagic stroke)		
	12	obese vs normal-weight	1.24 (0.99 –1.54) (haemorrhagic stroke)		
	5	BMI 18.5-21.9 kg/m^2	0.96 (0.93-0.99)		
	5	BMI ≥ 25 kg/m^2	1.21 (0.99-1.48)		

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Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
	13	each 5 kg/m² higher BMI	1.18 (1.14–1.22)		
	13	overweight vs normal-weight	1.13 (1.08–1.18)		
	13	obese vs normal-weight	1.47 (1.36–1.59)		
Smoking	14	current smoking vs nonsmoking		1.67 (1.49–1.88)	1.83 (1.58–2.12)
	14	current smoking vs nonsmoking		1.53 (1.28–1.82) (ischemic stroke)	1.54 (1.21–1.96) (ischemic stroke)
	14	former smoking versus never smoking		1.08 (1.03–1.13)	1.17 (1.12–1.22)
Hypertension / prehypertension	15	each 10mmHg increase in SBP	1.19 (1.15–1.23)		
	15	yes vs no	1.96 (1.66–2.30) (ischemic stroke)		
	15	yes vs no	3.11 (2.39–4.05) (haemorrhagic stroke)		
	16	morning blood pressure surge	1.26 (0.92–1.71)		
	16	10 mm Hg increase in the pre waking surge	1.11 (1.03–1.20)		
	17	prehypertension	1.55 (1.35–1.79)		
	17	low-range prehypertension	1.22 (0.95–1.57)		
	17	high-range prehypertension	1.79 (1.49–2.16)		
	18	prehypertension	1.66 (1.51-1.81)		
	18	low-range prehypertension	1.44 (1.27-1.63)		

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Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
	18	high-range prehypertension	1.95 (1.73-2.21)		
Diet: SSB, saturated or trans fat, and Omega-3 supplementation	19	SSB	1.06 (0.97-1.15)		
	20	saturated fats	1.02 (0.90-1.15) (ischemic stroke)		
	20	trans fats	1.07 (0.88-1.28) (ischemic stroke)		
	21	Omega-3	1.21 (0.99-1.47)		
Diabetes, Prediabetes, and Fasting insulin or Hyperinsulinemia	22	diabetes		1.83 (1.60-2.08)	2.28 (1.93-2.69)
	23	pre-diabetes (100 to 125 mg/dL)	1.08 (0.94-1.23)		
	23	pre-diabetes (110 to 125 mg/dL)	1.21 (1.02-1.44)		
	23	pre-diabetes or IGT	1.26 (1.10-1.43)		
	23	pre-diabetes (100 to 109 mg/dL)	0.94 (0.73-1.20)		
	24	highest vs lowest quantile of fasting insulin (FI)	1.18 (0.87-1.60)	1.67 (1.07-2.60)	
	24	highest vs lowest quantile of FI	1.24 (0.88, 1.76) (ischemic stroke)		
	24	Each 50-pmol/L increment in FI	0.999 (0.99-1.01)	1.20 (1.03-1.40)	
Depression	25	yes vs no	1.34 (1.17-1.54)	1.49 (1.28-1.74)	1.35 (1.05-1.72)
Physical activity	26	self-reported regular exercise	0.71 (0.64-0.80)	0.72 (0.64-.80)	0.71 (0.58-0.88)

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Risk factor	Ref. n°	Comparison	RR/HR/OR (Total)	RR/HR/OR (Men)	RR/HR/OR (Women)
	26	self-reported regular exercise	0.75 (0.67-0.84) (ischemic stroke)	0.73 (0.65-0.83) (ischemic stroke)	0.76 (0.56-1.02) (ischemic stroke)
	26	self-reported regular exercise	0.67 (0.52-0.86) (haemorrhagic stroke)	0.60 (0.43-0.83) (haemorrhagic stroke)	0.92 (0.44-1.93) (haemorrhagic stroke)

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2.4 CONCLUSIONS

Potassium intake

Both reviews on this topic indicates a favourable effect of higher K intake on risk of stroke. A higher potassium intake is associated to a lower risk of stroke from 20% to 24%. Increased potassium intake is potentially beneficial to most people without impaired renal handling of potassium for the prevention and control of stroke. These results confirm the appropriateness of worldwide recommendations for a population increased consumption of potassium-rich foods to prevent cardiovascular disease.

Alcohol consumption

The results from the analysed reviews suggest that the association between alcohol intake and stroke morbidity and mortality is J-shaped. In fact, low alcohol intake (≤ 1 drink/day o < 15 g/day) is associated with a reduced risk of total stroke, ischemic or haemorrhagic stroke: the risk reduction is estimated to be between 10% and 25%. The effect of alcohol intake seems to be protective for a consumption up to 3 drink/day. Instead heavy alcohol intake (> 30 g/day) is associated with a 20%-30% increased risk of total and ischemic stroke. Alcohol consumption of 15-30 g/day is not significantly associated with an excess of risk.

Body Mass Index

The analysis of the three selected reviews shows a risk not very high and sometimes not statistically significant of total or haemorragic stroke when the comparison is between overweight versus normal weight subjects. A 30% excess of total or haemorragic stroke risk was observed for obese subjects as compared with normal weight. The risk associated with elevated BMI was higher for ischemic stroke and it was up to 64%. In some cases a significant heterogeneity was observed between studies and results should be considered with caution.

In summary, all these observations had showed a statistically significant direct and graded association between excess body weight and incidence of ischemic stroke. Regarding the current obesity epidemic, these results reinforce the claim in favor of strong educational campaigns focusing on prevention of this condition.

Smoking

Compared with nonsmokers, smoking is a significant risk factor for stroke; the excess of risk attributable to this exposure is estimated to be between 70% and 80% and it is higher in women,

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but not significantly. The analysis limited to ischemic stroke shows a 50% excess of risk in current smokers compared to nonsmokers, this risk is similar in men and women. Also former smoking is a significant but limited risk factor for stroke, the excess of risk is 8% in men and 17% in women as compared to nonsmoking.

In conclusion, cigarette smoking is a major and modifiable risk factor for stroke. The lower risk for former smokers highlights that there is a benefits of smoking cessation on future risk of stroke. Tobacco control policies that target both smoking initiation and cessation should be a mainstay of stroke primary prevention programs.

Hypertension

The review of the existing literature evaluating the association between hypertension and the risk of stroke highlights significant risks for both ischemic and haemorrhagic stroke, the amount of risk has been estimated between 2 and three times higher than subjects with normal blood pressure. Using SBP as a continuous variable, the estimated excess of risk is about 20% each 10mmHg increase in SBP.

Also prehypertension is associated with a higher risk of incident stroke, between 55% and 65%. Although the increased risk is largely driven by high-range prehypertension, the risk is also increased, by more than 29%, in people with low-range hypertension (120-129/80-84 mm/Hg).

Diet: consumption of sugar-sweetened beverages, intakes of saturated or trans fat, and Omega-3 supplementation

Diet habits as the consumption of sugar-sweetened beverages, intakes of saturated or trans fat, and Omega-3 supplementation seems not to play an important role in stroke risk. In fact, the meta-analysis conducted within three reviews dealing with those topics highlighted no significant excess risk of stroke.

Diabetes and pre-diabetes

Diabetes is a significant risk factor for stroke incidence, both in men and women. The risk is higher in women (risk 2.3 times higher in women with diabetes compared to woman without diabetes) than in men (risk 1.8 times higher). These data add to the existing evidence that men and women experience diabetes-related diseases differently and suggest the need for further work to clarify the biological, behavioural, or social mechanisms involved.

Also people with pre-diabetes (above all those with fasting glucose of 110 to 125 mg/dL) should be

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aware that they are at increased risk of future stroke. Fasting glucose of 100 to 109 mg/dL is not associated increased risk of stroke.

Depression

The selected meta-analysis of 17 prospective studies involving 206 641 participants and 6086 cases confirms a significant positive association between depression and subsequent risk of stroke; people with a history of depression experiences 34% (95% CI, 17%–54%) higher risk for development of stroke after adjustment for potential confounding factors. In addition, the associations are similar between men and women.

Phisical activity

Physical activity, generally consisting of aerobic endurance tasks, has been found to lower the risk of cerebrovascular events and the associated mortality, in a manner that is probably independent of the known risk factors for such events, at least in men. In men, regular physical activity reduces the risk of suffering an ischemic stroke or dying from one by 27% and the risk of a cerebral hemorrhage by 40%. In women, no significant preventive effects are seen.

For persons whose occupations do not provide them with adequate physical activity, regular exercise for about 30 minutes per day is recommended, both to prevent cerebrovascular events and to obtain other health benefits as well.

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3 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND CARDIO VASCULAR DISEASES (CVDS)- CORONARY

3.1 BACKGROUND

Coronary Disease (CHD) is major cardiovascular disease responsible for major deaths due to Cardiovascular Diseases. It is estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million (42%) were due to coronary heart disease. It is estimated all CVDs are responsible for 10% of DALYs lost in low and middle-income countries, and 18% in high income countries. Most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies

3.2 METHODS

Objective. The goal of this paper is to synthetize the evidences on the determinants of coronary disease, undertaking a review of systematic reviews and meta-analysis published from 2005 to 2015. We focused on biomedical and behaviours determinants: smoking, physical activity, diet patterns, harmful use of alcohol, high blood pressure and depression.

Inclusion and exclusion criteria. We included only systematic reviews and meta-analysis with information about first events and with quantitative data (RR, OR, HR). We excluded papers on the effect of treatment on risk.

Database search. We performed a systematic literature search in PubMed and limited our search to human populations and articles published in English from 2005 to 2015, using the following search terms:

“Coronary disease [Mesh] AND (“Smoking [Mesh] OR “Exercise” [Mesh] OR “Diet” [Mesh] “OR “Blood Pressure” [Mesh] OR “Diabetes Mellitus” [Mesh] OR “Hyperlipidaemia” OR “Depression” [Mesh] OR “Alcohol use” [Mesh] AND “Meta-Analysis [Publication Type] AND (“2005/01/01” [PDAT] : “2015/12/31”).

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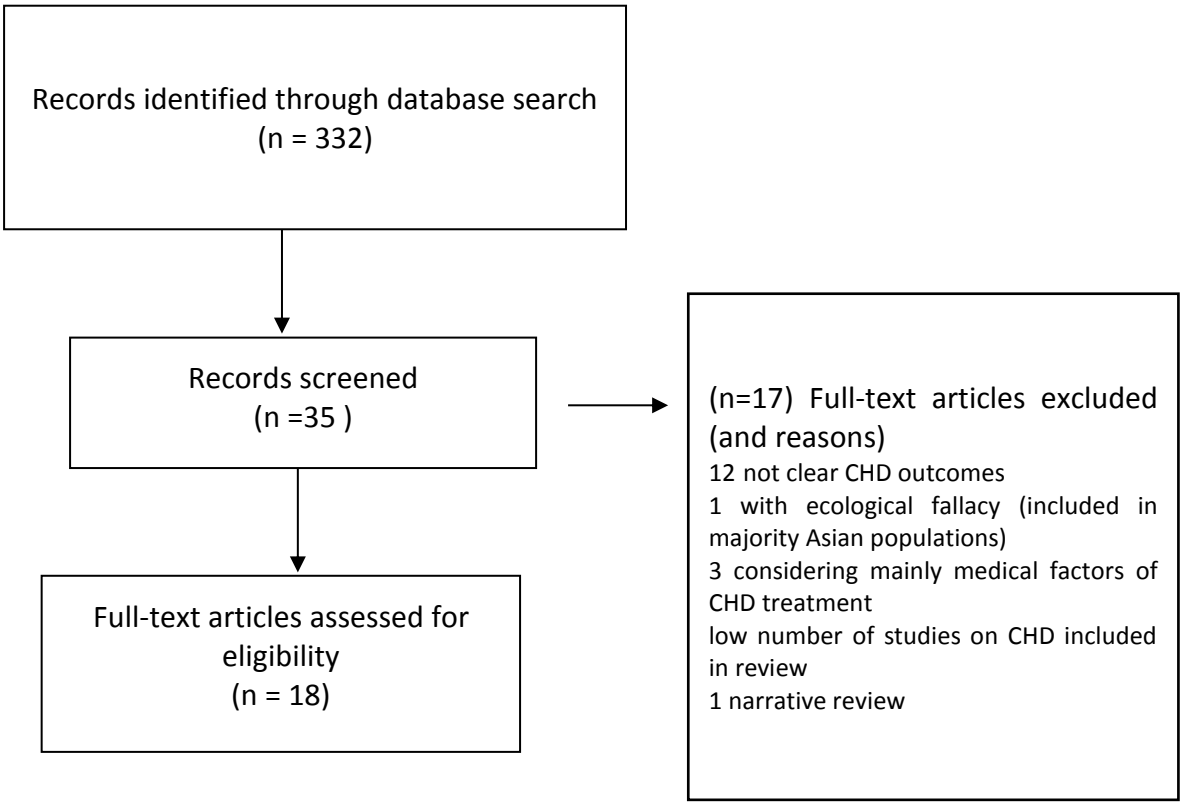
The electronic search produced 332 titles and abstracts. After reading these records, we selected 35 studies, according to our eligibility criteria. After reading the full-texts we excluded 12 were not showing full associations with coronary disease, and 3 because were considering mainly medical factors of risk and 1 paper was “narrative review”.Therefore a final set of 22 selected studies are fully taken into account in this review.

Figure below shows the process of paper selection process following PRISMA.

FIGURE 1. PROCESS OF THE PAPERS SELECTION



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3.3 RESULTS

Blood pressure

There were two reviews focusing on prehypertension. In first review [1-2] there was included eighteen studies, consisting of 934,106 participants and 14,952 cases, with a median follow-up period of 8.8 years. Prehypertension was associated with a significantly elevated risk for CHD (RR 1.36, 95% CI 1.22 to 1.53). Eight studies consisting of 12 cohorts further provided risk estimates for low-range prehypertension (120/80 to 129/84 mm Hg) and high-range prehypertension (130/85 to 139/89 mm Hg) separately. The risk for CHD increased significantly in high-range prehypertensive populations (RR 1.53, 95% CI 1.19 to 1.97) but not in low-range prehypertensive populations (RR 1.16, 95% CI 0.96 to 1.42). In conclusion, prehypertension is associated with a significantly increased risk for developing CHD, particularly high-range prehypertension. Further well-designed randomized controlled trials are needed to clarify the efficacy of blood pressure reduction in subjects with prehypertension. Second review on prehypertension was comparing western and Asian populations [2] and was covering 591 664 participants from 17 prospective cohort studies. Prehypertension increased the risk of CHD (RR 1.43, 95% CI 1.26 to 1.63, P<0.001) compared with optimal blood pressure (<120/80 mm Hg). The risk of CHD was higher in Western than in Asian participants (Western: RR 1.70, 95% CI 1.49 to 1.94; Asian: RR 1.25, 95% CI 1.12 to 1.38; ratio of RRs 1.36, 95% CI 1.15 to 1.61). The population-attributable risk indicated that 8.4% of CHD in Asian participants was attributed to prehypertension, whereas this proportion was 24.1% in Western participants.

Smoking

Smoking is one of the major factors of CHD. Significant review was published in 2011 [3] and was including 26 articles with data for 3,912,809 individuals and 67,075 coronary heart disease events from 86 prospective trials. In 75 cohorts (2·4 million participants) that adjusted for cardiovascular risk factors other than coronary heart disease, the pooled adjusted female-to-male RRR of smoking compared with not smoking for coronary heart disease was 1.25 (95% CI 1.12-1.39, p<0·0001). This outcome was unchanged after adjustment for potential publication bias and there was no evidence of important between-study heterogeneity (p=0·21). The RRR increased by 2% for every additional year of study follow-up (p=0·03). In pooled data from 53 studies, there was no evidence of a sex difference in the RR between participants who had previously smoked compared

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with those who never had (RRR 0.·96, 95% CI 0·86-1·08, p=0·53).

Second study was considering smoking patterns in diabetic patients [4]. A total of 89 cohort studies were included. The pooled adjusted relative risk (95% CI) associated with smoking was 1.55 (1.46-1.64) for total mortality (48 studies with 1,132,700 participants and 109,966 deaths), and 1.49 (1.29-1.71) for cardiovascular mortality (13 studies with 37,550 participants and 3163 deaths). The pooled relative risk (95% confidence interval) was 1.44 (1.34-1.54) for total cardiovascular disease (16 studies), 1.51 (1.41-1.62) for coronary heart disease (21 studies), 1.54 (1.41-1.69) for stroke (15 studies), 2.15 (1.62-2.85) for peripheral arterial disease (3 studies), and 1.43 (1.19-1.72) for heart failure (4 studies). In comparison with never smokers, former smokers were at a moderately elevated risk of total mortality (1.19; 1.11-1.28), cardiovascular mortality (1.15; 1.00-1.32), cardiovascular disease (1.09; 1.05-1.13), and coronary heart disease (1.14; 1.00-1.30), but not for stroke (1.04; 0.87-1.23).

Diet

First review was analysing association between dietary fibre intake and risk of coronary heart disease [5] Eighteen studies involving 672,408 individuals were included in analyze. The pooled-adjusted RRs of coronary heart disease for the highest versus lowest category of fiber intake were 0.93 (95% confidence interval (CI), 0.91-0.96, P < 0.001) for incidence of all coronary events and 0.83 (95% CI, 0.76-0.91, P < 0.001) for mortality. Further subgroup analyses based on fiber subtypes (cereal, fruit, and vegetable fiber), indicated that RRs were 0.92 (95% CI, 0.85-0.99, P = 0.032), 0.92 (95% CI, 0.86-0.98, P = 0.01), 0.95 (95% CI, 0.89-1.01, P = 0.098) respectively for all coronary event and 0.81 (95% CI, 0.72-0.92, P = 0.001), 0.68 (95% CI, 0.43-1.07, P = 0.094), 0.91 (95% CI, 0.74-1.12, P = 0.383) for mortality. In addition, a significant dose-response relationship was observed between fiber intake and the incidence and mortality of CHD (P < 0.001).

Another review evaluating the role of wholegrain diet [6] did not show clear evidence. Ten trials met the inclusion criteria. None of the studies found reported the effect of wholegrain diets on CHD mortality or CHD events or morbidity. All 10 included studies reported the effect of wholegrain foods or diets on risk factors for CHD. Studies ranged in duration from 4 to 8 weeks. There was also performed meta-analyse on role of fruit and vegetable consumption in CHD [7] Twenty-three studies involving 937,665 participants and 18,047 patients with CHD were included. Compared with the lowest consumption levels of total fruit and vegetable, fruit and vegetable, the

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RR of CHD was 0.84 (95% CI, 0.79–0.90), 0.86 (95% CI, 0.82–0.91), 0.87 (95% CI, 0.81–0.93), respectively. The dose–response analysis indicated that, the RR of CHD was 0.88 (95% CI: 0.85–0.91) per 477 g/day of total fruit and vegetable consumption, 0.84 (95% CI: 0.75–0.93) per 300 g/day of fruit intake and 0.82 (95% CI: 0.73–0.92) per 400 g/day of vegetable consumption. A nonlinear association of CHD risk with fruit or vegetable consumption separately was found (P for nonlinearity < 0.001). In the subgroup analysis of location, a significant inverse association was observed in Western populations, but not in Asian populations. In another review there was found that fish consumption reduces the risk of acute coronary syndrome [8]. There were analysed 11 prospective cohort and 8 case-control studies, totalling 408,305 participants. Among prospective cohort studies, the highest category of fish consumption (ie, ≥4 times per week) was associated with the greatest risk reduction in acute coronary syndrome (RR 0.79; 95% confidence interval (CI), 0.70-0.89). In dose-response analysis, each additional 100-g serving of fish per week was associated with a 5% reduced risk (RR per serving 0.95; 95% CI, 0.92-0.97). Subgroup analysis and meta-regression suggested that the risk reduction did not differ across sex or age groups.

Third meta-analyse was suggesting the rule of dietary flavonoids and CHD cases [9] Fourteen articles with 15 prospective studies involving 7,233 CHD cases and 452,564 participants were included in this review. Pooled results suggested that highest flavonoids intake versus lowest intake was significantly associated with the risk of CHD [summary relative risk (RR) = 0.850, 95% CI = 0.794-0.910, I(2) = 26.0%, τ(2) = 0.041]. Inverse associations were found both in Europe and in USA. Linear dose-response relationship was found between flavonoids intake and CHD risk. However, no significant association was found through the dose-response analysis (an increment of 20 mg/day, summary incidence rate ratios (IRR) = 0.95, 95%CI = 0.88-1.02). Also intake of linoleic (LA) acid reduces the risk of coronary heart disease [10] Authors identified 13 published and unpublished cohort studies with a total of 310 602 individuals and 12 479 total CHD events, including 5882 CHD deaths. When the highest category was compared with the lowest category, dietary LA was associated with a 15% lower risk of CHD events (pooled RR, 0.85; 95% confidence intervals, 0.78-0.92; I(2)=35.5%) and a 21% lower risk of CHD deaths (pooled RR, 0.79; 95% confidence intervals, 0.71-0.89; I(2)=0.0%). A 5% of energy increment in LA intake replacing energy from saturated fat intake was associated with a 9% lower risk of CHD events (RR, 0.91; 95% confidence intervals, 0.87-0.96) and a 13% lower risk of CHD deaths (RR, 0.87; 95% confidence intervals, 0.82-0.94).

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BMI

Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels was subject of one review [11]. Analyze was based on 21 cohorts (302.296 subjects). A total of 18 000 CHD events occurred during follow-up. The age-, sex-, physical activity-, and smoking-adjusted RRs (95% confidence intervals) for moderate overweight and obesity compared with normal weight were 1.32 (1.24-1.40) and 1.81 (1.56-2.10), respectively. Additional adjustment for blood pressure and cholesterol levels reduced the RR to 1.17 (1.11-1.23) for moderate overweight and to 1.49 (1.32-1.67) for obesity. The RR associated with a 5-unit BMI increment was 1.29 (1.22-1.35) before and 1.16 (1.11-1.21) after adjustment for blood pressure and cholesterol levels. Important meta-analyze on metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease was published in 2014 [12] There was estimated pooled data from 97 prospective cohort studies that collectively enrolled 1.8 million participants between 1948 and 2005. The hazard ratio for coronary heart disease (HR) each 5 kg/m^2 higher BMI was 1.27 (95% CI 1.23-1.31) Additional adjustment for the three metabolic risk factors reduced the HR to 1·15 (1·12-1·18).

Prediabetes

Dietary glycemic load and glycemic index in relation to risk of coronary heart disease was subject of one review [13]. 8 prospective studies were included in meta-analysis, consisting of 220,050 participants and 4,826 incident CHD cases. Pooled RRs of CHD in relation to dietary glycemic load were 1.08 (95% confidence interval [CI] 0.92 to 1.27) for men, 1.69 (95% CI 1.32 to 2.16) for women, and 1.36 (95% CI 1.13 to 1.63) for men and women combined. For dietary glycemic, corresponding pooled RRs were 0.99 (95% CI 0.84 to 1.16), 1.26 (95% CI 1.12 to 1.43), and 1.13 (95% CI 1.00 to 1.28), respectively.

Mental health and other social factors

Two meta-analyses [14-15] were reviewing associations of anxiety and stress and CHD one was analyzing association of depression with CHD [16]. In the first review authors identified 44 articles (N = 30,527 subjects) evaluating the prospective relationship between anxiety and mortality in individuals with established CHD. A series of 8 adjusted and unadjusted meta-analyses were performed to examine this relationship across all patients, with sensitivity analyses completed in post-Acute Coronary Syndrome and stable CHD cohorts. In unadjusted analyses, anxiety was

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associated with a moderate increase in mortality risk (odds ratio 1.21 per SD increase in anxiety). However, when adjusting for covariates, nearly all associations became nonsignificant. Authors of second review regarding perceived stress [15] Meta-analysis yielded an aggregate risk ratio of 1.27 95% CI (1.12 - 1.45) for the magnitude of the relation between high perceived stress and incident CHD. In conclusion, this meta-analysis suggests that high perceived stress is associated with a moderately increased risk of incident CHD. Third review meta-analyzes of 6362 events among 146 538 participants in 54 observational studies. The pooled relative risk of future CHD associated with depression was 1.81 (95% CI 1.53-2.15). Adjusted results were included for 11 studies, with adjustment reducing the crude effect marginally from 2.08 (1.69-2.55) to 1.90 (1.49-2.42). In 34 prognostic studies, the pooled relative risk was 1.80 (1.50-2.15). Results adjusted for left ventricular function result were available in only eight studies; and this attenuated the relative risk from 2.18 to 1.53 (1.11-2.10), a 48% reduction.

Perceived job insecurity as a risk factor for incident coronary heart disease was a topic of fifth meta-analyze published in 2013 [16]. Review was including 13 cohort studies with 174,438 participants. Outcomes showed that age adjusted relative risk of high versus low job insecurity was 1.32 (95% confidence interval 1.09 to 1.59).

Review on long working hours and risk of coronary heart disease and stroke was published in 2015 [17]. Authors identified 25 studies with 603,838 individuals. In cumulative meta-analysis adjusted for age, sex, and socioeconomic status, compared with standard hours (35-40 h per week), working long hours (≥55 h per week) was associated with an increase in risk of incident coronary heart disease –RR= 1·13, 95% CI 1·02-1·26.

Alcohol

We identified one review regarding amount of alcohol intake, combined with the frequency of alcohol consumption and/or pattern of alcohol drinking affecting the risk of CHD [18]. Six (4 cohort and 2 case-control) out of 118 studies reviewed met the inclusion criteria. Compared with those who abstained from alcohol, regular heavy drinkers and heavy irregular or binge drinkers showed significantly different pooled relative risks of 0.75 (95% confidence interval 0.64 to 0.89) and 1.10 (1.03 to 1.17) respectively. The dose-response relation between the amount of alcohol intake and CHD risk was significantly different in regular and irregular drinkers. A J-shaped curve, with nadir around 28 grams of alcohol per week, and last protective dose of 131 grams per week, was

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obtained including drinkers who consumed alcohol for 2 days a week or less. Conversely, in people who consumed alcohol for more than 2 days a week a significant protective effect was seen even when drinking high amounts of alcohol.

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4 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND CHRONIC LUNG DISEASE

4.1 BACKGROUND AND METHODS

The goal of this note is to analyse and synthetize determinants and trends on chronic lung disease by undertaking a review of published literature reviews and meta-analysis from 2001 to 2015; the focus being on biomedical and behaviours determinants.

This umbrella review was undertaken using PubMed website, the precise search terms used were:

- "determinants" AND "lung" OR "respiratory"
- "determinants" AND "lung" OR "respiratory" AND "behaviour" OR "psychological" OR "genetic" or "biomedical"
- "determinants" AND "lung" OR "respiratory" AND "disease"
- "determinants" AND "lung" OR "respiratory" AND "disease" AND "long term" OR "chronic"
- "determinants" AND "bronchopulmonary dysplasia" OR "BPD" OR "chronic obstructive pulmonary disease" OR "COPD"
- "determinants" AND "bronchopulmonary dysplasia" OR "BPD" OR "chronic obstructive pulmonary disease" OR "COPD" AND "behaviour" OR "psychological" OR "genetic" or "biomedical"

For all search, we selected the criteria "review" proposed by PUBMED.

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4.2 RESULTS

Chronic lung disease is a group of chronic diseases affecting the airways and the other structure of the lungs. We focused on pathologies considered by the World Health Organization: asthma, bronchopulmonary dysplasia (BPD) and chronic obstructive pulmonary disease (COPD) (including chronic bronchitis and emphysema)[1].

It is estimated that as many as 300 million people of all ages and all ethnic backgrounds suffer from asthma. A multinational study (the European Community Respiratory Health Survey (ECRHS) in adults (European Respiratory Journal 1996)) has assessed the prevalence of asthma around the world: Nord and Western Europe 5.1-7.5 %, Eastern Europe 2.5-5.0%, US ≥ 10.1% (proportion of population). For the 40 last years, the prevalence of asthma increased in all the countries in parallel with that of allergy. With a projected increase in the proportion of the world's population living in urban areas, it is expected to observe an increase amongst people suffering from asthma during the two following decades. It is estimated that there may be an additional 100 million people suffering from asthma by 2025 (Masoli M et al. 2004).

Until recently, most of the information available on COPD prevalence came from high income countries. It has been estimated to range from 4% to up to 20% in adults over 40 years of age (8–*9*), with a considerable increase by age, particularly among smokers. Large differences exist between countries. But national data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent (Pauwels RA 2004).

Literature reviews on asthma and COPD agreed that environmental exposures are important determinants in their development, the evidence was consistent for smoking and air pollution (Wong et al. 2006; Chipps 2004; Smith and Helms 2001; Pistelli, Lange, and Miller 2003). Indeed, 15% of cigarette smokers develop COPD (prevalence of COPD in the UK). Further supportive evidence for genetic component include observations that only 10-20% of smokers develop COPD. (Smith and Helms 2001). Cigarette consumption increases elastolysis, airway inflammation and parenchymal lung damage (Chipps 2004). Air pollution reduces the ability of macrophages to kill bacteria (Pistelli, Lange, and Miller 2003), notably exposure to ozone and ultrafine particles (Smith and Helms 2001; Chipps 2004) and the effects are even more important for children practicing team sports (Chipps 2004).

[1] http://www.who.int/respiratory/en/

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However, there are discussions regarding effects of atopy (genetic predisposition) and events occurring during childhood. Indeed, atopy is a major risk factor of chronic asthma and lower forced expiratory volume is associated with risk of severe asthma according to Chipps and colleagues (Chipps 2004). Infections during childhood would imply damages in airways in the sense that they remodel airways' architecture and thus imply an abnormal bronchial activity, increasing the risk of asthma (Pistelli, Lange, and Miller 2003; Smith and Helms 2001). These effects are more important for infections occurring during the first year of life (Chipps 2004). Conversely, some articles found that exposure to microbials in childhood protect children from asthma thanks to an immunological mechanism (Wong et al. 2006).

The literature has shown that alcohol consumption above 3 drinks a day increases the risk of developing chronic lung disease (Pistelli, Lange, and Miller 2003). There is also some evidence on risk of developing COPD and asthma when the mother smokes during pregnancy (Smith and Helms 2001; Chipps 2004). Moreover, when there is an adverse environment in utero, airways do not growth normally implying an alteration of lung function (Smith and Helms 2001). Some protective factors were studied like vitamin C and E intake which improve lung function due to their antioxidant properties, and omega-3 which inhibits airway inflammations (Smith and Helms 2001). However, the literature is poor regarding the impact of dietary factors on chronic lung diseases.

Some articles assumed that genetic factors can play a role because they observed a different prevalence of COPD among ethnics groups and that all individuals exposed to the same environment will not develop the same pathology Familial factors are clearly relevant, as between 15% and 60% of variability in pulmonary function can be accounted for by familial aggregation (Smith and Helms 2001). Indeed, Poon et. al (Poon, Litonjua, and Laprise 2011) have shown that a number of single nucleotide polymorphism are associated with asthma development. Conversely to genetic factors, environmental factors depends on the intensity and the duration of exposure (Chipps 2004).

4.3 LIMITATION

Focusing on reviews published presents a limitation. Indeed, there are lots of articles which deal with the subject matter at hand but they are not discussed here as they are not reviews.

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5 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND CANCER

5.1 BACKGROUND AND METHODS

The goal of this note is to analyse and synthetize determinants and trends on cancer by undertaking a review of published literature reviews and meta-analysis from 2001 to 2015; the focus being on biomedical and behaviours determinants. According to the others members of WP2, we focused on the most common cancers: breast, lung, colorectal, oral and prostate cancers. We took into account reviews analysing the occurrence of cancer, and not its development (apparition of metastasis).

This umbrella review was undertaken using PubMed website, the precise search terms used were:

- “determinants” AND “cancer”
- “determinants” AND “breast” OR “lung” OR “colorectal” OR “oral” OR “prostate” AND “cancer”
- “determinants” AND “breast” OR “lung” OR “colorectal” OR “oral” OR “prostate” AND “cancer” and “behaviour” OR “psychological”, OR “genetic” OR “biomedical” OR “smoking” OR “alcohol” OR “inactivity” OR “Sedentariness” OR “diet”

For all research, we selected the criteria “review” proposed by PUBMED.

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5.2 RESULTS

Cancer is a pathology which get the characteristics to replicate mutated cells into the tissues and to spread to organs. Cancer or malignant tumors and neoplasms include a group of diseases characterized by the fast creation of the abnormal cells which develop beyond their usual borders, and which can then invade the contiguous parts of the body and deviate with other bodies. The uncontrolled growth and spread of cells often invade surrounding tissue and can metastasize to distant sites Metastases are the principal cause of the death of cancer.

Within the next 2 decades, the number of new cases is expected to rise by about 70% and it is expected that annual cancer cases will rise from 14 million in 2012 to 22 (World Cancer Report 2014).

The cancers we focused on are the most common: breast, lung, colorectal, oral and prostate.

There are estimated to be 1.8 million new cases of lung cancer in 2012 (12.9% of the total). This disease remains as the most common cancer in men worldwide (1.2 million, 16.7% of the total) with the highest estimated age-standardized incidence rates in Central and Eastern Europe (53.5 per 100,000). In women, the incidence rates are generally lower and the geographical pattern is a little different, mainly reflecting different historical exposure to tobacco smoking.

Breast cancer is the second is the second most common cancer in the world. It is the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). Breast cancer is the most common cancer in women both in more and less developed regions with slightly more cases in less developed (883,000 cases) than in more developed (794,000) regions.

Colorectal cancer is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide. Almost 55% of the cases occur in more developed regions.

Prostate cancer is the fourth most common cancer in both sexes combined and the second most common cancer in men. An estimated. In 2012, 1.1 million men worldwide were diagnosed with prostate cancer, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions. Prostate cancer incidence varies more than 25-fold worldwide; the rate is high in Western and Northern Europe (ASR 97.2 per 100,000), because the practice of prostate specific antigen (PSA) testing and subsequent biopsy has become

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widespread in those regions.

The estimates of GLOBOCAN 2012 predict a substantial increase by 19.3 million new cases of cancer a year by 2025, due to the growth and the ageing of the global population. More than half of all cancers (56.8%) and of death of cancer (64.9%) occurred in 2012 in less developed areas of the world, and these proportions will increase by 2025 further.

Regarding all kinds of cancer, Greaves (Greaves 2015) and Taramelli and Acquati (Taramelli and Acquati 2004) showed that environment factors coupled with mutational modulations (inherited gene variants) are important determinants. In addition to genetic predisposition, behaviours of individuals and their lifestyle define the environment of cells (Colditz and Wei 2012): lung and liver react to carcinogenic chemicals in cigarette; solar UVB is a risk factor for skin cancer; infections increase the risk of cancers and notably in less developed countries, and finally physical activity and calorific restriction tend to decrease the risk of cancer. Among environment factors, exposure to carcinogens have to be limited and avoided because of their important impact on risk of developing cancer as studied by Hlatky and Hahnfeldt (Hlatky and Hahnfeldt 2014) and recommended by health authorities around the world.

Cancer depends also on a natural selection process: the first mutated (cancerous) cell is randomly selected among the entire cells exposed to a same environment, and this particular cell replicate itself, modifying the normal cycle of DNA replication.

Around one third of cancer deaths are due to the 5 leading behavioural and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use (the most important risk factor for cancer causing around 20% of overall cancer deaths and around 70% of overall lung cancer deaths), alcohol use (IARC 2015).

If we focused on the most common cancer and notably breast cancer, Njiaju and Olopade state that germline mutations are responsible for hereditary breast cancer (Njiaju and Olopade 2012). Genes with high-penetrance mutations were identified by means of family linkage studies and are rare in the general population, accounting for 20-25% of all cases of hereditary breast cancer. But Hagan et al. (Hagan and Lange 2014) showed that hormone levels also play a role in cancer development. Indeed, progesterone intake from progestin-only pills for example, has an impact on progesterone receptors and on mammary gland and increases the risk of breast cancer.

Regarding lung cancer, Kovarik et al. (Kovarik, Hronek, and Zadak 2014) analyses its determinants and malnutrition, sarcopenia and cachexia are preclinical markers. Moreover, weight loss is an

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important prognostic of lung cancer and surprisingly, obesity (body mass index upper 30) could be linked with a reduction of lung cancer deaths (adjusted hazard ratio (HR) 0.55; $p < 0.001$). Absence of obesity was found to be an independent predictor of a worse survival rate (HR 1.12; $p < 0.001$) and absence of weight loss to be an independent predictor of a longer survival rate (HR 0.087; $p < 0.001$) (Kovarik, Hronek, and Zadak 2014).

While tobacco is the most important factor associated to cancer, smokeless tobacco presents a moderate risk of oral cancer (Risk-Ratio (RR)=1.5 to 2.8), except for dry snuff tobacco (RR= 4 to 13), as highlited by Rodu and Jansson (Rodu and Jansson 2004). Regarding prostate cancer, Kral et al. found that the risk of developing prostate cancer is increased with environmental determinants like alcohol, smoking, obesity and history of vasectomy (Kral et al. 2011), and also with consumption of medication such as like statin and non-steroid, anti-inflammatory intake and sexual activity.

Moreover, genetic factors and notably genetic predisposition plays an important role in prostate cancer and its heredity: 97% of individuals with a genetic predisposition develop it by 85 years of age (Kral et al. 2011). Family risk of prostate cancer have shown that the relative risk of prostate cancer in man with a brother or father with prostate cancer is 3.4 and 2.2 respectively (Kral et al. 2011).

5.3 LIMITATION

Focusing on reviews published presents a limitation. Indeed, there are lots of articles regarding determinants of cancers which are not reviews but could have helped our analysis, like the effect of cigarettes on lung cancer with Poullis (2013) and effect of alcohol on oral cancer with Petti (2010) for examples.

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6 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND MUSCULOSKELETAL DISORDERS

6.1 BACKGROUND AND METHODS

The goal of this note is to analyse and synthetize determinants and trends on musculoskeletal disorders by undertaking a review of literature reviews and meta-analysis from 2001 to 2015; the focus being on biomedical and behaviours determinants.

This umbrella review was undertaken using PubMed website, the precise search terms used were:

- “determinants” AND “muskuloskeletal” OR “MSDs”
- “determinants” AND “low back pain” OR “LBP
- “determinants” AND “muscle” OR “skeletal” or “articular” OR “tissues” OR “ligaments” OR “tendons”
- “determinants” AND “muscle” OR “skeletal” OR “articular” OR “tissues” OR “ligaments” OR “tendons” AND “disorders” OR “troubles” OR “injury”
- “determinants” AND “muscle” OR “skeletal” OR “articular” OR “tissues” OR “ligaments” OR “tendons” AND “disorders” OR “troubles” OR “injury” AND “behaviour” OR “psychological” OR “genetic” OR “biomedical”

For all research, we selected the criteria “review” proposed by PUBMED.

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under Grant Agreement No 643576.

6.2 RESULTS

Musculoskeletal disorders (MSDs) are injury or pain in soft tissues like ligaments, muscles and tendons and low back pain (LBP) in one of the most common MSDs. Musculoskeletal Disorders or MSDs are injuries and disorders that affect the human body's movement or musculoskeletal system (i.e. muscles, tendons, ligaments, nerves, discs, blood vessels, etc.).

Musculoskeletal conditions are a diverse group with regard to pathophysiology but are linked anatomically and by their association with pain and impaired physical function. They gather a broad spectrum of diseases, including osteoarthritis, rheumatoid arthritis, osteoporosis, and low back pain (LBP). The prevalence of many of these conditions increases markedly with age. Osteoarthritis affects 9.6% of men and 18% of women aged ≥60 years. Increases in life expectancy and ageing populations are expected to make osteoarthritis the fourth leading cause of disability by the year 2020.

Rheumatoid arthritis affects 0.3–1.0% of the general population and is more prevalent among women and in developed countries. Worldwide estimates are that 9.6% of men and 18.0% of women aged ≥60 years have symptomatic osteoarthritis (13). The incidence of rheumatoid arthritis in populations of northern European origin is 20–300 per 100000 per year (28). The prevalence of rheumatoid arthritis in most industrialized countries varies between 0.3% and 1%. The general prevalence of osteoporosis rises from 5% among women aged 50 years to 50% at 85 years of age; among and 20% (40). Trends indicate that the number of hip fractures will increase in the world to reach 6.3 million worldwide for 2050.

Back pain is very common, but its prevalence varies according to the definitions used and the population studied. Low back pain affects men a little more than women and is most frequent in the working population, with the highest incidence seen in those aged 25–64 years (58). Lifetime prevalence is 58–84% and the point prevalence (proportion of population studied that are suffering back pain at a particular point of time) is 4–33% cultural changes (such a greater awareness of minor back symptoms and willingness to report them) could lead to an enormous increase in back pain burden.

In 2014, Fransen et al. (Fransen, Simic, and Harmer 2014) studied determinants of MSDs. They highlighted the fact that articles in the literature contradict each other regarding effects of regular

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and moderate consumption of alcohol, smoking and particular diet on the risk of developing MSDs. Some articles found that smoking reduces the risk of developing osteoarthritis because nicotine has a beneficial effect on chondrocyte metabolism but has important bad effects on overall health. A study evaluating the association between smoking and incident total hip or knee replacement surgery was conducted among elderly people (mean age 73 at baseline): a total of 3535 (8%) reported being a current smoker at baseline with 1528 incident hip replacements and 2077 1528 incident knee replacements over the follow-up period. After adjustment, smoking demonstrated a significant protective effect for incident hip replacement (0.7, 95% CI 0.6-0.9) and total knee replacement surgery (0.6, 95% CI 0.5-0.7) (Mnatzaganian G et al. 2013).

Authors highlighted the fact that it is difficult to measure the impact of a particular diet on MSDs and notably because the effects are mixed with lifestyles 'ones. However, there is evidence to suggest that increasing vitamin C consumption decreases the risk of MSDs pain, heating more red meat decreases the risk of knee replacement, and animal experiments have shown that a high-fat diet increases the risk of MSDs development. Obesity increases the risk of developing MSDs and knee replacements. Data, based on cohort case-control and cross-sectional studies identified in a systematic review (Muthuri SG et al. 2011), demonstrated that the PAR% (population-attributable risk percentage), that is, the reduction in risk of obesity was eliminated, for total knee replacement among those with obesity varied from 52 to 53% in the UK and Australia, to 60% (95% CI, 49.2-69.7) in the USA. PARs for the development of symptomatic knee clinical assessment due to obesity varied through 42% in the UK and Australia, to 50% (95% CI, 37.4-61.4%) in the USA.

Having injuries increases the risk of MSDs development in the long term and depends on the damage degree of tissues, the site of the injury, its severity and its management. It is recommended to undertake physical activity in order to reduce the risk of chronic disease such as diabetes and coronary heart disease, but the activity needs to be moderate so as not to increase the risk of MSDs. An evaluation of the effect of physical activity on incident knee OA (clinical assessment) was conducted with the 1946 British Birth Cohort at age 53 years (Martin KR et al. 2013). Among men, no association between leisure activity and incident knee OA was demonstrated. Among women, there was no association between leisure-time activity and incident knee; however, there was evidence of an interaction with BMI and leisure activity for

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knee OA risk (OR 1.8, 95% CI, 1.5-2.2) suggesting that women who are more active would benefit from reducing their BMI to avoid incident knee OA. In the same context, in 2008, Weigl (Weigl et al. 2008) has also shown that car drivers had fewer MSDs than non-drivers. Taking the case of a cosmonaut example, Bajotto and Shimomura (Bajotto and Shimomura 2006) have shown that the soft tissues adapt themselves to the inactivity of individuals and result in a skeletal muscle atrophy in their case, as confirmed by Van Vleit and Heneghan for a common context of physical activity (van Vliet and Heneghan 2006).

Vargas-Prada and Coggon (Vargas-Prada and Coggon 2015) analysed psychological and psychosocial determinants of MSDs and found that poor mental health (low mood and depressive symptoms) were correlated with pain intensity and functional limitations. They also have shown that high job strain is associated with MSDs symptoms, people reporting job dissatisfaction (Weigl et al. 2008) have a somatising tendency. They highlighted the role of neurotransmitters and cytokine receptors as plausible biological mechanisms.

Borg-Stein and Wilkins (Borg-Stein and Wilkins 2006) analysed the determinants of LBP and found that it is due to mechanical factors and repetition of a same task, which are highly correlated with individuals lifestyles and professional activity. Truchon (Truchon 2001) confirmed these results and found that work-related factors have an important impact on LBP development like physical demands of a task, subjective appraisal of the task's difficulty, dissatisfaction with work, stress related to monotonous work and to work pace. The author highlights also interactions between psychological and physical factors: physical stressors may involve hormonal changes and effects on skeletal muscles, and repeated activation can lead to illness. So, stress- related disorders can be the origin of chronic LBP.

6.3 LIMITATION

Focusing on reviews published presents a limitation. Indeed, there are lots of articles which could have helped us, but which are not reviews.

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7 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND DEPRESSION

7.1 BACKGROUND

Framing the question

The word depression is used to refer to psychiatric disorders whose the key feature is sad or depressed mood, but that entail also other distinct symptoms, such as loss of interest, tiredness, memory problems, insomnia and recurrent thoughts of death. Typically, the disorder causes suffering and renders the person partly or fully unable to carry on with their everyday life. The two depressive disorders included in the review are major depressive disorder (MDD) and dysthymia, a more chronic form of depression. Both are referred to as “depression” or “depressive disorders”.

The annual prevalence of major depressive disorder is approximately 5%, but this rough estimate depends on how the disorder is defined and measure, and on the population studied [1]. As awareness about depression in society as well as use of antidepressants in many countries have increased, there is a perception that its prevalence has also increased. However, there have been no indications of this in population studies [1, 2]. Some groups, such as women, unmarried persons, those with chronic physical illnesses or a disadvantaged social position have a higher prevalence of depression, but it is not always clear whether the associations are causal [3].

Therefore, it is important to clarify these concerns and provide up-to-date evidence on trends and risk factors of depression to inform public policies.

Purpose and original scope of the deliverable

This literature review examines the prevalence, trends and determinants of depressive disorders in Europe. It is developed as part of Work Package 2 of the Fresher (FoResight and Modelling for European HEalth Policy and Regulation) project, which aims to guide public policies by presenting quantitative estimates of the future global burden of non-communicable diseases (NCDs) in the EU.

The review is a “pragmatic umbrella review” that aims to identify the most relevant and recent reviews and meta-analyses of each topic, as described in the following chapter. The scope of the review was defined to include two databases (PubMed and Cochrane Database for systematic

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reviews). From the suggested table of contents, some headings were included as such (Prevalence and costs of depression in European countries; Prevention and screening of depression). Behavioural factors were operationalized to include smoking, alcohol use, cannabis use, obesity and exercise, whereas 'environment' was conceptualised as childhood living conditions and childhood adversity. Some suggested determinants (food, social innovations, biomedical and access to health care, communication) were considered less important for depression and thus omitted. The review on socioeconomic status was already carried out by another group, and was not repeated, but is commented on in the text. Finally, the four overarching priorities (ageing, gender, social inequalities and geographical differences) are commented on whenever relevant evidence was available, and in a separate paragraph 3.3.

7.2 METHODS

This umbrella review was performed according to the criteria of the Harvard Medical School Research Guide on systematic reviews and meta-analyses (http://guides.library.harvard.edu/meta-analysis). Two databases, PubMed and the Cochrane Database for Systematic Reviews were reviewed without publication date limitations. All searches were limited to human populations, articles in English, and systematic reviews or meta-analyses. Articles that study general populations were prioritised. Due to large number of articles on depression, the searches in PubMed were limited to MeSH Major topic "Depressive Disorder".

Further, the filter for observational design (http://guides.library.harvard.edu/c.php?g=309982&p=2079546) was used in PubMed searches as follows:

> "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw]

The Cochrane Database of Systematic Reviews (http://onlinelibrary.wiley.com/cochranelibrary/search) was searched with the keyword "depression", and the 420 results were manually searched. Three relevant reviews were identified and included under the chapters on prevention and screening. In addition, the 112 results under

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the topic "Depression" (http://www.cochranelibrary.com/topic/Mental%20health/Depression/) were reviewed but no further relevant articles were found. All searches were carried out in February 2016.

7.3 RESULTS

Epidemiology of depression in Europe

Prevalence and costs of depression in European countries

When describing prevalence of depression, it is important to note that there are varying definitions and was of measurement of depression across studies. The two diagnostic systems (ICD-10 and DSM-IV) produce slightly differing prevalence rates, but more importantly, it should be taken into consideration whether all depressive disorders (including bipolar depressive episodes, dysthymia and depression not otherwise specified) or only MDD were measured, and what psychometric instrument was used. Wider inclusion of diagnostic categories and use of symptom scales instead of structured diagnostic interviews increase observed prevalence rates [1]. Differences in methodology are likely to explain some, but not all of the variation in prevalence rates that are found across studies and countries.

The search was carried out in PubMed, using the review filter, as follows:

depression AND ("Prevalence" OR "Incidence" OR "Epidemiology" OR "Cost of Illness") AND "Europe" AND ("cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw])

The search yielded 63 results, out of which 10 are from general populations in Europe, out of which 8 are in English, and 4 describe epidemiology of depressive disorders in Europe, and were included (Figure 1). 2 were discarded because they described changes in prevalence from several decades ago and were therefore not considered relevant.

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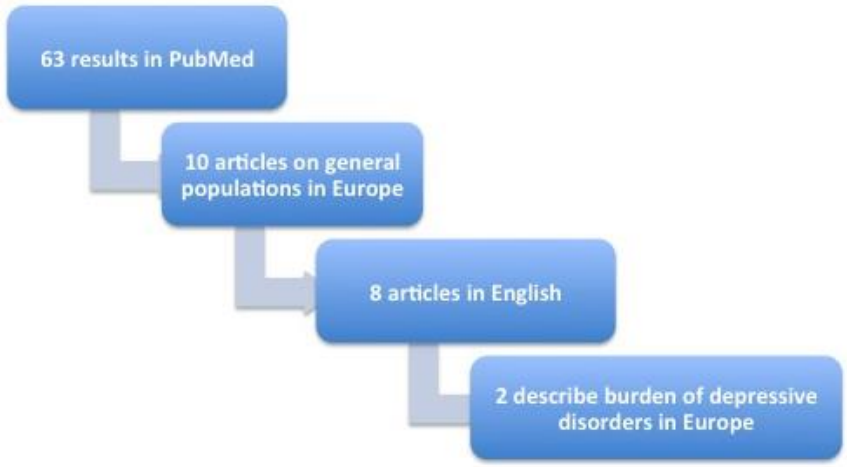

Figure 1.

The following articles were Included in the review:

1. Wittchen, H.U., et al., The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol, 2011. **21**(9): p. 655-79.
2. Wittchen, H.U. and F. Jacobi, Size and burden of mental disorders in Europe--a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol, 2005. **15**(4): p. 357-76.

In addition, one important article was identified through other means and included:

3. Olesen, J., et al., *The economic cost of brain disorders in Europe.* Eur J Neurol, 2012. **19**(1): p. 155-62.

Prevalence of depression in Europe

Wittchen et al. [4] report an update on their review on the 12-month prevalence and disability burden of mental and neurological disorders from 2005 [5]. Because the scope of the two studies is the same, and the 2011 study is an update of the 2005 study, only the former is reported in this review.

The methodology included systematic literature reviews, re-analyses of existing data, and expert consultations. The national expert consultation was used to validate the “best estimates” based on the literature review. Experts from 27 out of the 30 countries gave their opinion on the adequacy of the prevalence estimates for their country. In the case of depression, seven countries found that the true prevalence is lower than the best estimate. In addition, an epidemiological panel reviewed the best estimates, taking into consideration the median and the range, and the impact

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of individual outlier studies. The geographical scope includes all EU member states, Iceland, Norway and Switzerland. Disability is measured in DALYs (disability-adjusted life-years).

Compared to their 2005 review, there were no changes in the prevalence of mental disorders in 2010, although the total prevalence estimate was higher due to changes in definitions and methodology. An estimated 38.2% of the EU population suffer from a mental disorder annually. The most frequent disorders are anxiety disorders (14.0%), insomnia (7.0%), major depression (6.9%), somatoform (6.3%), alcohol and drug dependence (4%), ADHD (5%) in the young, and dementia (1–30%, depending on age). This review found no important differences in prevalence between countries or cultures, except for substance use disorders.

The prevalence of 6.9% for major depression is higher than that found in the ESEMeD study as part of the World Mental Health Survey, including only six countries (Belgium, France, Germany, Italy, the Netherlands and Spain), where the 12-month prevalence of depression was only 3.9% (95% CI 3.6-4.2) [6]. This is likely due to inclusion of more countries with possibly higher prevalence rates, and the use of expert opinions.

Table 1. Summary of prevalence studies of mental disorders, best estimates and number of persons affected in the EU, adapted from Wittchen et al. [4]

Diagnosis (DSM-IV)	Number of studies included	Prevalence range (%)	Prevalence median (%)	IQR * (%)	Expert-based best-estimate %	No. of persons affected (millions)	Age range	Gender ratio f:m	Prevalence (%) in 2005
Major depression	25	1.0-10.1	5.7	3.2-7.4	6.9	30.2	14+	2.3	6.9
Specific phobias	12	3.1-11.1	4.9	3.4-7.1	6.4	22.7	14-65	2.4	6.4
Somatoform disorders	6	1.1-11.0	6.3	2.1-7.8	4.9	20.4	18-65	2.1	6.3
Alcohol dependence	15	0.0-9.3	3.4	0.7-4.7	3.4	14.6	15+	0.3	2.4

*IQR, inter-quartile range

Mental disorders contribute 27% of the European disease burden, which is higher compared with other regions of the world. The largest contributors are depression (7.2% of total disease burden in Europe), dementia (3.7%), alcohol use disorders (3.4%) and stroke (2.6%). There were gender differences so that in women, 10.3% of all DALYs are due to major depression, whereas in men the

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figure is 4.5%, and alcohol use disorders are the largest contributor to male DALYs with 5.3% of the burden (Figure 2). In total, neuropsychiatric disorders account for 30.1% of the disease burden in women and 23.4% in men. The researchers note that their results "reveal that depression — in contrast to previous projections — is already now the most important single contributor to the total disease burden".

The authors report that there were no improvements in the low treatment rates and delayed and inadequate treatment compared with the findings in their earlier review, but no further details are given. In the 2005 review [5], based on the ESEMED study carried out in Belgium, France, Germany, Italy, the Netherlands and Spain, they report that 36.5% of persons with 12-month mood disorders had had any contact with formal health services. Out of them, 37.9% had medication treatment only, and 15.1% no treatment, while 33.1% had a combination of drug and psychological treatment.

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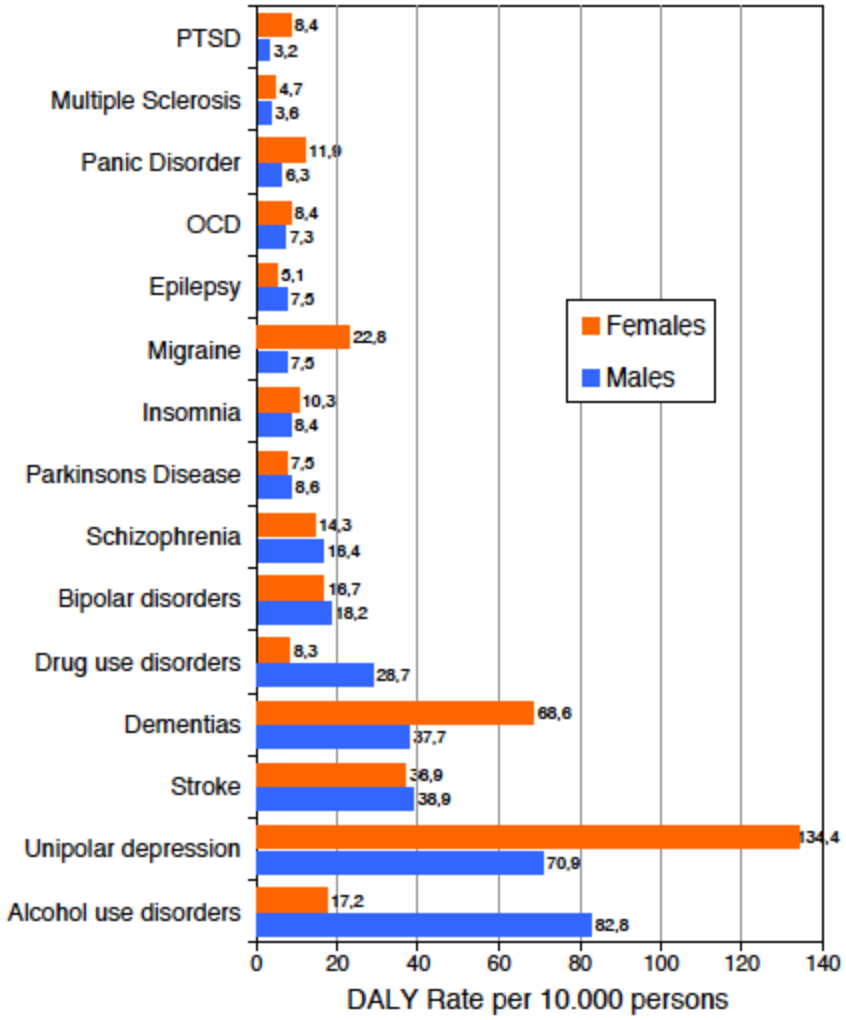

Figure 2. DALYs caused by mental and neurological disorders by gender, per 10.000 persons. From Wittchen et al. [4]

Costs of depression in Europe

Olesen et al. [7] report an update to their 2005 estimate on costs of brain disorders in Europe. They estimate annual prevalence and costs per person for 19 groups of disorders based on systematic literature reviews and panels of experts. For countries where no data were available, the costs were imputed, and estimates were adjusted to purchasing power parity and expressed in euros. The geographic scope included all EU member states, Iceland, Norway and Switzerland, in total 514 million persons. The cost estimate was based on a total cost model, including all costs irrespective of the payer.

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The total costs of brain disorders in Europe in 2010 were 798 billion[2] euros, consisting of 37% direct health care costs, 23% direct non-medical costs, and 40% indirect costs. Mood disorders are the most costly group, with a total annual cost of 113.4 billion €, followed by dementia (105 billion €), psychotic disorders (94 billion €), anxiety disorders (74 billion €), addiction (66 billion €) and stroke (64 billion €).

For major depression, an estimated 30 million persons are affected annually in Europe. The direct health care costs per patient are 797 purchasing power parity adjusted euros (PPP-€), direct non-medical costs 454 PPP-€ and indirect costs 1782 PPP-€. The total costs of major depression in Europe annually are 91 900 million PPP-€, with 58.7% being indirect costs, 26.3% direct medical costs and 15.0% direct non-medical costs.

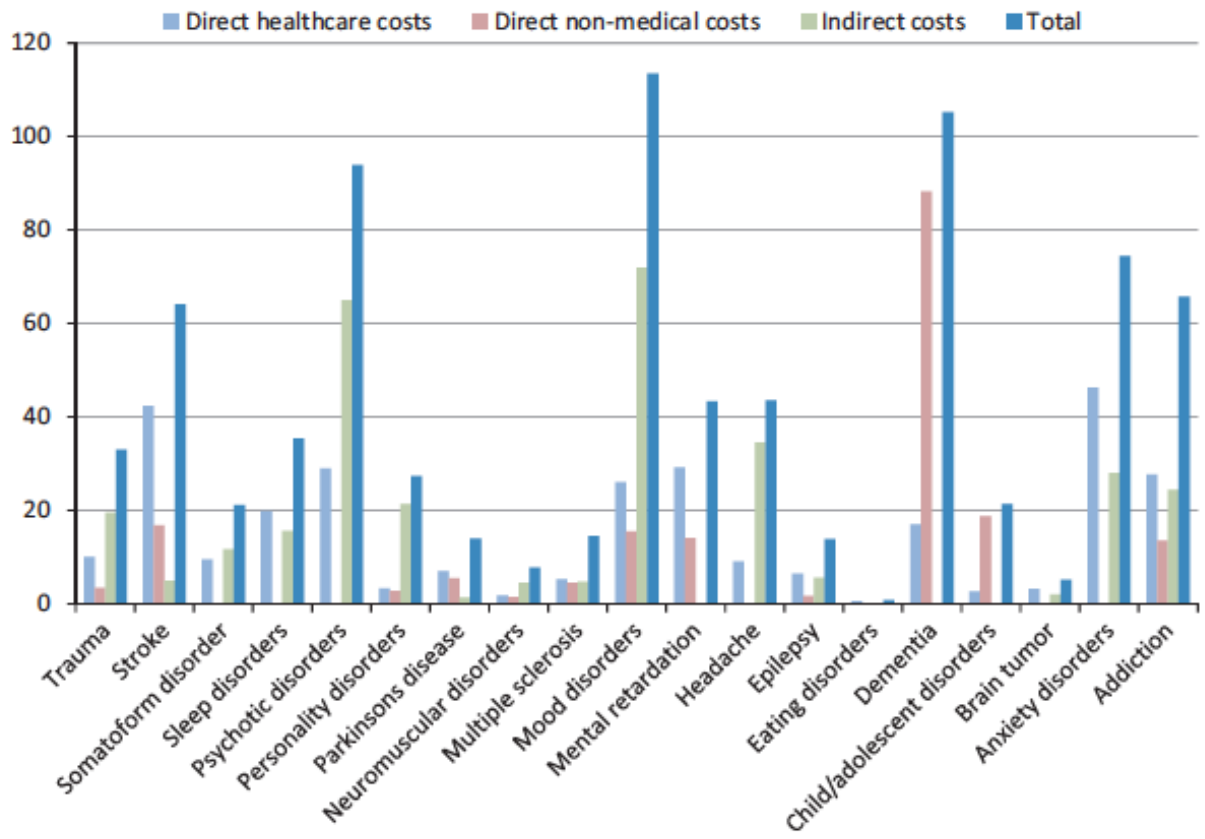

Figure 3. Absolute cost and type of cost of brain disorders in Europe (billion PPP-€ 2010). From Olesen et al. [7]

[2] 1 000 millions.

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Prevalence and trends of depression in selected European countries

Other relevant literature was reviewed to compare prevalence rates between countries. Prevalence of depression in selected European countries is presented in Table 2. Data were collected from the World Mental Health Survey and mental health surveys carried out in some European countries. A meta-analysis carried out for the Global Burden of Disease 2010 study (Ferrari 2013) found no significant differences in prevalence between Eastern and Western European regions (OR 1.5, 95% CI 0.9-2.4, p=0.132 for Eastern/Central Europe vs. Western Europe in meta-regression analysis for prevalence).

In the countries where trends in prevalence of depression have been studied, no increase or decrease has been found. Globally, the point prevalence of MDD has remained stable at 4.4% in 1990 and 2010 [1]. General population studies from the Netherlands and the UK have found no increase in the prevalence of depressive disorders from the 1990s to 2000s [8, 9]. However, in Finland there was an increase in the prevalence of depressive disorders (MDD and dysthymia) from 7.3% to 9.6% between 2000 and 2011 [10]. No other national studies were found that report results from the same time period, so it is not known whether this is a wider European phenomenon.

Table 2. 12-month prevalence of major depressive disorder (MDD) in selected European countries

Country	12-month prevalence, %	Study
Belgium	5.0	WMHS [11]
Czech Republic	2.0	ICPE [12]
Estonia	5.6	EHIS [13]
Finland	7.4	Health 2011 [10]
France	5.9	WMHS [11]
Germany	3.0-6.8	WMHS [11], DEGS1-MH [14]
Hungary	7.1	[15]
Ireland	6.2-8.9	ODIN [16]
Italy	3.0	WMHS [11]
Netherlands	4.9-5.2	WMHS [11], NEMESIS-2 (de graaf)
Norway	7.0-8.4	ODIN [16]
Spain	4.0	WMHS [11]
Ukraine	8.4	WMHS [11]

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United Kingdom	4.8-15.0	ODIN [16]

Determinants of depression

Behavioural factors: smoking, alcohol use, cannabis use, obesity, exercise

Depressive disorders are associated with several negative health behaviours, such as alcohol use, smoking, poor diet and lack of exercise. It is understandable that the core symptoms of depression – anhedonia, insomnia, and lethargy – directly impact on the individual's ability and willingness to pursue healthy behaviours. Moreover, the hopelessness and cognitive problems may negatively influence the decisions a depressed person takes regarding their health behaviours. However, the causal relationships are not as simple. A good example is smoking, where depression increases the risk of taking up smoking and decreases the likelihood of quitting smoking. At the same time, nicotine dependence is a risk factor for developing depression, and some of this is due to a shared genetic risk [17-19]. Therefore, these relationships merit careful study, before policy conclusions can be drawn.

The search was carried out in PubMed, using the review filter, as follows:

"Depressive Disorder"[Majr] AND ("smoking" OR "alcohol" OR "cannabis" OR "obesity" OR "physical activity") AND ("cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw])

The results of the search are described in Figure 4.

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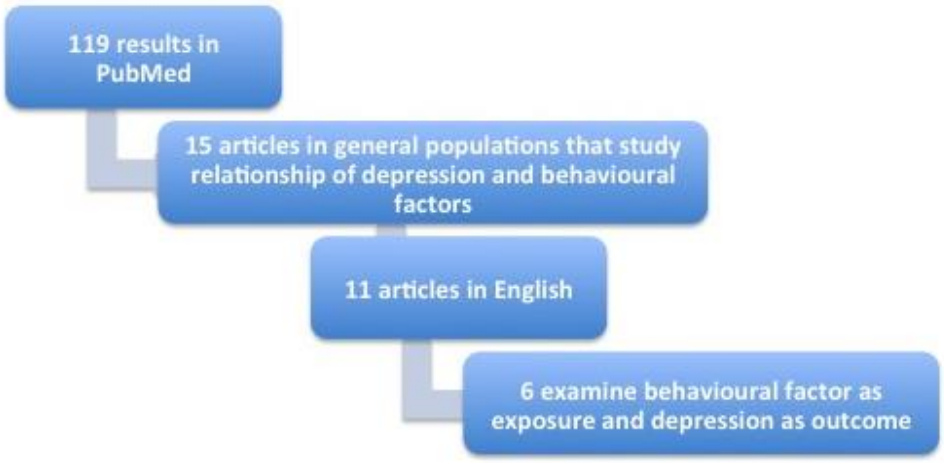

Figure 4.

The following articles were identified:

1. Degenhardt, L., W. Hall, and M. Lynskey, Exploring the association between cannabis use and depression. Addiction, 2003. 98(11): p. 1493-504.
2. Atlantis, E. and M. Baker, Obesity effects on depression: systematic review of epidemiological studies. Int J Obes (Lond), 2008. 32(6): p. 881-91.
3. Luppino, F.S., et al., Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry, 2010. 67(3): p. 220-9.
4. Lev-Ran, S., et al., The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med, 2014. 44(4): p. 797-810.
5. Luger, T.M., J. Suls, and M.W. Vander Weg, How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. Addict Behav, 2014. 39(10): p. 1418-29.
6. Cairns, K.E., et al., Risk and protective factors for depression that adolescents can modify: a systematic review and meta-analysis of longitudinal studies. J Affect Disord, 2014. 169: p. 61-75.

In addition, the following paper was identified through other methods and included, as the search did not yield any results on alcohol and depression.

7. Boden, J.M. and D.M. Fergusson, Alcohol and depression. Addiction, 2011. 106(5): p. 906-14.

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However, the first article did not describe their review methodology, such as number and type of studies included, and was thus excluded from this review.

Atlantis and Baker [20] reviewed studies on **obesity and depression**. They included 4 prospective and 20 cross-sectional representative population studies where obesity was the exposure and depression (disorder or symptoms) the outcome. Of the four prospective studies, three report results from the same study (Alameda County Study, US), and two of them found an association between baseline obesity and later depression in both men and women (OR 1.79, 95% CI 1.06-3.02 for BMI 30 or higher vs. lower; OR 1.73, 95% CI 1.04-2.87 for BMI 85th percentile or higher) The fourth is from the Northern Finland 1966 Birth Cohort Study, which did not control for baseline depression, and therefore reliable conclusions cannot be drawn.

Luppino et al. [21] carried out a new systematic review two years later, identifying 8 longitudinal studies where obesity or overweight was the exposure and depression the outcome. The adjusted OR for baseline obese people developing depression was 1.57 (95% CI 1.23-2.01). There was no significant heterogeneity between studies, and the finding was robust to different tests (publication bias, removal of outliers or other studies). However, there were geographical differences so that the association was stronger in American than European studies (p=0.05), and when clinical depression diagnosis as opposed to symptoms was used as an outcome.

When overweight was examined as exposure, the adjusted OR for developing depression was lower, 1.08 (95% CI 1.02-1.14). The finding was robust to tests for publication bias and outliers. Subgroup analyses showed that the risk was only increased in subjects aged 20 years and older.

The same study also demonstrated an increased risk of obesity in persons with depression of similar magnitude, and concludes that there is a strong bidirectional link between the two conditions, with a dose-response gradient. According to the authors, the pathway from obesity to depression could be mediated through biological mechanisms such as inflammation, HPA axis dysregulation, or brain-level changes caused by diabetes. In addition, psychological and social mechanisms related to the stress of being overweight in a society that favours thinner body types.

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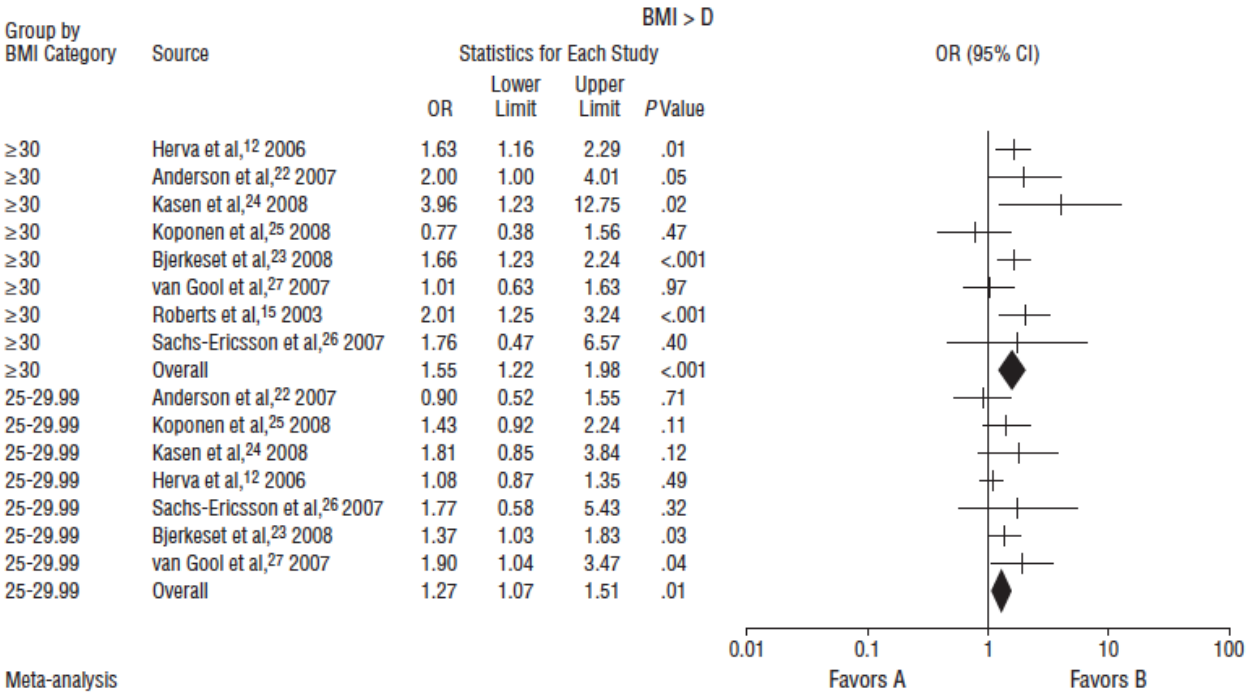

Figure 5. Forest plot of studies describing baseline obesity and overweight as risk factors for depression, from Luppino et al. [21]

Lev-Ran et al. [22] carried out a systematic review and meta-analysis of longitudinal studies examining the relationship **cannabis use and depression**. The exposure was cannabis use, and outcome measure was depression, and cases with depression had to be excluded at baseline.

They included 14 studies with 76,058 subjects. Heavy cannabis use was defined as weekly use or DSM-IV-defined cannabis use disorder. Depression was defined as either depressive disorder or depressive symptoms measured with a validated tool.

They found a modestly elevated risk of developing depression (OR 1.17, 95% CI 1.05-1.30) for any cannabis users vs. non-users, and a moderate risk (OR 1.62, 95% CI 1.21–2.16) for heavy users vs. non-users or light users. Meta-regression did not find any significant differences based on age of the studied group, and a marginally significant difference based on length of follow-up, where the risk attenuated over longer follow-up. The studies accounted for confounding factors varyingly, ranging from none to 20 factors accounted for. They note, however, that based on comparisons between adjusted and non-adjusted odds ratios, confounding does not explain the heterogeneous findings of the different studies. Two causal mechanisms are proposed: direct neurobiological effects of cannabinoids on regulation of emotional experience, which has little scientific evidence,

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and cannabis use influencing the risk of life events or circumstances that increase risk of depression.

Luger et al. [23] examined the relationship between **smoking and depression** in adults in a meta-analysis of 85 studies, out of which 7 were prospective. In the prospective studies, the odds for developing a new depressive episode, or new depressive symptoms when there were no baseline symptoms, were increased (OR 1.62, 95% CI 1.10-2.40). In the analysis of cross-sectional studies, both current and former smoking increased the risk of depression compared with never-smokers, but for prospective studies such comparison is not reported, and the definition of "smoker" is not specified. The authors lament the low number of prospective studies found, which limits the conclusions that can be drawn.

Boden et al. [24] carried out a systematic review to analyse links between **alcohol use disorders and depression**. They found a pooled adjusted OR of 2.00 (95% CI 1.19–3.35) of having depression among persons with alcohol use disorder. They conclude that the "most plausible causal association between AUD and MD is one in which AUD increases the risk of MD, rather than vice versa", and potential mechanisms include neurophysiological and metabolic changes. It should be noted that the review included mostly cross-sectional studies, thereby complicating the inference of causality, and secondly, that it does not report its results in PRISMA format, and leaves unclear whether the review was systematic.

Behavioural risk factors in adolescents

Cairns et al. [25] carried out a systematic review and meta-analysis of longitudinal studies that examine **potentially modifiable risk factors of depression in adolescence** (12-18 years), identifying 113 studies. They found evidence for substance use (alcohol, tobacco, cannabis and other illicit drugs), dieting, negative coping strategies, weight, healthy diet and sleep as potentially modifiable risk factors for depression, as follows:

- Alcohol use: small but significant effect size for frequent alcohol use (correlation coefficient r=0.059[3]); small but significant effect size for larger quantities of alcohol (r=0.119). This could be due to neurotoxic effects of alcohol. The authors note that reverse causality could not be excluded.

[3] Pearson's r varies between -1 and 1; 0.1-0.3 is considered a small effect, 0.1-0.3 moderate and 0.5 or higher large effect size

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- Cannabis use: small but significant effect size (r=0.118). This could be due to neurobiological, social, or common underlying factors.
- Dieting (deliberate food restriction in order to lose weight): small but significant effect size (r=0.187). It was considered plausible that this is related to shared comorbidity between eating disorders and depressive disorders.
- Healthy diet: small but significant mean effect size (r=-0.026)
- Negative coping strategies (e.g. avoidant or withdrawal coping, using substances, distraction or disengagement from the problem, and emotion-focused coping) (r=0.106)
- Other illicit drug use (r=0.167). This was considered possible consequence of the neurotoxic effects of drugs such as ecstasy and amphetamines.
- Polydrug use (r=0.075)
- Sleep (r=-0.210). Evidence suggests that sleep is important for cognitive and emotional development during adolescence.
- Tobacco use (r=0.093)
- Weight (r=0.054)

No significant association was found for dating during adolescence, early moving out of home, early sex, extracurricular activities, media use, part-time employment, physical activity, positive coping strategies, or relationships with positive peers.

Socio-economic Status

An umbrella review on socio-economic status (SES) and depression was included in the work carried out by Drs. Sing-Manoux and Fayosse, who identified one meta-analysis on the subject. Therefore, the literature review was not repeated here.

As noted in the review by Sing-Manoux and Fayosse, the meta-analysis of 51 studies, published in 2003, found an OR 1.8 for the lowest SES group for current (prevalent) depression, OR 1.2 for incident depression and OR 2.0 for persistence of depression [26]. These results support the co-existence of both causation, where lower SES is a risk factor for depression, and selection, where depression leads to downward social mobility or prevents moving upward [27]. Further, the higher persistence of depression in the lowest SES groups supports the stress theory, where persons with higher SES are thought to have better coping mechanisms in the event of stress and depression.

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Environment: childhood living conditions and childhood adversity

Early childhood living conditions and adversity experienced as a child impact on later risk of developing depression through several pathways [28, 29]. Low parental education [30], being exposed to bullying [31, 32] and family discord [33], or physical, emotional or sexual abuse [34, 35] are well-known risk factors for depression. In retrospective studies memory bias presents a problem, as current depression and stress are associated with increased reporting of childhood adversities that were previously unreported [36]. Therefore, the most reliable study settings are longitudinal studies. The impact on increased risk of depression is partly mediated through personality pathology, and thus may remain increased throughout adult life [37, 38]. Adverse experiences also contribute to the development of negative self-cognitions, and can be traumatic interpersonal events [32, 39].

The search was carried out in PubMed, using the review filter, as follows:

"Depressive Disorder"[Majr] AND ("childhood adversity" OR "childhood living conditions" OR "abuse" OR "child maltreatment" OR "child abuse") AND ("cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw])

The search results are presented in Figure 6.

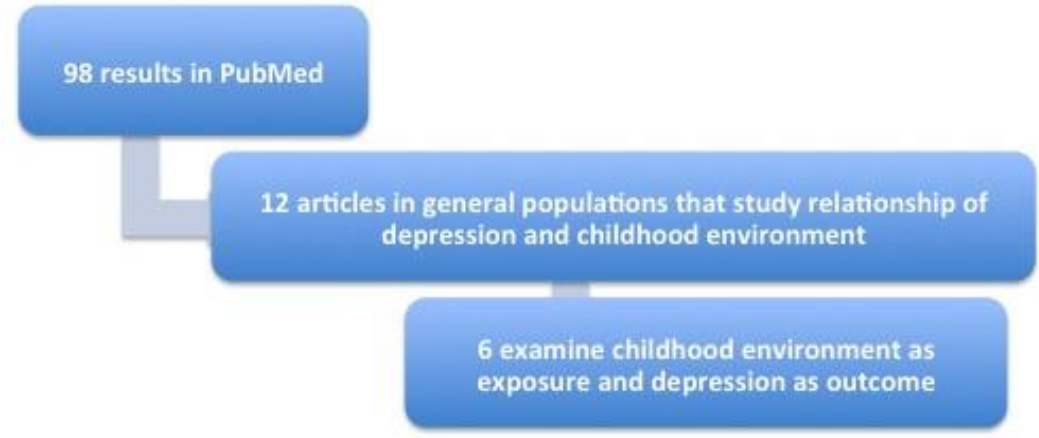

Figure 6.

The following articles are included:

1. Weiss, E.L., J.G. Longhurst, and C.M. Mazure, Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. Am J Psychiatry, 1999. 156(6):

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p. 816-28.

2. Weich, S., et al., Family relationships in childhood and common psychiatric disorders in later life: systematic review of prospective studies. Br J Psychiatry, 2009. 194(5): p. 392-8.

3. Alvarez-Segura, M., et al., Are women with a history of abuse more vulnerable to perinatal depressive symptoms? A systematic review. Arch Womens Ment Health, 2014. 17(5): p. 343-57.

In addition, the following article was identified through other means and added as it was relevant to the topic:

4. Norman, R.E., et al., The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med, 2012. 9(11): p. e1001349.

Weiss et al. [40] studied **childhood sexual abuse as a risk factor for depression in women**. They included seven cross-sectional community studies and five cross-sectional studies of college women, representing a high-functioning group of possible abuse sufferers. The review does not describe its methodology and it is unclear whether the review was systematic. All studies found higher prevalence of depression among women with a history of sexual abuse than those without. However, all studies were cross-sectional, which limits the interpretation. Four out of five studies found higher incidence of depression among women with a history of childhood sexual abuse. Possible explanations for the association include other related childhood psychosocial factors, lifestyle and negative life events such as divorce or low adult SES, and dysregulation of the HPA axis as a result of early stressors.

Weich et al. [41] examined the impact of **poor family relationships on later risk of depression** in a systematic review of 17 cohort studies with 10-37 years of follow-up. Both exposure and outcome definitions and measurement varied. Different studies examined physical or sexual abuse and neglect, lack of family cohesion, parental disharmony, family violence, parental disagreement about discipline, emotional responsiveness, parental rejection and lack of affection, harsh discipline, and poor care and mothering. Outcomes were either clinical depression diagnoses or depressive symptoms. 8 out of 17 studies found significant associations between negative family relationships and later depression in both genders. Three further studies found significant associations in one gender only (two in women and one in men). Four studies did not find significant associations after adjusting for confounding (such as maternal depression, socioeconomic status and child's earlier internalising problems), and only two studies did not find

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any association. The authors conclude that parental abuse in childhood is inextricably linked with common psychiatric disorders in later life. The findings are most robust for severe abuse and neglect, where all but one low-quality study found significant associations, and suggestive for milder forms of dysfunction of parent-child relationships (e.g. quality of marital relationship), where eight out of ten studies found positive associations with depression, although some restricted to one gender only.

Alvarez-Segura et al. [42] studied the relationship between **childhood abuse and perinatal depressive symptoms** in a systematic review of 43 articles, out of which 14 were longitudinal and 29 cross-sectional. The studies were heterogeneous in terms of definition of abuse as well as definition and measurement of depression. Despite this variability, the authors conclude that evidence suggests increased risk of depressive symptoms in the perinatal period in women with history of any lifetime abuse, which persists after adjustment for confounding factors. The strongest predictor was intimate partner violence (IPV).

Norman et al. [43] reviewed different **long-term health consequences of non-sexual childhood maltreatment** in a systematic review and meta-analysis of 124 studies, out of which 16 were prospective. They studied separately physical abuse (use of physical force that results in harm for the child's health, survival, development or dignity), emotional abuse (failure to provide a developmentally appropriate and supportive environment for the child) and neglect (failure to provide for the well-being of the child in the areas of health, education, emotional development, nutrition, shelter and safe living conditions). A possible publication bias as well as significant heterogeneity was observed. There were no significant differences between genders. There was a statistically significant association between the three types of abuse studied and depression: physical abuse OR 1.54 (95% CI 1.16–2.04), emotional abuse OR 3.06 (95% CI 2.43–3.85), and neglect OR 2.11 (95% CI 1.61–2.77). The evidence was considered strong for all three types.

Summary of reviewed risk factors

All the reviewed risk factors of depression (behavioural, environment and SES) are summarized in Table 3. Emotional abuse and neglect appear as the most important risk factors for developing depression, but also smoking, obesity and substance abuse increase the risk of depression. Lower socioeconomic status is a risk factor for developing depression, but in particular for its persistence.

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Table 3. Reviewed risk factors of depression.

Exposure	Outcome	Risk Ratio
Smoking **[23]**	**Depression** (depressive disorder or symptoms)	Smoking (ever or current) vs. no smoking • OR 1.62, 95% CI 1.10-2.40
Cannabis **[22]**	**Depression** (depressive disorder or symptoms)	Any cannabis use vs. no use • OR 1.17, 95% CI 1.05-1.30 Heavy cannabis use vs. no or light use • OR 1.62, 95% CI 1.21–2.16)
Obesity and overweight **[20]**	**Depression** (depressive disorder or symptoms)	Obesity (BMI 30 or higher) vs. no obesity • OR 1.79, 95% CI 1.06-3.02 BMI 85th percentile or higher vs. 84th or lower • OR 1.73, 95% CI 1.04-2.87
[21]	**Depression** (depressive disorder or symptoms)	Obesity (BMI 30 or higher) vs. no obesity • 1.57, 95% CI 1.23-2.01 Overweight (BMI 25-30) vs. normal weight • 1.08, 95% CI 1.02-1.14
Alcohol **[24]**	**Depression**	Alcohol use disorder vs. no disorder • 2.00, 95% CI 1.19–3.35
Socioeconomic status **[26]**	**Depression** (depressive disorder or symptoms)	Lowest SES vs highest, current depression • OR 1.81, 95% CI 1.57-2.10 Lowest SES vs highest, incident depression • OR 1.24, 95% CI 1.04-1.48 Lowest SES vs. highest, persistent depression • OR 2.06, 95% CI 1.39-3.05
Childhood abuse **[43]**	**Depression** (depressive disorder or symptoms)	Physical abuse • OR 1.54 (95% CI 1.16–2.04) Emotional abuse • OR 3.06 (95% CI 2.43–3.85) Neglect • OR 2.11 (95% CI 1.61–2.77)

Prevention of depression

In this search, only primary prevention was included.

The search was carried out in PubMed, using the review filter, as follows:

"Depressive Disorder"[Majr] AND "Primary Prevention"[Majr] AND ("cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw])

The search yielded 6 results, out of which 3 dealt with prevention of depressive disorders in the

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general population and were included:

1. Waddell, C., et al., Preventing mental disorders in children: a systematic review to inform policy-making. Can J Public Health, 2007. 98(3): p. 166-73.

2. Carnevale, T.D., Universal adolescent depression prevention programs: a review. J Sch Nurs, 2013. 29(3): p. 181-95.

3. Bellon, J.A., et al., Effectiveness of psychological and/or educational interventions to prevent the onset of episodes of depression: A systematic review of systematic reviews and meta-analyses. Prev Med, 2015. 76 Suppl: p. S22-32.

In addition, two articles from Cochrane database were included:

4. Merry, S.N., et al., Psychological and educational interventions for preventing depression in children and adolescents. Cochrane Database Syst Rev, 2011(12): p. Cd003380.

5. Forsman, A.K., I. Schierenbeck, and K. Wahlbeck, Psychosocial interventions for the prevention of depression in older adults: systematic review and meta-analysis. J Aging Health, 2011. 23(3): p. 387-416.

One article was identified through other means and included as it was relevant to the topic:

6. van Zoonen, K., et al., Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. Int J Epidemiol, 2014. 43(2): p. 318-29.

Waddell et al. [44] carried out a systematic review to identify randomised controlled trials (RCT) on interventions to **prevent conduct disorders, anxiety and depression in children** aged 0-18 years. Five studies reported interventions to prevent depression. All five targeted at-risk groups: children with depressive symptoms and/or depressed parents. Three of the five trials did not find significant reductions in depressive symptoms, although one of them reduced anxiety symptoms. They used school-based drama therapy or school-based cognitive-behavioural therapy (CBT) with few individual sessions or universal format. Two trials provided CBT in a school- or clinic-based format over 15 sessions, and found significant reductions in diagnostic measures of depression at 1- and 2-year follow-up (11-17% reductions).

Carnevale [45] carried out a systematic review on interventions to **prevent depression in adolescents**, identifying eleven studies. The studies provided universal (non-targeted) cognitive-behavioural sessions in classroom settings, imparted by school psychologists, students, school counsellors or teachers. The author concludes that cognitive–behavioural universal prevention

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interventions can be effective on decreasing depressive symptomology in adolescents. Unfortunately the review does not provide a more detailed summary of how many of the reviewed interventions were effective.

Bellon and colleagues [46] carried out a systematic review of systematic reviews and meta-analyses on **psychological and educational interventions to prevent depression**, identifying 12 articles, which comprised 156 non-repeated trials and 56,158 participants. Nine (75%) reviews found that interventions to prevent depression were effective, although the effect sizes were often small (32.8% of trials) or medium (19.1%), and less often large (18.2%). 29.9% of trials were not effective.

Trials were selective, universal or indicated, but no trial implemented universal prevention in adults. Broadly, there were two categories of preventive interventions: cognitive behavioural (cognitive behavioural therapy, "coping with depression", problem solving therapy, social skills training, reducing negative cognitions, and self-help guidelines) and other (interpersonal psychotherapy, counselling, other psychotherapies, telephone support, support groups etc.). The interventions were provided by four types of professionals: mental health specialists (psychologists, psychiatrists, psychiatric nurses, and therapists), teachers and other school professionals, primary care staff (nurses, midwives, and others) and "other" (social workers, paediatricians, researchers, trained facilitators, and lay persons).

When examining effectiveness by subgroup, four out of five systematic reviews on children and adolescents found small to moderate effects, which were observed up to 12 months but not over longer follow-ups. In the postpartum period, only 3 out of 10 trials found an effect. In specific populations, prevention was effective among women with low socioeconomic status and persons who had suffered a stroke. In general populations, all three reviews found prevention to be effective (Incidence rate ratio 0.62-0.78).

The authors conclude that psychological and educational interventions are effective in preventing depression, and can be expected to contribute to reducing the burden of depression. The effect sizes of preventive interventions are usually small or moderate, similar to primary prevention of cardiovascular diseases.

Merry et al. [47] authored a Cochrane review on p**sychological and educational interventions for preventing depression in children and adolescents** (age 5-19), including 53 studies with 14,406

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participants. However, only six studies were properly blinded, and 16 studies with 3240 participants reported depressive diagnoses as outcomes. The risk of developing a depressive disorder after the intervention was reduced immediately after the intervention, at 3-9 months, 12 months and 36 months, but not 24 months, as described in Table 4. The authors conclude that targeted and universal depression prevention programmes may prevent the onset of depressive disorders, and that the persistence of the effect points towards a real, not a placebo effect.

Table 4. Effect of psychological and educational interventions for preventing depression in children and adolescents by length of follow-up.

	Number of studies	Number of participants	Risk difference (95% CI)
Immediately	15	3115	-0.09 (-0.14 to -0.05)
3-9 months	14	1842	-0.11 (-0.16 to -0.06)
12 months	10	1750	-0.06 (-0.11 to -0.01)
24 months	8	2084	-0.01 (-0.04 to 0.03)
36 months	2	464	-0.10 (-0.19 to -0.02)

Forsman et al. [48] authored a Cochrane review to assess the **effectiveness of psychosocial interventions for the prevention of depression in older peopl**e (65 years or older), including 30 studies. They found that psychosocial interventions had a small but statistically significant effect in reducing depressive symptoms (standardized mean difference calculated from 17 trials -0.17, 95% CI -0.31 to -0.03). However, when the outcome was dichotomised into depression diagnosis, the reduction in new cases was not significant (3 trials, OR 0.69, 95% CI 0.41-1.17). There was no significant impact on quality of life (3 trials) or overall functional capacity (2 trials).

The interventions were universal (12 trials), targeted (15) or indicated (3) in nature. Save for one trial, the interventions were delivered by professionals in health or social care. The most common types of interventions were physical exercise (7 trials), skills training (7) and reminiscence (6). When the effect was studied by type of intervention, only social activities (2 trials) reduced depressive symptoms significantly, whereas in other types of interventions the reduction was non-significant, which is considered to be a combination of small effect size and lack of statistical power because of small number of studies and participants. One difference between the social activities studies and the other trials is the intensity of the intervention, which lasted over 30

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weeks and included several sessions, whereas many other interventions comprised a few sessions only.

The authors conclude that psychosocial interventions with a focus on the primary prevention of depressive symptoms among older adults in general "are characterized by a small or no effect".

Finally, van Zoonen et al. [49] meta-analysed 32 studies with 6214 participants to assess the **effectiveness of psychological interventions in the prevention of major depression**. They found an incidence rate ratio of 0.79 (95% CI 0.69-0.91) of major depressive disorder in the intervention vs. the control groups, resulting in a NNT (number needed to treat) 20. In sensitivity analyses, there were no differences between different types of interventions (cognitive behavioural therapy, interpersonal therapy or other therapy), nor type of prevention (selective, indicated or universal). However, the NNT differed as follows: CBT NNT 71, IPT NNT 7, other therapy 12, indicating that IPT would be the most effective preventive therapy.

Screening for depression

Even though the non-detection and –treatment of depression is a considerable problem, screening of depression remains a controversial topic, and currently most countries recommend against it, a notable exception being the US.

The search was carried out in PubMed, using the review filter, as follows:

"Depressive Disorder"[Majr] AND "Mass Screening"[Majr]

The search results are presented in Figure 7.

Figure 7.

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The following articles were included:

1. Schade, C.P., E.R. Jones, Jr., and B.J. Wittlin, A ten-year review of the validity and clinical utility of depression screening. Psychiatr Serv, 1998. 49(1): p. 55-61.
2. Cuijpers, P., et al., Screening and early psychological intervention for depression in schools : systematic review and meta-analysis. Eur Child Adolesc Psychiatry, 2006. 15(5): p. 300-7.
3. Williams, S.B., et al., Screening for child and adolescent depression in primary care settings: a systematic evidence review for the US Preventive Services Task Force. Pediatrics, 2009. 123(4): p. e716-35.
4. Thombs, B.D., et al., There are no randomized controlled trials that support the United States Preventive Services Task Force Guideline on screening for depression in primary care: a systematic review. BMC Med, 2014. 12: p. 13.

Additionally, one review was identified from the Cochrane library

5. Gilbody, S., A.O. House, and T.A. Sheldon, Screening and case finding instruments for depression. Cochrane Database Syst Rev, 2005(4): p. Cd002792.

Schade et al. [50] carried out a systematic review to assess **validity and clinical utility of depression screening**, identifying 59 studies. Out of these, 39 studies were validation studies of screening instruments, thirteen reviews and seven outcome studies. The papers that reviewed effectiveness had contradicting findings, and the outcome studies did not show any measurable benefit from screening a population. The authors conclude that there is no evidence to support screening the population for depression.

Pim Cuijpers et al. [51] reviewed and meta-analysed eight RCTs (5803 students) to assess **effectiveness of screening and early psychological intervention for depression in schools**. They found a mean effect size of 0.55 (95% CI 0.35-0.76), indicating that the mean of the experimental group is half a standard deviation larger than the mean of the control group. The effect size is in the moderate to large range. 31 students needed to be screened to achieve one successfully treated case. They conclude that screening may be an effective strategy to reduce the burden of depression among children and adolescents. It is important to note that in these studies, screening was combined with treatment (CBT, relaxation training, or other therapy) of varying intensity (up

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to 16 weekly sessions).

Williams et al. [52] carried out a systematic review to assess effectiveness of **screening for child and adolescent depression in primary care**. In a broad search, they did not find any outcome studies comparing screened and unscreened populations. Studies with younger children had worse results in terms of validity, and results improved when also parents were interviewed. They identified nine studies assessing six screening instruments that performed adequately in the adolescent population. No studies assessed the possible harm caused by screening.

Thombs et al. [53] carried out a systematic review to evaluate **evidence from randomized controlled trials (RCTs) of screening primary care patients for depression**. The review was carried out explicitly to respond to the United States Preventive Services Task Force (USPSTF) recommendation to screen for adults for depression in primary care settings. They assessed a review performed by the USPSTF, which had included nine RCTs. They found that none of these filled the three criteria for a test of depression screening which were 1) determine patient eligibility and randomize patients before screening, 2) exclude patients already diagnosed or treated for depression and 3) provide similar depression management options to both screening and control groups. Additionally, two RCTs from a Cochrane review were identified, and also failed to meet the criteria. They also carried out a new systematic search, finally identifying three RCTs, out of which none met the three criteria. The authors conclude that this recommendation is not supported by evidence from any RCT, and call for re-evaluation of the recommendation. They fear that screening would exacerbate the problem of over-diagnosis and –treatment of depression present in the US.

Finally, Gilbody [54] carried out a systematic review for the Cochrane Library to determine the **clinical and cost effectiveness of screening and case finding instruments**. They found twelve studies with 5693 patients. The found that for recognition/detection of depression, screening instruments had a small impact on the detection of new cases (RR 1.38, 95% CI 1.04-1.83), but this was based on rather low-quality studies with risk of publication bias. For management of depression, there was a near-significant increase in intervention rate among the patients whose physician received feedback of screening instruments (RR 1.35, 95% CI 0.98-1.85), but this result was dependent on one very positive study. Thirdly, of the four studies that reported outcomes of depression, three did not find any clinical effect at 6-12 months. No studies assessed cost-

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effectiveness of screening.

The authors conclude that the evidence regarding the impact of screening for depression on detection, treatment or outcomes of depression is minimal, and recommend against adopting this as an isolated strategy.

Overarching topics: gender, age and depression

Gender and depression

Women have a 1.5-2-fold risk of developing depression, compared with men [11, 55]. The relative risk increases from puberty onwards, peaks at 20 years, and then approximates the risk of men after 40 years [56, 57]. The difference in prevalence of depression is explained by higher incidence among women; the prognosis of depression does not differ by gender. The risk factors for men and women differ slightly: for women, problems in caring relationships and interpersonal issues are more important, whereas for men, the role of stressful life events of financial, occupational or legal nature is more emphasised.

In this review, unfortunately no study presented the results by gender, except for the prevalence studies. Therefore, it cannot be concluded whether these specific risk factors are more important in men or women, or whether prevention and screening are more pertinent in one gender or the other.

Ageing and depression

Depression is more prevalent in younger age groups, and several longitudinal studies have established younger age as a risk factor for developing depression [3, 55, 58]. However, the association is less clear or reverse in low- and middle-income countries [3, 11]. In a Danish register-based study, the incidence of depression increased steeply from 10 years of age until 20 and then reduced, until there was another peak at 80-90 years of age [56]. However, there are some methodological problems in diagnosing depression among older persons with questionnaires and interviews not specifically designed for them; the complex questions may confuse them, causing false negative responses and thereby underestimation of the prevalence of depression in the older age groups [59].

Due to the limitations of the psychometric instruments in the older age groups, it is difficult to assess the exact impact of ageing on the prevalence of depression. However, according to current knowledge, in high-income countries the prevalence and incidence of depression decreases with

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age. Therefore, an increase in the prevalence of depression due to ageing of the population is not expected.

7.4 CONCLUSIONS

- The annual prevalence of major depression in Europe is 6.9%, being the most prevalent individual mental disorder. 30 million Europeans are affected annually. There are no indications of changes in prevalence in the past decade.
- Depression contributes 7.2% of the total disease burden in Europe (10.3% in women and 4.5% in men), being the most important single contributor to the total disease burden
- One third of persons with depression access any formal healthcare, and about one third of them receive optimal combination treatment.
- The total costs of major depression in Europe annually are 91 900 million PPP-€, with 58.7% being indirect costs, 26.3% direct medical costs and 15.0% direct non-medical costs.
- Obesity, smoking and cannabis use in adults, and alcohol use, cannabis and other drug use, dieting, unhealthy diet, overweight, smoking, lack of sleep and negative coping styles in adolescents are behavioural factors that increase the risk of depression. Lower SES increases the risk of depression slightly, and is associated with worse prognosis.
- Different types of childhood abuse (emotional, physical and sexual) increase the risk of depression in adult life.
- Preventive interventions have a small to moderate effectiveness in preventing onset of depression in general populations, children and adolescents, and older people. Studied interventions include cognitive behavioural based interventions, other therapy based interventions, and different psychosocial models. Results have been found to persist up to 12 months. Intensity (frequency and duration) of the intervention appears to be related to higher effectiveness.
- There is no evidence to support screening of healthy adults or primary care patients for depression.

On the gaps in available evidence

Recent, representative prevalence data is not available for many European countries, and very few

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countries have assessed trends in prevalence. This complicates the assessing of the burden and costs at the country-level. Of the reviewed risk factors, no good-quality review on alcohol as a risk factor for depression was found. Regarding screening, most studies do not fill the criteria to reliably answer the question whether screening of healthy (non-depressed) individuals will result in better health outcomes at the population level.

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8 ASSOCIATION BETWEEN BEHAVIOURAL AND BIOMEDICAL FACTORS AND NEUROLOGICAL DISORDERS

8.1 BACKGROUND

Neurological disorders are diseases of the central or peripheral nervous system. In this paper, the pathogenesis, etiology and risk factors of defined neurological disorders were examined using current literature (systematic reviews, meta-analyses and original articles). Neurological disorders are a heterogenic group of diseases containing a variety of diseases of different etiology, pathogenesis. In this review the focus is on dementia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, migraine and on polyneuropathies (alcohol related, diabetic and B_{12}-vitamin related), which are the most common neurological diseases in the European population. Dietary and life style factors of neurological disorders were as well covered.
The search was limited to review, meta-analysis and original articles published in the last 10 years (from 01/01/2005 to 31/12/2015).
Database searches using Pubmed and Cochrane were performed according to the provided guidelines.
Appropriate search terms were used to filter out the desired data described in the guidelines. The process tree of the database search is presented in Figure 1.

Search terms based on the WP2 plan: "pathogenesis", "risk factors", "etiology", "environmental factors" "Dementia", "Alzheimer", "Parkinson", "multiple sclerosis", "epilepsy", "migraine" and "polyneuropath*".
In addition, a separate search were performed using the search terms "dietary factors", "diet" and "life style" to investigate their association with the following neurological disorders ("Dementia", "Alzheimer", "Parkinson", "multiple sclerosis", "epilepsy", "migraine" and "polyneuropath*")

Schedule

This work was performed in January-March 2016.

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8.2 METHODS

Search-terms for Pubmed

Pathogenesis, etiology, risk factors and neurological disorders

("risk factors"[All Fields] OR "environment"[All Fields] OR "pathogenesis"[All Fields] OR "etiology"[All Fields]) AND ("parkinson"[All Fields] OR "alzheimer"[All Fields] OR "dementia"[All Fields] OR "multiple sclerosis"[All Fields] OR "epilepsy"[All Fields] OR "migraine"[All Fields])

AND

((Meta-Analysis[ptyp] OR Review[ptyp]) AND "2005/01/01"[PDAT] : "2015/12/31"[PDAT] AND English[lang])

Dietary factors and Neurological disorders

((“dietary factors”) OR diet OR “life style”) AND (Dementia OR Alzheimer OR Parkinson OR “multiple sclerosis" OR epilepsy OR migraine OR polyneuropath*)

AND

((Meta-Analysis[ptyp] OR Review[ptyp]) AND "2005/01/01"[PDAT] : "2015/12/31"[PDAT] AND English[lang])

Search-terms for Cochrane

Pathogenesis, etiology, risk factors and neurological disorders

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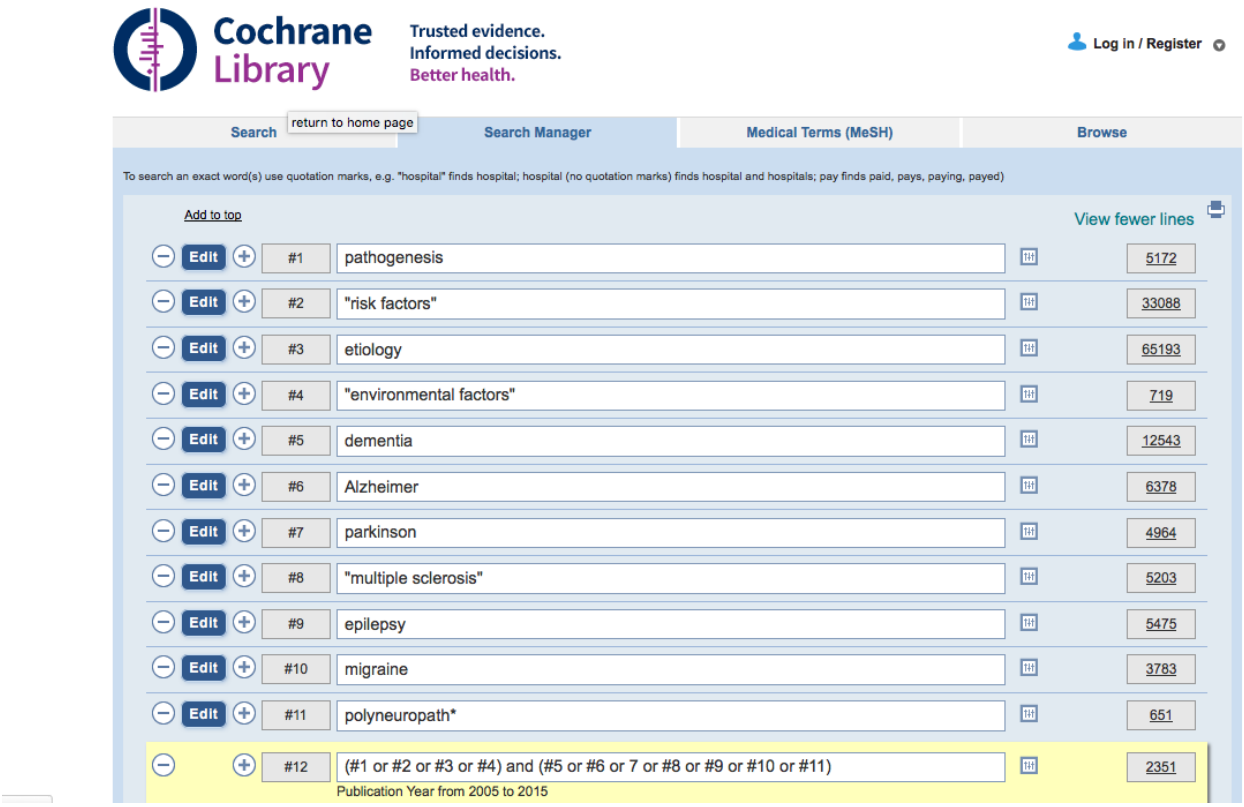
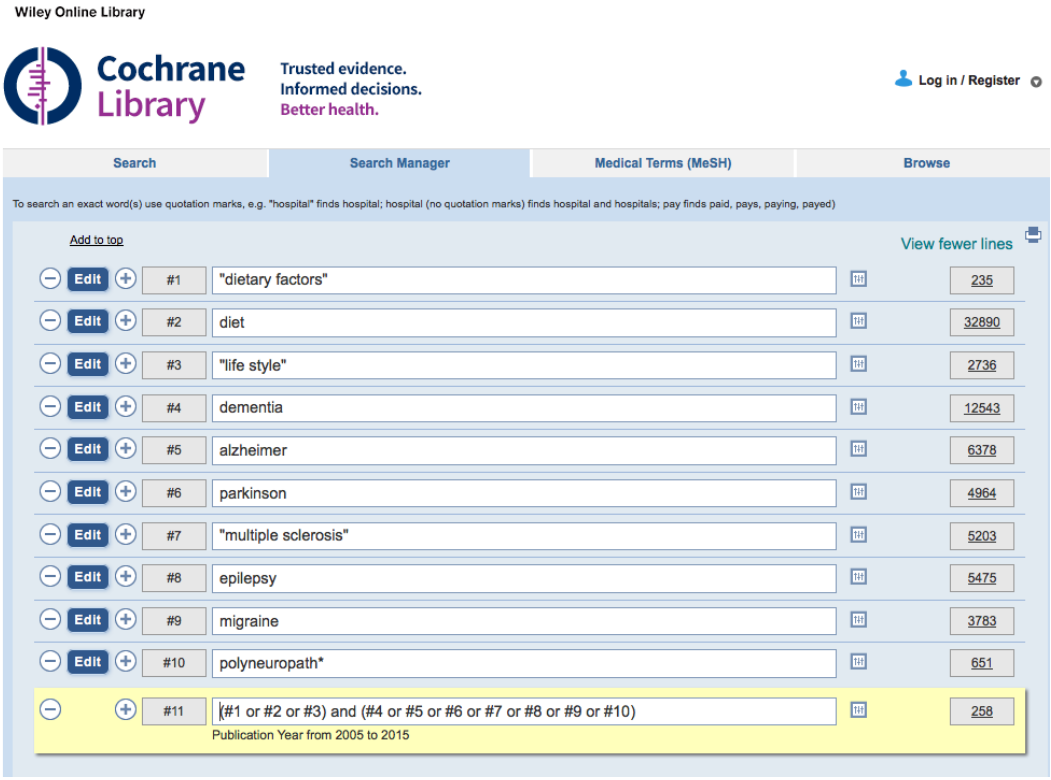


Dietary factors and Neurological disorders



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Pubmed and Cochrane search results were combined in a single Excel file and the database were searched for the terms “meta-analys*” and “systematic”. Articles containing at least one of these terms were extracted for further scrutiny.

1. The abstracts of the articles were searched for pathogenesis, risk factors and etiology of the defined neurological disorders.
2. Only articles written in English were selected.
3. Meta-analyses and systematic reviews of the pathogenesis, risk factors and etiology of neurological disorders were selected for further scrutiny.
4. The full versions of the articles included in the meta-analyses and reviews were examined further to ensure their quality.

A workflow of the work plan is presented in Figure 1. A disease specific summary of pathogenesis, risk factors and etiology of the defined neurological disorders is described.

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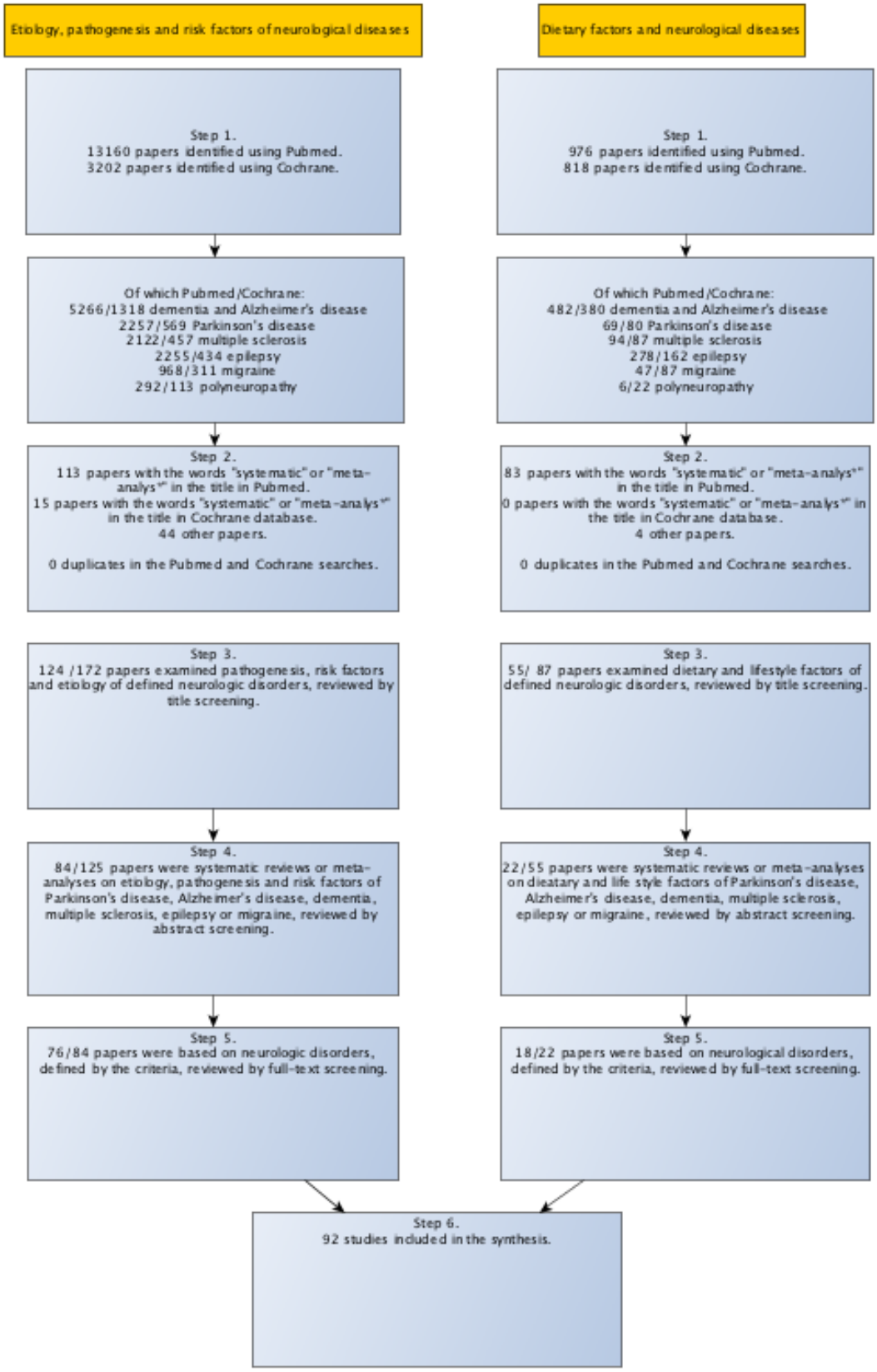
FIGURE 1 (DATABASE SEARCH)



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8.3 RESULTS

Dementia

Prevalence, incidence and trends

The prevalence of dementia increases with age (1). In Europe, the prevalence of dementia is 6.4% in subjects over the age of 65 years, and in subjects over 85 years, the prevalence can be as high as 43% (1). There are about 35 million people, who have Alzheimer's disease in the world (2), and Alzheimer's disease is the most frequent cause of dementia (prevalence 4.4% in Europe), accounting for over half of the dementia cases (3-5). Vascular dementia (prevalence 1.6% in Europe) is the second most common cause of dementia after Alzheimer's disease and it accounts about 20% of all dementia cases (4, 6). Dementia is often a combination of these two common causes of dementia (mixed dementia), which is estimated to be the most common cause of dementia (4). In Europe, the prevalence of mixed dementia ranges from 2 to 7 per 1000, in elderly subjects (7) (reference from year 2002).

The incidence of overall dementia in Europe is 12.47 per 1000 person-years (4). The incidence of Alzheimer's disease in Europe ranges from 1.59 to 6.55 per 1000 person-years. The incidence doubles every 5 years after 65 years of age, with 12.75 new cases per year per 1000 persons older than 65 years of age (8). Approximately 12% of the burden of neurological diseases is contributed by Alzheimer's disease and other dementias (5). There is expected to be a 66% increase in Alzheimer's disease and other dementias from 2005 to 2030 (5). The incidence for vascular dementia ranges from 0.99 to 3.30 per 1000 person-years, and the incidence of mixed dementia 3.8 per 1000 person-years (4).

According to the World Health Organization's report, the prevalence of dementia will continue to increase along with the increasing life expectancy, while the overall population incidence is expected to diminish due to rapid declines in the ischemic heart disease and stroke in the Western countries (5, 9).

Pathogenesis and etiology

Alzheimer's disease

Alzheimer's disease is a progressive condition characterized by deterioration in cognition and memory causing several neuropsychiatric symptoms. The cause of Alzheimer's disease is

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multifactorial, but there are some specific risk factors strongly associated with Alzheimer's disease. The greatest risk factor for Alzheimer's disease is increasing age, although Alzheimer's disease is not inevitable the outcome of aging (2). In Alzheimer's disease an accumulation of misfolded proteins (beta-amyloid in neocortical terminal fields and formation of neurofibrillary tangles in medial temporal lobe) causes oxidative and inflammatory damage, leading to energy failure and synaptic dysfunction (2). It has been also proposed that APOE ε4 (allele) has a role in the progression of impaired memory in subjects with mild cognitive impairment (10-12). APOE ε4 may increase the likelihood of the disease by flooding cholesterol into the sites of nerve damage and complexing with amyloid-beta-peptide into the senile plaques (10, 12). About one-fourth of the population in different geographic areas have one or more copies of the APOE ε4 allele of the gene (5, 10, 11). Those individuals with APOE ε4 allele might carry an increased risk for developing dementia (11, 12). Hypertension plays a crucial part of the Alzheimer's disease process leading to atherosclerotic changes in blood vessels (leading to atrophy in the Hippocampus area due to a lower blood flow) (13).

Vascular dementia

Vascular dementia is a cognitive impairment of cerebrovascular origin. At early stages it can be difficult to distinguish from Alzheimer's disease or other types of dementia (6). The main causes of cognitive impairment of vascular origin are cerebral small vessel disease, multi-infarct dementia, haemorrhage, hypoperfusion and hereditary vasculopathy (6).

Risk factors

Both Alzheimer's disease and vascular dementia partially share common risk factors (14). The evidence of the impact of risk factors comes mainly from cohort follow-up studies (with a follow-up of 5 years or less (14). The evidence based on randomized controlled trials is scarce (14).

According to cross-sectional and follow-up studies hypertension, hypercholesterolemia, obesity, diabetes mellitus, smoking, neuropsychiatric symptoms, prediabetes, metabolic syndrome, high homocysteine levels, physical inactivity, low education attainment and depression are risk factors for cognitive decline and dementia (1, 15-20). Chronic kidney disease has been recognized as an independent risk factor of cognitive decline (21). No linkage has been found between exposure to anesthetic gases and Alzheimer's disease (22). Some evidence has been presented that there might be familial coaggregation of risk of dementia in subjects who have Parkinson's disease (23).

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Late-life depression has been associated with both all-cause dementia and vascular dementia in the follow-up studies ranging from 1 to 17 years (24, 25). Poor social interactions (poor social network and poor participation in social activities) have been associated with dementia (26).

Stroke itself has been found to be an underlying vascular risk factor for dementia in epidemiologic follow-up studies (27, 28). The incidence of stroke has declined in Western Europe, however the incidence is still higher in Eastern Europe than in Western Europe (5, 29). High blood pressure level, smoking and poor diet are probably the most important factors behind the difference in the incidence of strokes between Eastern and Western Europe (5). High blood pressure is directly related to vascular mortality (stroke and ischemic heart disease) (reference from the year 2002) (30). A meta-analysis made specifically on Alzheimer's disease, it could not be determined whether high blood pressure had a causal relationship with the development of Alzheimer's disease (31), but there is still strong evidence based on the follow-up studies that high blood pressure increases the risk of Alzheimer's disease in later life (5).

Analyses of randomized controlled hypertension treatment trials suggest that treatment of hypertension decreases the risk of dementia (14, 15, 32). Combination blood pressure lowering drug therapy with renin-angiotensin blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) together with diuretics and/or calcium-channel antagonists seems to be the most effective means to prevent stroke and dementia (32-34). In the intervention studies the treatment of dyslipidemia (using statins), treatment of diabetes mellitus type 2 (using insulin or oral hypoglycemic agents), or treating high homocysteine levels (using oral vitamin B_6, B_{12} or folic acid) have not shown any clear favorable effect on cognitive decline in randomized controlled trials (14). Randomized controlled trials have suggested that donepezil and galantamine improves cognition in subjects with vascular dementia in the follow-up of 6 months (35).

Longer follow-up studies and randomized controlled trials are still needed to verify the effect of lifestyle and drug therapy interventions on cognitive decline (14, 15).

The treatment and prevention of vascular risk factors (high blood pressure, dyslipidemia, diabetes mellitus and smoking) and their lifestyle causes remain the most important modifiable factors in preventing cognitive decline and development of Alzheimer's disease or vascular dementia.

Dietary factors

Increased intake of vegetables has been associated with a lower risk of dementia and slower rates

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of cognitive decline in follow-up studies (16, 36).

The protective effect of vegetables and fruits is hypothesized to be based on their ability to protect against oxidative damage in the brain, which is thought to an important mechanism behind Alzheimer's disease and dementia (36-38). There are enriched concentrations of vitamin C in fruits and vegetables which acts as co-antioxidant for vitamin E (36). The nutritional composition of fruits and vegetables is not limited to vitamin E and C only, because they are also rich in dietary fibres, lycopenes, beta-carotenoids and monosaccharides (36). Therefore the protective effects of vitamin E on dementia are still unclear (36). Low dietary folate has been found to be a risk factor for dementia in cross-sectional and follow-up studies, but intervention studies do not confirm these findings (15). Both cross-sectional and longitudinal studies suggest that there is an association between cognitive impairment and vitamin D deficiency (OR 2.39, 95% CI 1.91-3.00, subjects with normal vitamin D versus subjects with vitamin D deficiency (see Figure below) (38, 39). It has been proposed that cognitive decline related to vitamin D deficiency may partly share common pathways with neurodegenerative dementias (based on impaired neuroprotection) (see Figures below) (39). Randomized controlled trials are needed to assess the impact of vitamin D on cognitive performance (39).

Cohort follow-up studies have shown that fish-derived long-chain n-3 polyunsaturated fatty acids protect against cardiac mortality and ischemic stroke (40). However, omega-3 fatty acids supplementation has not shown any effects on cognition (41).

Moderate alcohol consumption is considered to be protective against cognitive decline and dementia in follow-up studies, but non-drinkers and heavy drinkers have a higher risk for dementia (16). Evidence on coffee, tea and caffeine consumption in the prevention of dementia is still insufficient (42).

Salt reduction plays a crucial part in the prevention of cardiovascular diseases by lowering blood pressure levels in the population level. This will probably reduce the incidence of dementia from vascular origin.

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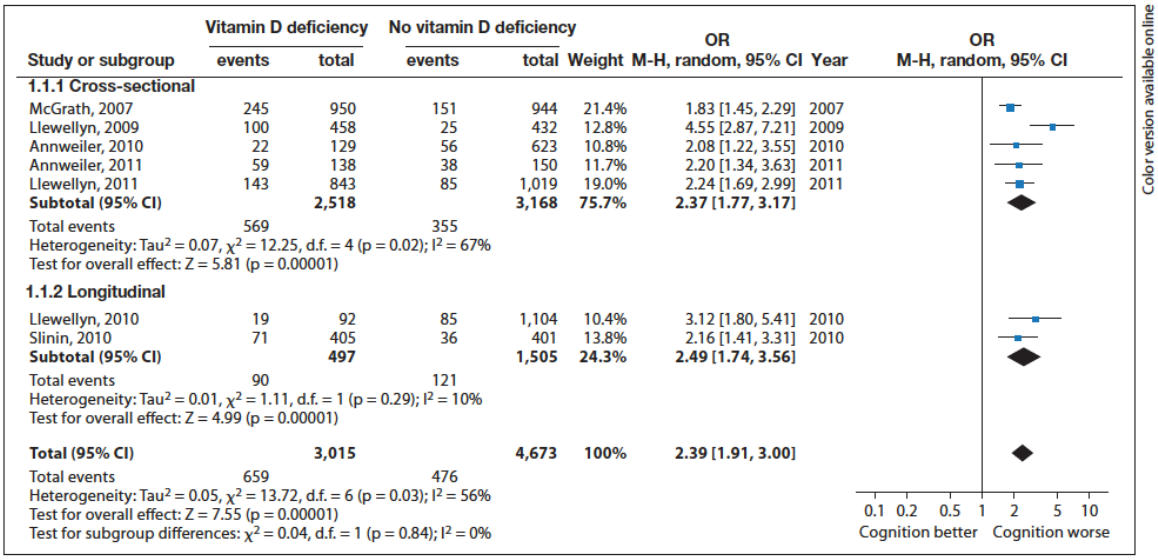

Fig. 3. Forest plot of cross-sectional and longitudinal studies assessing vitamin D concentration and cognitive impairment.

Reference of the Figure: (39)

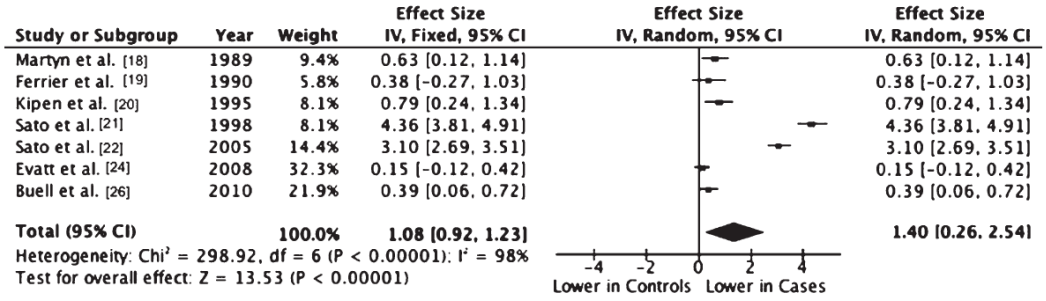

Fig. 2. Forest plot comparing serum 25-hydroxyvitamin D concentrations in cases with Alzheimer's disease and controls. The black box area is proportional to the sample size of each study, and horizontal lines correspond to the 95% confidence interval. Black diamond represents the summary value. The vertical line corresponds to an effect size of 0.0, equivalent to no difference.

Reference for the Figure: (38)

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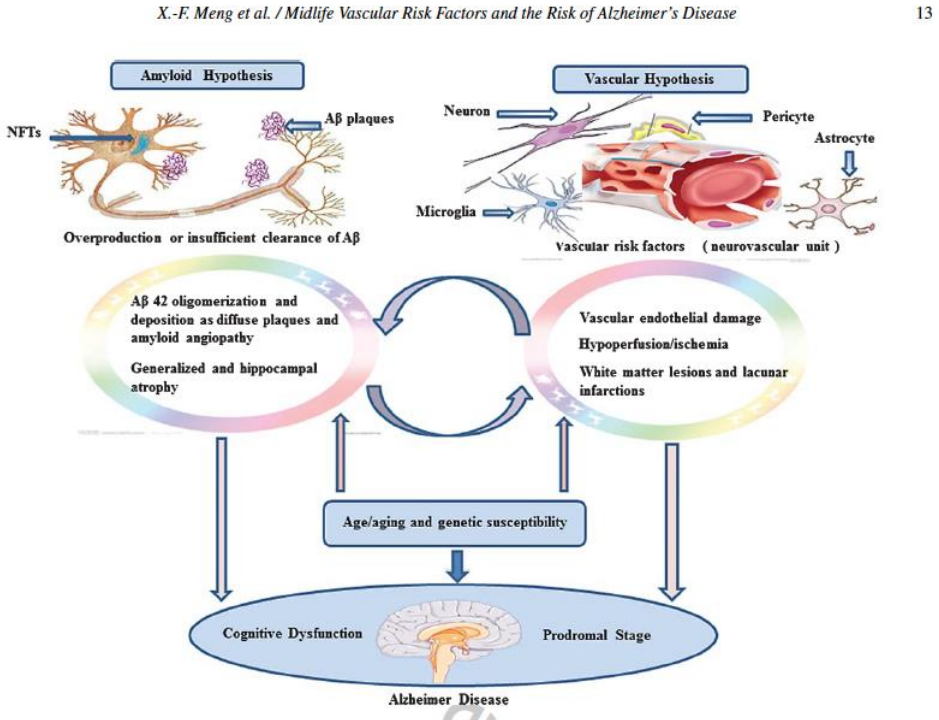

Fig. 4. This figure presents a simplified scheme, in which some of the interactions between the amyloid hypothesis and the vascular hypothesis in the etiology of Alzheimer's disease are indicated. NFT, neurofibrillary tangles; Aβ, amyloid-β.

Reference for the Figure: (18)

Parkinson's disease

Prevalence, incidence and trends

The prevalence of Parkinson's disease in Europe is 1.8% in population over 65 years (3). The standardized incidence rates are 8–18 per 100 000 person-years (3). There is a rising prevalence of Parkinson's disease with age (43).

According to the estimates of the World Health Organization's report the prevalence of Parkinson's disease contributing of the disability-adjusted life years will remain unchanged between the years 2005 and 2030 (5).

Pathogenesis and etiology

Parkinson's disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra (44, 45). The loss of dopamine-producing nerve cells causes the symptoms of Parkinson's disease (45). The diagnosis of Parkinson's disease is based solely on clinical criteria, and the clinical symptoms arise when there is about 60% damage in the dopaminergic substantia

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nigra cells (46).

The etiology of Parkinson's disease involves both genetic and environmental factors (45). Several genes have been identified causing familial Parkinson's disease (44). These genes have been identified interfering with the pathways of oxidative stress or mitochondrial dysfunction (44, 45).

Risk factors

Head injury (that results in concussion), constipation, physical inactivity, nonsmoking, the use of beta-blockers, low serum uric acid levels, anxiety and depression are associated with increased risk of Parkinson's disease in cross-sectional follow-up studies (46, 47). There is some evidence based on cross-sectional studies that exposure to toxic environmental agents (organic solvents, pesticides, rural living, well water drinking and welding) are associated with Parkinson's disease (46, 48).

Based on the follow-up studies there is a small but significant association between higher levels of education and a reduced rate of cognitive decline in subjects with Parkinson's disease (49).

Although constipation and physical inactivity are strongly associated with Parkinson's disease, they are probably preclinical or clinical manifestations of the disease and therefore do not represent genuine risk factors (see Figure below) (46). No follow-up or intervention studies have been found of the risk factors associated with Parkinson's disease (50). Therefore, no conclusions of the cause-effect relationships of the risk factors and Parkinson's disease can be drawn.

Dietary factors

The associations between Parkinson's disease and dietary factors have been examined in various cross-sectional studies, but there are not any follow-up studies available (46, 51). The associations between carotenoids, vitamin A, C, D, E, B_{12}, B_6 intake are weak or non-existent (46, 52). It has been found in cross-sectional studies that subjects with vitamin D deficiency (<50mmol/l) have a twofold risk of Parkinson's disease compared with subjects without vitamin D deficiency (51). No associations have been found between energy, protein, cholesterol and total fat intake and Parkinson's disease in cross-sectional studies (46). Dairy products intake have been associated with an increased risk and alcohol and coffee drinking with a decreased risk of Parkinson's disease (46). An inverse association was found between caffeine intake and the risk of Parkinson's disease in cross-sectional studies (53). There are no follow-up or intervention studies to prove the causal mechanism of these associations (46).

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Table 2
Quantitative synthesis of the prospective cohort studies for the 4 associations with convincing (Class I) or highly suggestive (Class II) evidence.

References	Risk factors	Number of cases	Number of primary studies	Effect sizes	Random-effects summary effect size (95% CI)	P random	95% PI	I^2	Class of association
Adams-Carr, 2015 [51]	Constipation	2625	4	RR	2.36 (2.00–2.80)	1.4×10^{-23}	1.63–3.42	0	I
Yang, 2015 [52]	Physical activity	1348	5	HR	0.66 (0.57–0.78)	3.0×10^{-7}	0.55–0.80	0	I
Noyce, 2012 [22]	Anxiety or depression	11,687	2	RR	1.79 (1.72–1.86)	8.2×10^{-188}	NE[a]	0	II
Noyce, 2012 [22]	Smoking	2623	6	RR	0.64 (0.53–0.76)	3.4×10^{-7}	0.38–1.07	63.8	II

HR: hazard ratio, NE: not estimable because less than three studies were available, PI: prediction interval, P random: P value under random-effects meta-analysis, RR: risk ratio.
[a] Only two prospective cohort studies were available.

Reference for the Figure: (46)

Multiple sclerosis

Prevalence, incidence and trends

The prevalence of multiple sclerosis in Europe is 0.1% (108 per 100000) (54). The incidence rate is 7 per 100000 (55). Multiple sclerosis is more common in women than in men, however the reason for this is not currently fully understood (54, 56).

The disability-adjusted life years related to multiple sclerosis will remain unchanged between the years 2005 and 2030 according to the World Health Organization's report (5).

Pathogenesis and etiology

Multiple sclerosis is chronic inflammatory and autoimmune disease of the central nervous system. It is characterized by deterioration of the blood brain barrier, perivascular inflammation, axonal and oligodendrocyte injury and myelin sheath degradation (57). Inflammation and demyelination occur in the white matter of the central nervous system. Both genetic and environmental factors contribute to the development of multiple sclerosis.

Risk factors

According to the meta-analyses on case-control studies there is strong evidence between premorbid head trauma and the risk for developing multiple sclerosis (58).

Furthermore, anti-EBNA IgG seropositivity (a biomarker to Epstein-Barr virus), infectious mononucleosis, and smoking have been identified to have strong associations with multiple sclerosis in cross-sectional studies (59). Tumor necrosis factor polymorphism has as well been investigated in case-control studies, but the meta-analysis does not support the role of tumor necrosis alfa 308 G/A polymorphism in the development of multiple sclerosis (60).

There are no follow-up studies or randomized controlled trials available to verify the causal

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associations between multiple sclerosis and the above mentioned risk factors. Especially intervention studies with a long follow-up time are needed to test the effect of Epstein-Barr virus vaccine in the prevention of multiple sclerosis (59).

Dietary factors

Excessive calorie intake has been suggested as a risk factor for multiple sclerosis in cross-sectional studies, as it increases the production of free radicals and levels of inflammation (57). Cross-sectional studies suggest that hypo-caloric, low-fat diets with specific vitamins, fish oil and polyphenols, may slow-down the progression of multiple sclerosis (57). Cross-sectional and follow-up studies suggest that vitamin D deficiency is thought to be a risk factor for recurrent central nervous system inflammations leading into demyelination (61). Prospective studies and randomized controlled trials are needed to confirm these findings (61).

Intervention studies and randomized controlled trials are needed to validate the effectiveness of dietary intervention (vitamin or antioxidant supplements) in the slowing-down the development of multiple sclerosis by reducing inflammation (57, 62).

Epilepsy

Prevalence, incidence and trends

The prevalence of epilepsy ranges from 0.37-0.80% (370 to 800 per 100000) in Europe (63). The incidence of active epilepsy is 40-70 per 100000 (63).

According to the World Health Organization's report the prevalence of epilepsy will remain unchanged between the years 2005 and 2030, assessed by using disability-adjusted life years (5).

Pathogenesis and etiology

According to the definition of International League Against Epilepsy, epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition (64). Available experimental evidence suggests that inflammation in the brain, caused by sterile injuries or infections may contribute to acute seizures and lead into development of epilepsy (65).

Risk factors

Risk factors for developing epilepsy include both genetic and environmental risk factors. Congenital, developmental and genetic conditions are associated with the development of epilepsy in childhood, whereas head trauma, infections and tumors can occur at any age, and lead

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into epilepsy (65). A variety of central nervous system infections (bacterial, viral, parasites (e.g. malaria), fungal and prion) can lead into status epilepticus based on case reports and cross-sectional studies (65). Follow-up studies have demonstrated a clear relationship between severity of brain injury and likelihood of developing epilepsy (risk approaching 50% in direct traumatic brain injury) (66).

Dietary factors

Based on case-control studies, there is a dose–response relationship between the amount of alcohol consumed daily and the probability of the onset of epilepsy; the relative risk rises from those who consume 4 drinks per day to those who drink 8 drinks, from 1.81 to 3.27, compared to non-drinkers (63). Based on short-term intervention studies ketogenic diet has been proposed to be one possible treatment option to reduce the frequency of epileptic seizures in children, however it should be used with caution, because the possible adverse effects of the diet and the length of the diet remains still unanswered (67).

Intervention studies are therefore needed to clarify whether therapeutic interventions could suppress the symptoms of epilepsy and also interfere with key pathogenic mechanisms (65).

Migraine

Prevalence, incidence and trends

The lifetime prevalence of migraine is 33% in women, and from 13.3% in men, in Europe (68). The incidence of migraine ranges from 2.9-22.0 in women and 1.4-5.0 in men per 1000 person-years (68).

No change in the prevalence of migraine will be expected between years 2005 to 2030, according to the World Health Organization's report, assessed by disability-adjusted life years (5).

Pathogenesis and etiology

Headache disorders are divided into primary and secondary headaches (68). Secondary disorders have an identifiable underlying cause, while in primary disorders the cause is unidentifiable (68). Migraine with or without aura is the most common form of primary headaches in patients who seek medical care for headache (68). Migraine is a chronic episodic neurologic disorder characterized by recurrent attacks of headache, often combined with symptoms of the gastrointestinal or autonomous nervous system (69).

Risk factors

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Both cross-sectional and follow-up studies have shown that smoking, high body mass index, sleep disorders, depression and stressful life events are risk factors for migraine (69). Follow-up studies suggest that the risk of stroke is increased in people with any type of migraine (relative risk 1.73, 95% CI 1.31-2.29) (69, 70). Women have a higher risk for migraine than men (69). Migraine from any cause does not increase the risk of coronary heart disease and cardiovascular disease mortality in case-control and cohort studies (71). Although there has not been found a clear relationship between migraine and hypertension, (72), the management of hypertension is important because uncontrolled hypertension may lead into worsening of headache, and into increased cerebrovascular risk, which is already higher in subjects with migraine with aura (72).

Cardiovascular risk factors may play a crucial role in the development of migraine. Therefore, the effort should be put on the prevention of strokes by focusing on modifiable traditional cardiovascular risk factors (hypertension, lipid profile, and increased risk of coronary heart disease) (69).

Dietary factors

In patient based studies the patients with migraine have reported that a particular food or drink as a trigger for migraine ranges from 7 to 44% (73). Foods and beverages that are known to trigger migraine include cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer (73, 74). Tyramine (in cheese), histamine, phenolic flavonoids, and sulfites are the trigger-mechanisms of headache (73). Red wine has high concentrations of histamine and phenolic flavonoids (73). Tyramine induces the headache by releasing norepinephrine, histamine by releasing nitric oxide from the vascular endothelium and flavonoids by releasing serotonin from platelets (73). Caffeine discontinuation is the only substance shown to cause withdrawal headache under placebo-controlled double-blind conditions (74).

Polyneuropathy

Prevalence, incidence and trends

Diabetic neuropathy is the most common type of peripheral neuropathy, affecting 1.9% of the population worldwide (75), and approximately 28% of the subjects with diabetes in Europe (overall prevalence in Europe is 2.4% (the prevalence of polyneuropathy in European population is calculated from estimate of diabetic subjects.)) (5, 76-79). There are no direct estimates of the

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trends in polyneuropathy. Because the prevalence of diabetes (an important cause of polyneuropathy) continues to increase especially in the developing countries, it is expected that there is a rising trend in the prevalence of polyneuropathies as well (5, 76).

Pathogenesis and etiology

Polyneuropathy is a damage or disease which affects multiple peripheral nerves. Peripheral neuropathy and peripheral vascular disease are the most frequent causes of foot ulcers in diabetics (76, 79). Other neuropathies include alcoholic neuropathy, autoimmune diseases, infections and genetic disorders. The etiology of diabetic polyneuropathy results from diabetic microvascular damage of arteries supplying nerve axons (76, 79).

Risk factors

There is some evidence that low-grade inflammation, that is higher C-reactive protein and IL-6 and lower IL-8, are associated with diabetic polyneuropathy (79). Based on the follow-up studies, long-term complication of diabetes mellitus is peripheral polyneuropathy, which is the most important pathway leading into foot ulcerations (79).

Dietary factors

Alcoholism, often related to neurotoxicity and vitamin B_1, B_6, B_3 (niacin), B_{12} and E deficiency can also be the underlying cause of neuropathy based on cross-sectional studies (80).

Although, the risk factors and etiology of peripheral neuropathy are still poorly understood, concentrating on traditional cardiovascular risk factors has the most important role in the prevention of polyneuropathy (79).

Screening and prevention of neurologic disorders

Mini Mental State Examination has a sensitivity between 71-92% and specificity between 56-96% in dementia screening, in primary care setting (81). There are no studies addressing the cost-effectiveness of dementia screening (81).

The clinical diagnosis of Parkinson's disease is based on the identification of the characteristics related to dopamine deficiency. Parkinson's disease is highly possible if the subject has at least two of three symptoms (tremor, hypokinesia or rigidity) (82). There has been developed several non-motor rating scales for screening of symptoms in Parkinson's disease. They screen for sleep, excessive daytime sleepiness, dysautonomia, fatigue, psychosocial aspects, depression, and quality of life (82). The unified Parkinson's disease rating scale is the gold standard of motor measurement

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in Parkinson's disease and it is effective in clinical management and research (82).

The screening and diagnosis of multiple sclerosis is based on McDonald criteria (based on anamnesis and status of the patient, cerebrospinal fluid assessment (leukocytes, IgG, and magnetic resonance imaging of the central nervous system) (83). The sensitivity and specificity in the diagnosis of McDonald's criteria are high (83).

There have been developed validated questionnaires to screen epilepsy in the populations with good sensitivity and specificity (94% and 99%) (84).

Validated Migraine Screen Questionnaire has been proven to be efficient in detecting hidden migraine in primary care setting, with sensitivity of 0.97, specificity of 0.82(85). Nausea, disability and photophobia (OR 3.97, 3.82 and 3.30) are the best predictors of a screening diagnosis of migraine (68).

There are no studies which would recommend screening of diabetic polyneuropathy at population level, however studies support the screening of high risk patient groups, such as diabetic patients (86).

Cardiovascular risk factors have a crucial role in the development of neurologic disorders (dementia, polyneuropathy, and migraine) (75, 87). Therefore effort should be put on the screening of the underlying cardiovascular risk factors, rather than on the screening of individual neurologic disorders. A comprehensive cardiovascular risk screening combined with the risk management would be the most beneficial in reducing prevalence and incidence of neurologic disorders in the future (75, 87). Building community-based screening programs to address the leading risk factors is essential (87). The screening should include hypertension, excessive use of alcohol, physical inactivity, diabetes and obesity, dietary salt intake, and use of tobacco products (87). There is as well evidence that secondary prevention of mild cognitive impairment is possible with lifestyle interventions (88).

Overarching topics

Ageing and neurologic disorders

Old age is a risk factor for Alzheimer's. However, Alzheimer's disease is not inevitable the outcome of aging (2). The prevalence of dementia will continue to increase along with the aging population in Europe, while the overall population incidence is expected to diminish due to rapid declines in the ischemic heart disease and stroke in the Western countries (5, 9). There is a steady increase in

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the prevalence of Parkinson's disease with age across all regions of the world (43). There is a peak of incidence of Parkinson's disease occurring between the ages of 70 and 79 (43). The usual onset of multiple sclerosis is at early adult life, average age of 30 years (58). The highest incidence of epilepsy is under age 1 or over 60 (50% of the cases) (63). The overall prevalence of migraine is highest between ages 25 and 55, and the peak in the prevalence is seen especially in females (68). Polyneuropathy related to diabetes is more common in older persons (79).

Gender and neurologic disorders

Almost two-thirds of the individuals diagnosed with Alzheimer's disease are women according to recent study, but some studies have not found any difference between men and women (89). Parkinson's disease is more common in men than in women with the ratio of 2:1 (90). The prevalence ratio of multiple sclerosis is 3.5:1 (women to men) (54, 56). The prevalence of migraine is four times higher in women than in men (69). The overall incidence of epilepsy is slightly higher in men than in women (91). There are no studies of possible gender differences of polyneuropathy.

Geographical differences of neurologic disorders

Dementia (2.04%) and Parkinson's disease (0.30%) account a higher share of the disability adjusted life years in Europe than in other regions of the world (average 0.75% and 0.11%) (5). Multiple sclerosis accounts for 0.20 % of disability adjusted life years in Europe, where as the the worldwide average is 0.10% (5).The frequency of multiple sclerosis increases with distance from the equator in both hemispheres (Less common among non-whites. Infections and living conditions have an important effect on the frequency) (5).

8.4 SUMMARY

Estimating the prevalence and incidence, and evaluating the risk factors of neurologic disorders is challenging for several reasons. They are a diverse group of diseases with different etiology and origin. Manifestations of the neurologic disorders vary. In addition, the prevalences of some neurologic disorders were not directly available, but were calculated estimates. There was as well some uncertainty with risk ratios of neurologic disorders associated with certain risk factors, because some studies were made on smaller populations or specific groups of subjects. Studies

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included in this report may have concentrated to report new potential risk factors of neurological disorders. Therefore there may be an underreporting bias of the essential risk factors of neurological disorders. In this review the focus was on the most common neurologic diseases including dementia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, migraine and polyneuropathies. Dementias, Parkinson's disease, multiple sclerosis and migraine contribute together approximately 2% of the global burden of disease (5). The prevalences of neurologic disorders are presented in Table 1, Prevalence of neurologic disorders in Europe. The summary of risk ratios of neurologic disorders and risk factors are presented in Table 2, Some important risk factors for neurologic disorders.

Alzheimer's disease is the most common neurodegenerative disorder and a leading cause of dementia in the elderly. Parkinson's disease is the second most common neurodegenerative disorder. Studies have shown that both Alzheimer's disease and vascular dementia share common risk factors. Several factors have been associated with dementia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, polyneuropathies and epilepsy. However, long-term follow-up studies on the risk and protective factors of neurological disorders are limited, and sufficiently powered randomized controlled trials to test the hypotheses have not been conducted.

Future trends of neurologic disorders

Dementia contributed between 1990-2010 worldwide 6.4% of combined burden of neurologic diseases assessed in disability adjusted life years (87). As the average life expectancy increases, the prevalence of dementia is expected to increase as well. However, World Health Organization has estimated that the incidence of dementia will decline in high-income countries (5). In general, World Health Organization has estimated that neurological disorders, assessed by using disability-adjusted life years will increase approximately 12% between years 2005 and 2030 (see figure below) (5). The prevalence of dementias assessed in disability-adjusted life years will increase, while the prevalences of Parkinson's disease, multiple sclerosis, migraine and cerebrovascular diseases remain mostly unchanged (5).

Cost of neurologic disorders

It has been estimated that the total annual costs of all brain disorders in Europe are approximately 798 000 million euros, of which dementia accounts for 105 200, Parkinson's disease 13 900,

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multiple sclerosis 14 600, epilepsy 13 800, and migraine 18 500 million euros (92). Of the neurologic disorders, dementia plays quantitatively the most important role. The costs of dementia are high (5). Detailed studies of the costs of dementia in Europe are scarce. In the United Kingdom the estimated direct formal care costs (health, social and community care) of dementia are 13000 US$ per person per year (5). It has been estimated that caretakers spend approximately 3 hours per day taking care of the most severely affected patients with dementia (5).

Table 2.4 Number of DALYs for neurological disorders and as percentage of global DALYs projected for 2005, 2015 and 2030

Cause category	2005		2015		2030	
	No. of DALYs (000)	Percentage of total DALYs	No. of DALYs (000)	Percentage of total DALYs	No. of DALYs (000)	Percentage of total DALYs
Epilepsy	7308	0.50	7419	0.50	7442	0.49
Alzheimer and other dementias	11078	0.75	13540	0.91	18394	1.20
Parkinson's disease	1617	0.11	1762	0.12	2015	0.13
Multiple sclerosis	1510	0.10	1586	0.11	1648	0.11
Migraine	7660	0.52	7736	0.52	7596	0.50
Cerebrovascular disease	50785	3.46	53815	3.63	60864	3.99
Poliomyelitis	115	0.01	47	0.00	13	0.00
Tetanus	6423	0.44	4871	0.33	3174	0.21
Meningitis	5337	0.36	3528	0.24	2039	0.13
Japanese encephalitis	561	0.04	304	0.02	150	0.01
Total	**92392**	**6.29**	**94608**	**6.39**	**103335**	**6.77**

Reference for the figure: (5)

On the gaps in available evidence

Currently, there is not enough evidence about the cause-effect relationship of risk factors for neurologic disorders, although in many studies strong associations have been found. Most studies have been made in a cross-sectional setting. Only a few longitudinal studies have been done. The data is scarce on intervention studies, which would be the best way to assess effects of modifications in the observed risk factors on the neurological disorders and their symptoms. However, large-scale primary prevention studies are needed to assess reliably the true causal relationships. No direct estimate of the prevalence of polyneuropathy was found in the European population.

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Taking action on preventive measures

Same risk factors can be identified across several neurologic disorders. Cardiovascular risk factors play an important role in the development and manifestations of dementia, polyneuropathy, and migraine. Dementias remain the most common neurologic disorders in the future. However, it takes decades before the clinical manifestations of dementias occur. Therefore, the primary prevention and treatment of vascular risk factors at early stage plays the most important role. The actions on the population level include primary intervention and treatment of cardiovascular risk factors and diseases by lifestyle changes (healthy diet (low-salt, high fruit and vegetable and low-saturated fat diet enriched with unsatured fats, sufficient physical activity avoidance of smoking and excessive alcohol consumption), and by appropriate choices of antihypertensive medication (combination blood pressure lowering drug therapy with renin-angiotensin blockers together with diuretics and/or calcium-channel antagonists). The effect of lipid-lowering drugs in the prevention of dementia and other neurological disorders has not been demonstrated. Subjects with APOE ε4 (allele) should be identified as being in a high risk in developing dementia. Reducing head traumas are is the common modifiable risk factor in the prevention of developing Parkinson's disease, epilepsy, and multiple sclerosis.

8.5 CONCLUSIONS

Neurological disorders and especially dementias have usually multifactorial etiology and pathogenesis. Dementias with mixed pathology are common, meaning that they include characteristics of both Alzheimer's disease (amyloid plaques and neurofibrillary tangles) and vascular dementia (frequent oxygen disturbances caused by strokes) (5). Vascular damage can be a cofactor accelerating the symptoms in subjects who already have Alzheimer's disease (5). The prevalence and incidence of neurologic diseases are increasing worldwide because of the increasing number of aging population. Therefore, a thorough knowledge of etiology, risk factors, prevention and treatment of these disorders is highly important. According to the present knowledge, the efforts and actions should be focused on the prevention and treatment of cardiovascular risk factors and their complications, which have a great impact on the development of neurologic disorders (especially dementias). Cardiovascular diseases account for the major part

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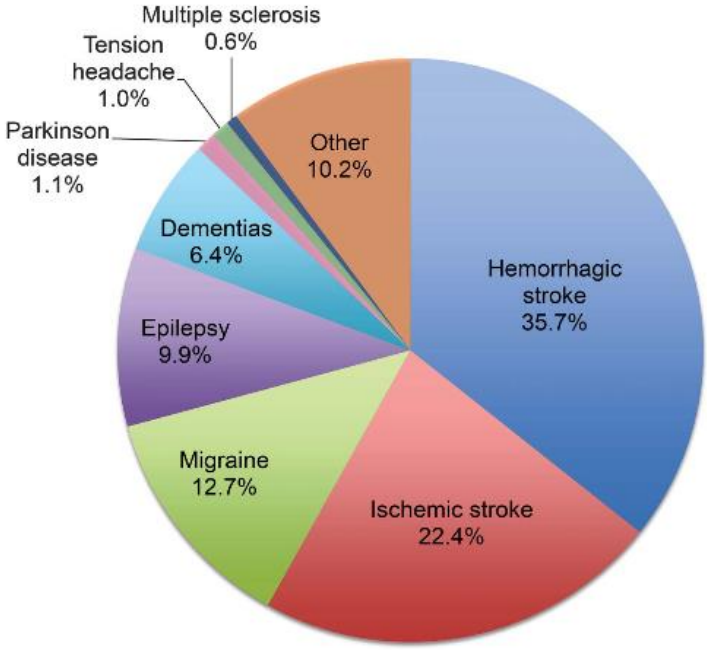
of the disability-adjusted life years (see Figure below (87).

Figure Contribution of specific causes to the combined burden of neurologic disorders and cerebrovascular disease (percent of total disability-adjusted life-years)



Source: GBD 2010 Results by Cause 1990-2010. Available at: http://ghdx.healthmetricsandevaluation.org/global-burden-disease-study-2010-gbd-2010-data-downloads.

Reference for the figure: (87)

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Table 1. Prevalence of neurologic disorders in Europe.

Neurologic disorder	Prevalence in Europe (%)
Dementia	6.4
Alzheimer's disease	4.4
Vascular dementia	1.6
Parkinson's disease	1.8
Multiple sclerosis	0.1
Epilepsy	0.4-0.8
Migraine, men	13.3
Migraine, women	33
Polyneuropathy*	1.9 (2.4)

*Global prevalence. Calculated prevalence of polyneuropathy in European population is calculated from estimate of diabetic subjects (in parentheses).

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Table 2. Some important risk factors for neurologic disorders.

	Risk factor			
	diabetes	**vitamin D**	**dyslipidemia**	**obesity**
Dementia	OR 1.32, 1.13-1.55 (18)	OR 2.39, 1.91-3.00 (38, 39)	OR 1.70, 1.11-2.62 (18)	OR 1.69, 1.17-2.43 (18)
	homocysteine	**depression**	**stroke**	**high BP**
	OR 2.13, 1.22-3.73 (18)	OR 2.03, 1.73-2.38 (25)	RR 1.59, 1.25–2.02 (28)	OR 1.37, 1.06-1.75 (18)
	apoE ε4			
	OR 2.83, 1.61-4.97 (11)			
	constipation	**physical activity**	**depression**	**smoking**
Parkinson's disease	OR 2.36, 2.00-2.80 (46)	HR 0.66, 0.57-0.78 (46)	OR 1.79, 1.72-1.86 (46)	OR 0.64, 0.56-0.76 (46)
	head trauma	**smoking**	**mononucleosis**	**Ebstain-Barr virus**
Multiple sclerosis	OR 1.27,1.1-1.44 (58)	OR 1.52, 1.39-1.66 (59)	OR 2.17, 1.97-2.39 (59)	OR 4.46 (3.26-6.09) (59)
	excessive alcohol use	**traumatic brain injury**		
Epilepsy	RR 3.27, 2.52-4.26 (63)	RR 17.0, 12.3-23.6 (66)		
	stroke	**obesity**	**stress and depression**	**caffeine**
Migraine	RR 1.73*, 1.31-2.29 (69, 70)	RR 2.2, 1.5-3.2 (74)	OR 2.73, CI NA (74)**	OR 1.50, CI NA (74)
	excessive use of alcohol	**diabetes**	**high (> 0.90) ankle brachial index**	
Polyneuropathy	NA	NA	RR 1.25, 1.05-1.47 (79)	

References are in parenthesis. BP, blood pressure; CI, confidence interval; HR, hazards ratio; NA, not available; OR, odds ratio; RR, relative risk. *Migraine is a risk factor for stroke. ** Calculated from prevalences.

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