Dietary Factors and Hypertension in Adult Women in France and Mexico

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ABSTRACT

Background: Hypertension is the major risk factor for cardiovascular disease, the principal cause of mortality in the world, representing a significant health burden and is associated with both cardiovascular and renal outcomes. Modifiable risk factors, such as the diet, have been identified for hypertension; nonetheless some aspects of the role of the diet remain unclear.

According to the evidence antioxidant intake could be an alternative against the detrimental effects of oxidative stress, thus to prevent hypertension. However, inconsistent results have been observed when the relation between the intake of individual antioxidants and hypertension risk has been assessed. The evaluation of individual antioxidants may not reflect the total antioxidant power from the diet as well as the possible synergistic effects of antioxidants, resulting in an inaccurate measure of antioxidant consumption.

Dairy products have a complex nutritional content and are an important source of energy, protein, and can contribute significantly to meeting the required intakes of calcium, magnesium, selenium, riboflavin, and vitamin B12. The bioavailability of calcium from dairy products is high compared with other foods in the diet. Because of this, dairy products are widely consumed in different populations worldwide. However, recently, due to the appreciable amount of sodium and saturated fat in dairy products, its consumption has been questioned, as both nutrients have been associated with cardiovascular disease. However, the studies assessing the association between dairy products and hypertension have shown inconsistent results.

Objectives: Therefore, the main objectives of this thesis were to evaluate the role and impact of dietary factors, particularly, the dietary total antioxidant capacity (TAC), and the consumption of dairy products and the risk of hypertension using data from both the French E3N and Mexican MTC cohort studies.

Materials and Methods: For this work, I conducted three secondary analyses from data of two similar studies of women. The first study was the French E3N study, and included 98 995 teachers aged 40 - 65 years at the beginning of the study in 1990. The second, the Mexican Teachers' Cohort study, is a prospective cohort of 115 314 teachers aged 25 years or older, initiated in 2006 - 2008. I used Cox regression models to estimate Hazard Ratios (HR) and 95% Confidence Intervals (CI), data were analysed with the Statistical Analysis Systems software package version 9.4 (SAS Institute, Cary, NC, USA).

Results: Dietary total antioxidant capacity (TAC) was inversely associated with risk of hypertension in the E3N cohort study, after adjustment for the main risk factors of hypertension. The strength and direction of the association was consistent in fruit and vegetable consumers below the median population value. The spline regression curve demonstrated a steep inverse dose-effect relationship between dietary TAC and risk of hypertension, then leveled off, suggesting a maximal effect of TAC. In addition, the results suggest no association between total dairy intake or each type of dairy product

consumed and hypertension risk in both the E3N and MTC cohort studies. Only processed cheese consumption was directly associated with hypertension. These are rich in lipids, sodium and sugar but has a lower content of proteins, magnesium and calcium, potential protective nutrients against hypertension.

Conclusions: This research emphasizes the important and complex role that the diet plays in the development of hypertension. It confirms that hypertension is largely preventable and also illustrates the impact of a healthy lifestyle in the etiology of hypertension. Dietary TAC was inversely associated with the risk of hypertension. On contrary, dairy product was not associated to hypertension, the usefulness of replicating analyses in different populations where the patterns of consumption of foods and their correlated maybe different, thus the results are likely robust. Therefore, hypertension prevention should aim to reduce the impact of modifiable risk factors, such as the diet, by promoting varied and balanced diets.

Keywords: Hypertension, women, diet, nutrition, dietary total antioxidant capacity, dairy products, lifestyle, cohort, epidemiology

RÉSUMÉ

Introduction : L'hypertension est un facteur de risque majeur des maladies cardiovasculaires et rénales. Il s'agit d'une cause majeure de mortalité dans le monde représentant un enjeu majeur de santé publique. Les facteurs de risque modifiables comme l'alimentation ont été identifiés néanmoins certains aspects du rôle de l'alimentation ne sont pas clair.

La prise d'antioxydants pourrait être une alternative contre les effets délétères du stress oxydant car ils ont un effet protecteur dans le développement de l'hypertension. Cependant des résultats discordants sont observés pour la relation entre la consommation d'antioxydants et l'hypertension. L'évaluation des antioxydants individuelle pourrait ne pas refléter la charge antioxydante totale de l'alimentation ainsi que la possible synergie ou les interactions.

Les produits laitiers ont un contenu nutritionnel complexe et sont une source importante d'énergie, de protéine et peuvent contribuer significativement à respecter les besoins en calcium, magnésium, sélénium, riboflavine et en vitamine B12. La biodisponibilité du calcium venant des produits laitiers est élevée en comparaison à d'autres aliments. De ce fait, les produits laitiers sont largement consommés dans différentes populations à travers le monde. Cependant, du fait de la quantité de sodium et d'acides gras insaturés dans les produits laitiers leur consommation est remise en question. En effet ces nutriments ont été associés aux maladies cardiovasculaires. Cependant, les études récentes qui évaluent l'association entre les produits laitiers et l'hypertension montrent des résultats discordants.

Objectif : L'objectif principal de cette thèse est d'évaluer le rôle et l'impact des facteurs alimentaires, en particulier, la capacité antioxydante totale et la consommation de produits laitiers et le risque d'hypertension en utilisant des données de la cohorte E3N et la cohorte mexicaine MTC.

Matériels et Méthodes : Pour ce travail, j'ai conduit trois analyses secondaires venant de données de deux études similaires sur des femmes. La première étude est l'étude française E3N incluant 98 995 enseignants âgés de 40 à 65 ans au début de l'étude en 1990. La seconde cohorte « the Mexican Teachers » est une cohorte prospective de 115 314 enseignants âgées de 25 ans et plus, initié en 2006 - 2008. Le modèle de Cox a été utilisé et les données ont été analysées à l'aide du logiciel SAS version 9.4 (SAS Institute, Cary, NC, USA).

Résultats : La capacité antioxydante totale (CAT) a été inversement associé au risque d'hypertension dans la cohorte E3N, après ajustement sur les principaux facteurs de risque de l'hypertension. La force et la direction de l'association est cohérent chez les consommateurs de fruits et légumes en dessous de la médiane de la population. La courbe de regression en spline a montré une forte relation dose effet inverse entre la CAT alimentaire et le risque d'hypertension pour ensuite se stabiliser, suggérant un effet maximal de la CAT. De plus, les résultats ne suggèrent pas d'association entre la

consommation totale ou chaque type de produit laitier consommé et de risque d'hypertension.

Conclusions : Ces recherches mettent en évidence le rôle important et complexe de l'alimentation dans le développement de l'hypertension. Elles confirment que l'hypertension est largement évitable et illustre l'impact d'un mode de vie sain dans l'étiologie de l'hypertension. Comme l'étude a été répliquée dans deux populations différentes, les résultats sont robustes. Cependant la prévention de l'hypertension devra aider à réduire l'impact des facteurs de risque modifiables comme l'alimentation en promouvant une alimentation variée et équilibrée.

Keywords: Hypertension, women, diet, nutrition, dietary total antioxidant capacity, dairy products, lifestyle, cohort, epidemiology

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SCIENTIFIC PRODUCTION

- **Articles accepted for publication**

Villaverde P, Lajous M, MacDonald CJ, Fagherazzi G, Bonnet F, Boutron-Ruault MC. High dietary total antioxidant capacity is associated with a reduced risk of hypertension in French women. Journal of hypertension. 2019 ;18(1) :31.

- **Articles under review**

Villaverde P, Lajous M, MacDonald CJ, Boutron-Ruault M, Bonnet F. Dairy consumption and risk of hypertension in French women.

Villaverde P, Bonnet F, Flores M, Boutron-Ruault M, López-Ridaura R, Lajous M. Dairy and types of cheese consumption and risk of hypertension in Mexican women.

- **Scientific communication**

Bonnet F, Villaverde P, Fagherazzi G, Lajous M, Boutron Marie-Christine. Total dietary antioxidant capacity and the risk of Hypertension in French women. French Hypertension Society; Oral presentation. Paris, December 2016.

Bonnet F, Villaverde P, Fagherazzi G, Lajous M, Boutron Marie-Christine. Types of cheeses and risk of hypertension. French Hypertension Society; Oral presentation. Paris, December 2017.

Villaverde P, Bonnet F, Fagherazzi G, Lajous M, Boutron Marie-Christine. Total dietary antioxidant capacity and the risk of hypertension. Francophone Day of Nutrition; Poster presentation. Paris, Nantes December 2017.

Villaverde P, Bonnet F, Lajous M, Boutron Marie-Christine. Types of cheeses and risk of hypertension. Francophone Day of Nutrition. Poster presentation. Nantes, December 2017.

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LIST OF ABBREVIATIONS

ACE Angiotensin converting enzyme
ATP Adenosine triphosphate
BMI Body mass index
CESP Centre de recherche en Épidémiologie et Santé des Populations
CI Confidence intervals
CNIL Commission Nationale Informatique et Libertés
CIQUAL Centre d'Information sur la Qualité des Aliments
CRP C-reactive protein
CLA Conjugated linoleic acid
CVD Cardiovascular disease
DALYS Loss of disability-adjusted life-years
DBP Diastolic Blood pressure
E3N Etude Epidémiologique auprès de femmes de l'Education National
EPIC European Prospective Investigation into Cancer and Nutrition
ENSANUT Encuesta Nacional de Salud y Nutrición
ENNS Étude Nationale Nutrition Santé
ESTEBAN Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition
FA Fatty acids
FAO Food and Agriculture Organization of the United States
FRAP Ferric Reducing-Antioxidant Power
FFQ Food Frequency Questionnaire
HDL High density lipoproteins
HAT Hydrogen atom transfer
HTA Hypertension
HR Hazard ratio
IHME Institute for Health Metrics and Evaluation
IARC International Agency for Research on Cancer
INSERM Institut National de la Santé et de la Recherche Médicale
INCA 2 Étude individuelle nationale des consommations alimentaires 2
INCA 3 Étude individuelle nationale des consommations alimentaires 3
INSP Instituto Nacional de Salud Pública
JNC7 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDL Low-density lipoproteins
LIA Laboratoire International Associé
MGEN Mutuelle Générale de l'Education Nationale
MMHG Millimeters of mercury
MUFA Monounsaturated fatty acid
MTC The Mexican Teacher´s Cohort
NADPH Nicotinamide adenine dinucleotide phosphate
ORAC Oxygen radical absorbance capacity
PNNS Programme National Nutrition Santé

PMO Pension Management Organizations
RAS Renin angiotensin system
RCT Randomized controlled trials
RNS Reactive nitrogen species
ROS Reactive oxygen species
RONS Reactive oxygen and nitrogen species
SET Single electron transfer
SES Socioeconomic status
SBP Systolic Blood Pressure
SFA Saturated fatty acids
TAC Total Antioxidant Capacity
TIP Teacher´s Incentives Program
TRAP Total Radical Absorbance Parameter
TEAC Trolox equivalent antioxidant capacity
USDA United States Department of Agriculture
WHO World Health Organization

INTRODUCTION

INTRODUCTION

Hypertension is a multifactorial disease with a hereditary component because of the genetics but also due to the learning of lifestyle factors specific to the family. This is a major cause of disease burden expected to rise in the future due to the aging of the population. This disease is also considered the first risk factor for cardiovascular disease which are the leading cause of mortality worldwide. Several cardiovascular and renal outcomes such as ischemic heart disease, cerebrovascular disease and chronic kidney disease have been associated with hypertension.

This thesis considered hypertension as a disease which is largely preventable and modifiable risk factors including the diet, have been identified. Nonetheless, among dietary factors, the only considered as causal for hypertension nowadays, is sodium consumption. The effect of some dietary factors on hypertension risk remains unclear, and forms the basis for this investigation. Identifying and studying the potential factors associated with hypertension is key for its prevention. It is a challenge for hypertension prevention to decrease the impact of these risk factors including diet.

This joint international supervision PhD (co-tutelle) was conducted between the Université Paris Saclay-France and National Institute of Public Health-Mexico (INSP) within the framework of the International Associated Laboratory (LIA) between two research laboratories in both countries. The French laboratory was at the Center of Research in Epidemiology and Population Health in the team “Generations and Health” (Institut National de la Santé et la Recherche Médicale-INSERM, U1018) directed by Dr. Gianluca Severi; and the Mexican laboratory was at the Center for Research on Population Health, in the team the “Mexican Teacher's Cohort” (from INSP) directed by Dr. Martin Lajous.

This manuscript presents the research work performed on the relation between dietary total antioxidant capacity and the risk of hypertension in the French E3N cohort study, as well as the investigation of the relation between dairy products and the risk of hypertension using both French and Mexican data. This thesis is divided into 4 parts. The first chapter presents a review of the literature on hypertension in general, as well as background on total antioxidant capacity and dairy products. Then, the objectives of this work will be presented. Next, I will describe the material and methods used. In the following three chapters, I will report, in detail, the results of the research performed during my PhD, and finally, the summary of the findings and the conclusion will be described.

CHAPTER I: LITERATURE REVIEW

This chapter is divided into four sections. The first part describes the epidemiology of hypertension. The second includes: a general background on hypertension, its pathophysiology, risk factors, and the relation between oxidative stress and hypertension. The third explains the details surrounding antioxidant capacity of the diet, methods for measurement, and the main food antioxidant contributors. Finally, the last part describes dairy products, their importance, consumption, nutritional content, and their relation with hypertension.

1. HYPERTENSION EPIDEMIOLOGY

1.1. Hypertension as a risk factor

Cardiovascular disease (CVD), has been the leading cause of death around the world for the last 26 years. This disease was responsible for 278 deaths per 100 000 in 2016 (1). Hypertension is the main risk factor for CVD and global mortality, followed by diet (**Figure 1**) (1). Globally, hypertension is a leading risk factor disability and illness (1). Elevated blood pressure (2) represents 7.6 million premature deaths (13.5% of all deaths) and 92 million years lived with disability or illness (DALYs, 6.0% of the global total). Also, 54% of strokes cases and 47% of ischaemic heart disease are attributed to hypertension (2).

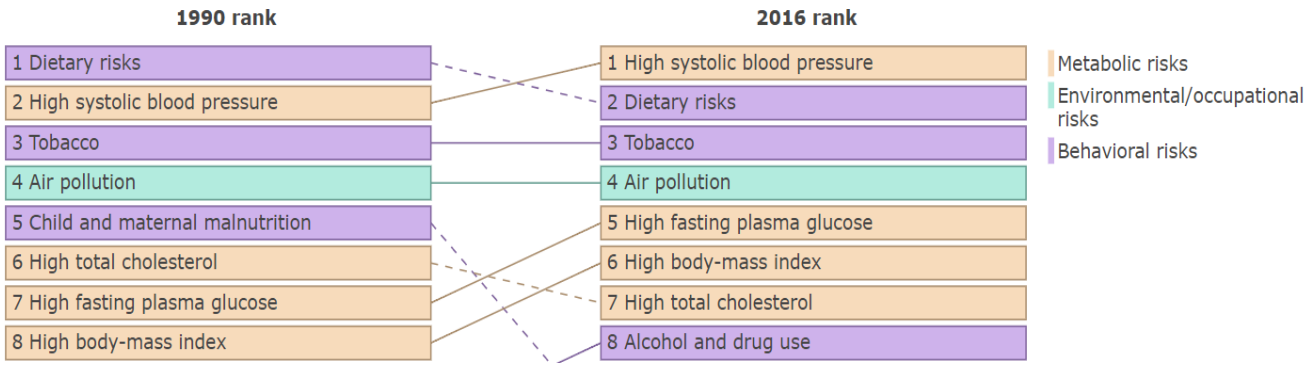


Figure 1 Global mortality risk factors worldwide, 1990-2016. (Both sexes, age standardized, death per 100 000)
Source: IHME.

1.2. Hypertension around the World

In 2010, a report including 135 population-based studies of 968 419 adults, estimated the regional and global numbers of hypertensive adults (3). The prevalence of hypertension in adults was 31.1% (equivalent to 1.39 billion people) there were no differences between men (31.9%; 95% CI 30.3 - 33.5%) and women (30.1%; 95% CI 28.5 - 31.6%) (3). The prevalence of hypertension reveals important disparities. Most of hypertensives live in low and medium income countries and a large proportion of them are undiagnosed and untreated (3). Also, high-income countries have a lower prevalence (28.5%) of hypertension than low-income countries (31.5%) (3). As we can observe in **Figure 2**, the map is shaded according to prevalence, from light for countries with lower prevalence to dark for countries with higher prevalence. In the last years (2000 - 2010), an increase of 5.2% in the prevalence of hypertension has been observed, but mainly in countries with medium and low income (7.7%) (3). In contrast the prevalence has decreased in high-income countries (2.6%). Countries with lower income also have a higher cardiovascular mortality rate attributable to hypertension (79 vs 215 deaths per 100 000), as well as years lived with disability (DALYS) (3) (**Figure 2**). Furthermore, the prevalence is expected to increase, mainly due to the aging population, as well as changes in lifestyle, and consequently, the mortality for CVD. Thus, the first leading cause of death globally in 2030 is projected to be cardiovascular disease followed by cancer (**Figure 3**) (4).

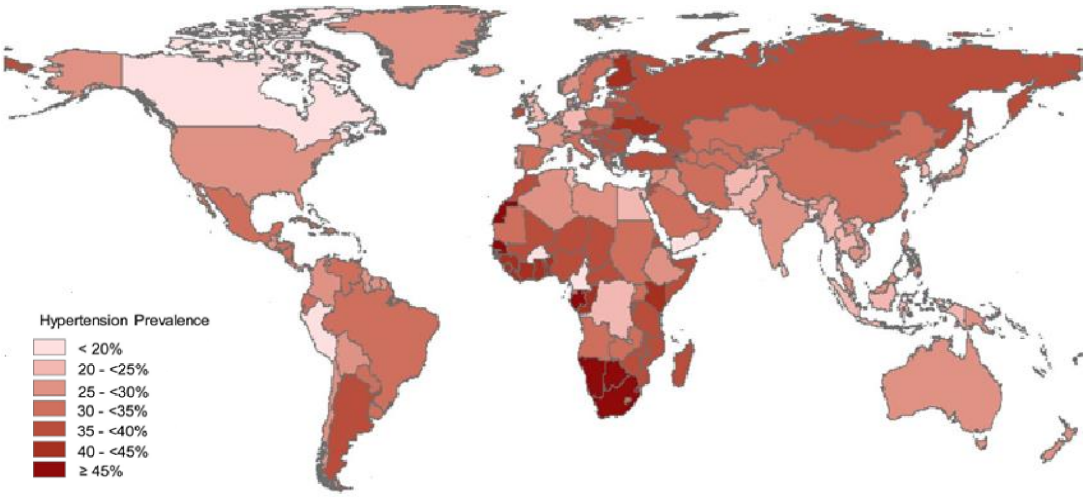


Figure 2. Worldwide age and sex standardized hypertension's prevalence rate in adults 20 years and older by country in 2010.
Source: Mills KT et al., Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016; 134(6):441-50.

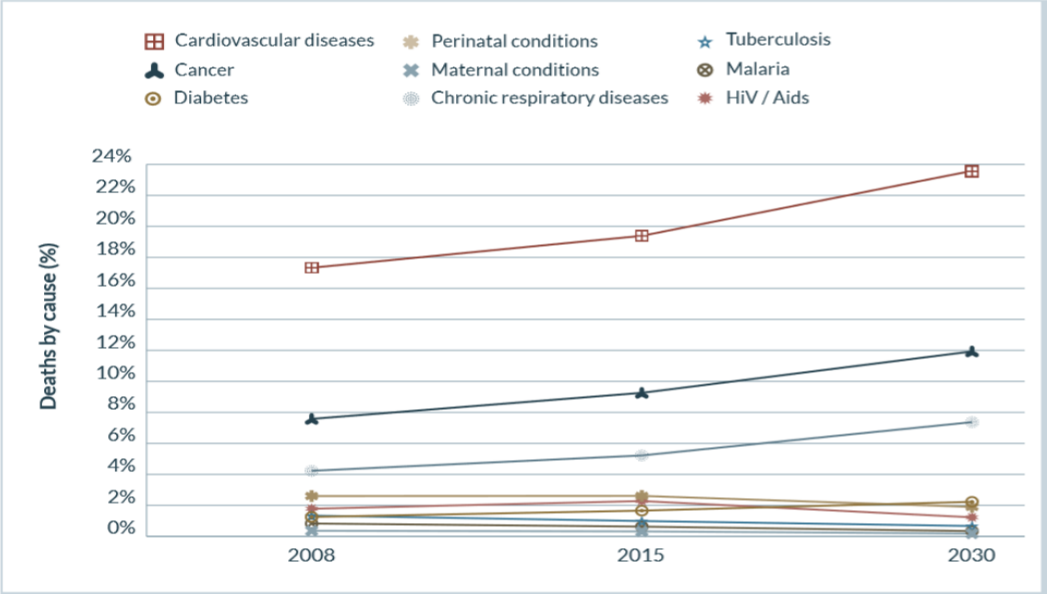


Figure 3. Projected mortality trend from 2008 to 2030 for major non – communicable diseases and communicable diseases.
Source: The Global Burden of Disease, 2004 update. Geneva, World Health Organization, 2008.

1.3. Hypertension's Epidemiology in France

In 2015, according to the National French ESTEBAN study, the prevalence of hypertension was 30.6% (95% CI 28.1 - 33.2) (5), diagnosed through medical evaluation and defined as diastolic blood pressure (DBP) ≥ 90 mmHg and systolic blood pressure (SBP) ≥ 140 mmHg. The prevalence of hypertension increased significantly with age, from 6.3% among adults aged 18 - 34 years to 67.8% among adults aged 65 - 74 years, with prevalence higher in men than in women for all age groups (36.5% vs. 25.2%) (**Table 1**).

Only half of the participants knew that they had hypertension, this proportion was more important in women than in men (62.9% vs. 50.1%). Among individuals with hypertension, almost half received treatment (47.3%) and among those treated, only 55% controlled their blood pressure (**Table 1**). Women, regardless of age, had better control of their blood pressure levels.

Table 1. Hypertension prevalence, treatment and control. Esteban Study 2015.

	18-34 years	35-44 years	45-54 years	55-64 years	65-74 years	18-74 years
Men						
Measure in the year (%)	64.6	74.6	88.1	96.1	93.0	82.2
HTA prevalence* (%)	11.7	17.0	36.6	58.7	73.1	36.5
Known HTA* (%)	19.1	35.9	42.3	58.9	57.5	50.1
Known and treated HTA * (%)	**	91.6	55.3	75.3	85.2	74.5
Treated HTA* (%)	**	39.4	25.5	52.2	65.6	45.9
Treated and controlled HTA (%)	**	48.2	48.4	48.1	31.4	41.4
Women						
Measure in the year (%)	83.5	79.9	87.1	87.4	95.5	85.8
HTA prevalence* (%)	1.5	9.1	21.2	48.3	62.1	25.1
Known HTA* (%)	35.4	43.5	49.0	69.0	67.4	62.9
Known and treated HTA * (%)	**	55.9	65.6	70.7	73.9	70.6
Treated HTA* (%)	35.4	31.8	41.3	52.6	53.2	49.1
Treated and controlled HTA (%)	**	54.8	58.2	63.8	58.3	60.1
Total						
Measure in the year (%)	74.4	77.3	87.6	91.5	94.3	84.1
HTA prevalence* (%)	6.3	12.9	28.6	53.2	67.8	30.6
Known HTA* (%)	21.1	38.6	44.8	63.7	61.9	55.5
Known and treated HTA * (%)	20.2	77.2	59.6	72.9	79.7	72.6
Treated HTA* (%)	4.3	36.7	31.5	52.4	60.0	47.3
Treated and controlled HTA (%)	**	50.3	53.3	55.6	42.0	49.6

* Hypertension (HTA): SBP ≥140 mmHg or DBP ≥90 mmHg or reimbursement of at least one antihypertensive treatment.
Known HTA: proportion of hypertensives reporting having knowledge of their hypertension.
Known and treated HTA: proportion of hypertensives treated among those who reported having knowledge of their pathology.
Treated HTA: proportion of hypertensives treated among hypertensives.
Controlled HTA: proportion of controlled hypertensives among treated hypertensives.
** Insufficient sample. NS : not significant.
Source : Perrine AL, Lecoffre C, Blacher J, Olié V. L'hypertension artérielle en France : prévalence, traitement et contrôle en 2015 et évolutions depuis 2006. Bull Epidémiol Hebd. 2018;(10) :170-9.

1.4. Hypertension's Epidemiology in Mexico

In Mexico, according to the National Health and Nutrition Survey (ENSANUT, 2012) (6), the prevalence of hypertension was 31.5% (95% CI 29.8 - 33.1). The 47.3% of hypertensive were unaware of their diagnosis. 73.6% of hypertensive adults received pharmacological treatment and less than half had the disease under control. According to the ENSANUT MC 2016 (7), the prevalence rate was lower 25.5%. However, the results were not comparable with any of the previous National Surveys ENSANUT, because the methodology used to measure blood pressure changed. Further, the distribution of hypertension risk factors did not change substantially during this time period neither an intervention or any public politic was applied to explain this decrease in hypertension prevalence. Nonetheless, an estimate of the hypertension's prevalence rate was made applying the sensitivity and specificity of the instrument used in 2016 to the ENSANUT 2012 survey concluding that there were not statistically significant changes observed in the national hypertension's prevalence rate. For this reason, the results from ENSANUT 2012 are presented in this section.

Similar to France, prevalence of hypertension increased with age (**Figure 4**). The lowest prevalence was observed among young adults aged 20 and 29 years, while, the highest was found among adults aged 70 and 79 years. Hypertension was more prevalent among obese adults (42.3%) compared to adults with normal weight (18.5%), and in diabetic patients (65.6%) compared to people without diabetes (27.6%) (6).

The prevalence of hypertension varied across Mexico, it was significantly different by location area, region and socioeconomic level. The prevalence was higher in the urban relative to rural areas (31.9% vs. 29.9%), higher in the north of Mexico than the south (36.4% vs. 28.5%) and higher in the highest socioeconomic class compared with the lowest (31.1% vs. 29.7%) (**Figure 5**) (6).

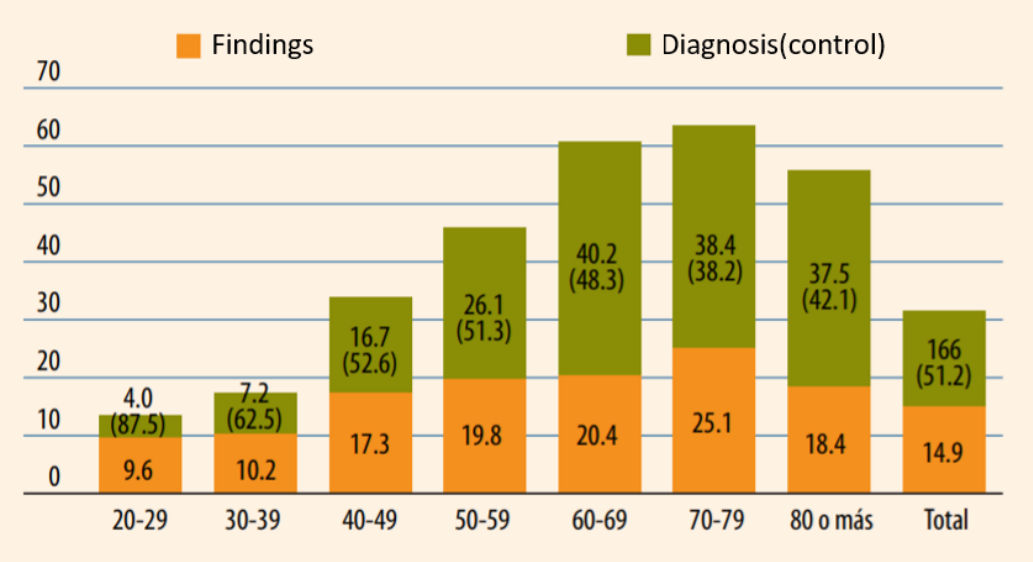


Figure 4. Hypertension's prevalence in adults by age group.
Source: National Health and Nutrition Survey (ENSANUT 2012). Note: The value in parentheses represents the percentage of hypertensive and diagnosed adults who maintain blood pressure levels under control.

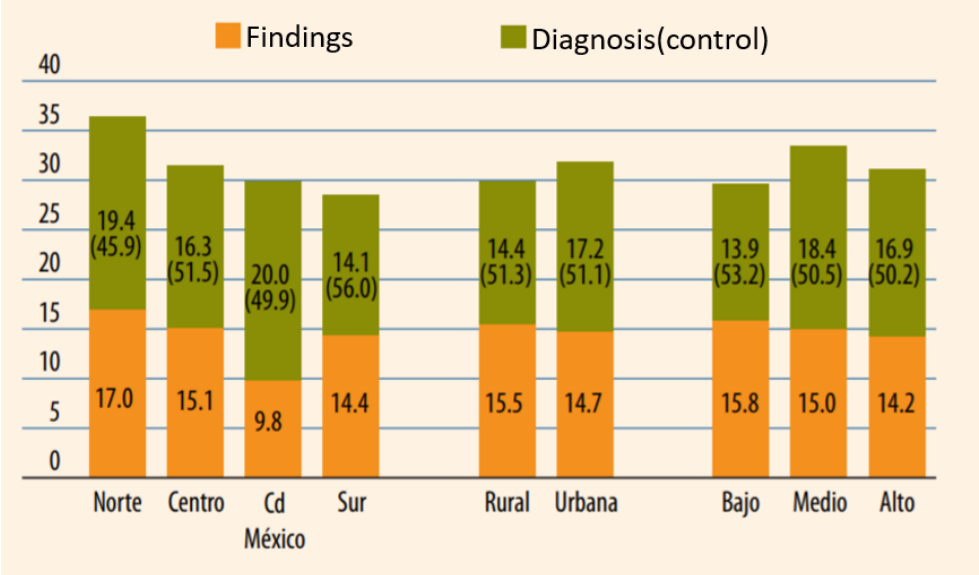


Figure 5. Hypertension's prevalence in adults aged 20 years or more stratified by location area, geographic region and socioeconomic level.
Source: National Health and Nutrition Survey (ENSANUT 2012). Note: For this survey, an adult was considered to have hypertension when he reported having received a diagnosis from a doctor or presented Figures of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, using the technique and procedures recommended by the American Heart Association.

2. GENERAL POINTS

2.1. Definition and Classification

Blood pressure can be defined as the cardiac output (amount of blood volume expelled by the ventricle) multiplied by the total peripheral resistance (the opposing force the blood vessel creates while circulating the blood). The diameter of the blood vessels is of the utmost importance since it affects the flow of blood. The resistance and pressure increase when the diameter decreases in size (8).

The blood vessels transport the blood from the heart to the rest of the body. Each time the heart beats, the blood sent exerts pressure on the vessels. The force of blood against the blood vessels creates the blood pressure. Hypertension, also known as high blood pressure, is a disease as well as a risk factor (cardiovascular diseases) in which the blood vessels have consistently raised pressure (9). Millimeters of mercury (mmHg) are used to measure the blood pressure, which has two parts systolic (SBP) and diastolic pressure (DBP). The systolic pressure is the force exerted by the blood on the vessels when the heart beats and the diastolic is the pressure between heartbeats when the muscles relax. According to the World Health Organization (WHO), a normal blood pressure in adults is defined as a SBP of 120 mmHg and a DBP of 80 mmHg.

Due to recent data and the increase in the risk of cardiovascular complications related to levels of blood pressure, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) introduced the concept of pre-hypertension. This is defined as a systolic pressure of 120 to 139 mmHg or a diastolic pressure of between 80 and 89 mmHg. JNC-7, a group of experts, have defined hypertension as a SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg (**Figure 6**). Further, lifestyle changes are strongly recommended for individuals with prehypertension to avoid chronic high blood pressure (10).

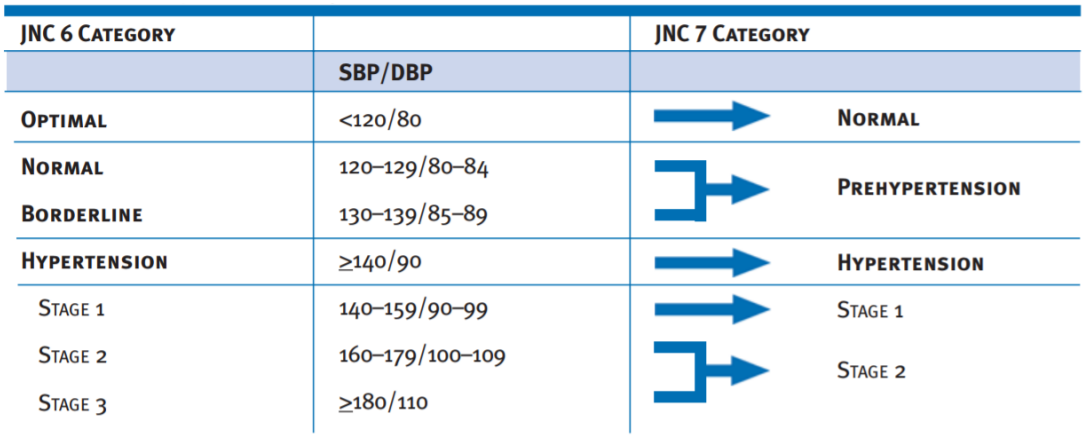


Figure 6. Classification of hypertension.
Sources: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997; 157:2413–46. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003; 289:2560–71.

2.2. Pathophysiology of Hypertension

There is still uncertainty about the pathophysiology of hypertension. Multiple physiological mechanisms have been involved in the regulation of blood pressure and their failure may play a key role in the development of this disease. Many interrelated factors may contribute to the increased blood pressure in hypertensive patients, and their roles may differ between individuals (11).

2.2.1. Cardiac output and peripheral resistance

For normal blood pressure, a balance between the cardiac output and peripheral vascular resistance is needed (**Figure 7**). Most of hypertensive patients have a normal cardiac output however the peripheral resistance is increased. The small arterioles which walls contain smooth muscle cells determine the peripheral resistance. The contraction of smooth muscle cells has been associated to an increase in intracellular calcium concentration, thus the vasodilatory effect of drugs blocks the calcium channels (11). It is possible that prolonged smooth cells contraction induces structural changes in thickening of the arteriolar walls, mediated by angiotensin, resulting into a permanent rise in peripheral resistant (11). In early hypertension, it has been postulated, that the peripheral resistance is not raised on contrary the increment of the blood pressure is due to an increase of the cardiac output, related to sympathetic overactivity. Then a

compensatory mechanism rises the peripheral arteriolar resistance to prevent the raised pressure which would affect cell homeostasis (9).

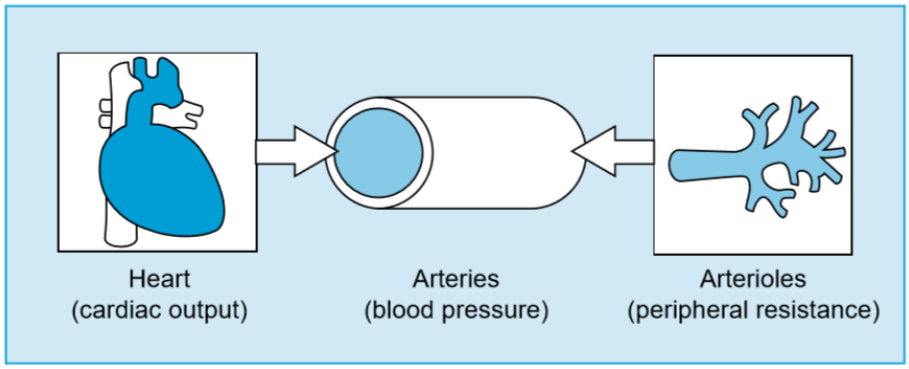


Figure 7. The heart, arteries, arterioles in hypertension.
Source: Beevers G, Lip GY, O'Brien E. ABC of hypertension: The pathophysiology of hypertension. BMJ. 2001;322 (7291):912-6.

2.2.2. Renin-angiotensin system

The renin-angiotensin system could be the most important system involved to control blood pressure (**Figure 8**). The kidney secrets an enzyme, renin, in consequence of underperfusion, reduction of salt consumption or in response to stimulation from the sympathetic nervous system (11). This enzyme is responsible for converting angiotensinogen to angiotensin I, an inactive substance that is in turn rapidly converted by angiotensin converting enzyme (ACE) to angiotensin II. Angiotensin II is a potent vasodilator provoking the increase of blood pressure. Also, it stimulates the release of aldosterone (a hormone that inhibits the excretion of sodium in the urine) which increases blood pressure due to sodium and water retention (9).

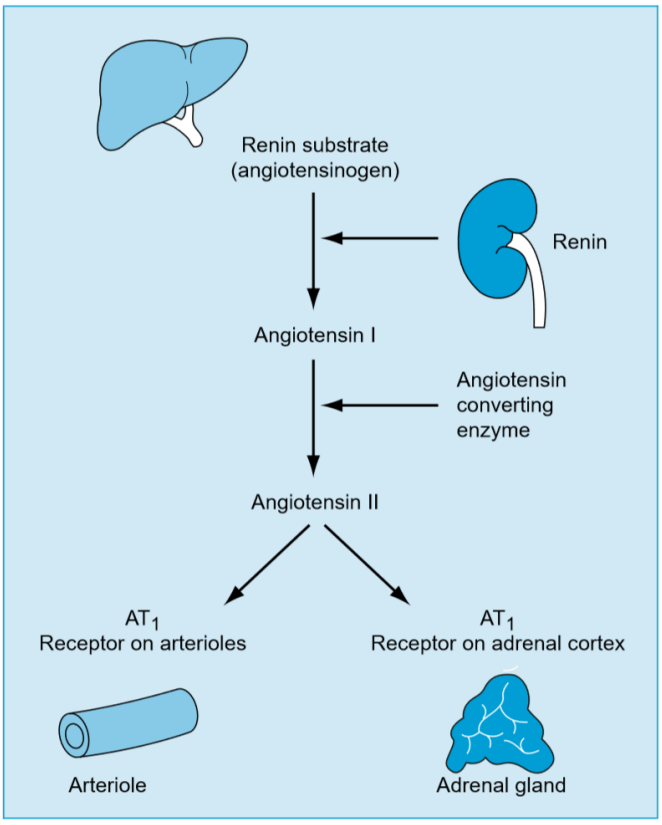


Figure 8. Renin-angiotensin systems in hypertension.
Source: Beevers G, Lip GY, O'Brien E. ABC of hypertension: The pathophysiology of hypertension. BMJ. 2001;322 (7291):912-6.

2.2.3. Autonomic nervous system

Arteriolar constriction and arteriolar dilatation can be provoked by the stimulation of the sympathetic nervous system. Therefore, this system has an important role for maintaining a normal blood pressure, particularly in short term control of blood pressure (stress or physical activity). Noradrenaline is a powerful vasoconstrictor hormone, as well as adrenaline but this last has less power (9). Little evidence suggested a clear role of epinephrine (adrenaline) and norepinephrine (noradrenaline) in the aetiology of hypertension (11). However, drugs which block the sympatic nervous system have a well-established role by lowering blood pressure. Probably, hypertension is mediated by interaction between the autonomic nervous system, the renin-angiotensin system, together with other factors, like sodium, circulating volume, and some hormones (11).

2.2.4. Endothelial dysfunction

The cells in the vascular endothelial produces a number of potent vasoactive agents playing a key role in cardiovascular regulation. The endothelium produces nitric oxide a vasodilator molecule and endothelin a vasoconstrictor peptide being the major regulators of blood pressure and vascular tone (11). In hypertensive patients the balance between vasodilator and vasoconstrictor molecules is upset, leading to changes in the endothelium and their functions. The antihypertensive therapy seems to restore the impaired on the production of nitric oxide; but not repaired the damages endothelium dependent vascular relaxation to endothelial agonist. This could indicate that such endothelial dysfunction is primary and irreversible once hypertensive process is established (11). The endothelial dysfunction has been associated previously with hypertension; this relation is going to be explained deeply, later in this chapter in section 2.4.

2.2.5. Vasoactive substances

There are other vasoactive systems and mechanisms which affect sodium transport and vascular tone that are involved into the control of blood pressure. Nonetheless, it is unclear their contribution in the development of hypertension (11). Therefore, bradykinin is a peptide with vasodilators properties which can be inactivated by angiotensin converting enzyme. Probably, the ACE inhibitors may have an effect by blocking bradykinin inactivation. Another molecule is endothelin, a powerful endothelial vasoconstrictor, which may produce a salt sensitive increase on blood pressure and also can activate local renin angiotensin systems. Also, the secretion of the hormone atrial natriuretic peptide by the heart induces a raise of blood volume. This hormone increases sodium and water excretion from the kidney similar as a natural diuretic, fluid retention and hypertension may be caused by a fail of this system (11).

2.2.6. Sodium and potassium

The excessed intake of sodium, especially in the form of sodium chloride, and the reduced of potassium intake, are determinants along with other factors, of an increase in the incidence of hypertension (11). Sodium is the main extracellular cation and has been considered the most important dietary factor in the maintenance of blood pressure

thus in hypertension. In contrast, potassium is the main intracellular cation usually viewed as a minor factor in hypertension, however the evidence showed that the deficiency of this nutrient has a critical role (12).

There is a relation between sodium and potassium intake, through the Na/K ATPase enzyme. A solute pump which enter the potassium ions into the cells and pumps sodium ions out against their concentration gradients. This is an active pumping using energy from the ATP molecule (Adenosine triphosphate), thus for each ATP molecule used, two ions of extracellular potassium and three ions of intracellular sodium are exchanged (13). The excess of sodium intake, is absorbed in the intestine, provoking an increase in plasma osmolality. This stimulates the sensation of thirst and forces the consumption of water with the consequent expansion of the intravascular volume. To compensate and control this increase in volume, the kidneys respond by eliminating the overload of sodium and water (14). By the other hand, a decrease of potassium intake causes a deficit of potassium in the cells which in order to maintain their tonicity and tone volume gain sodium (15).

The modern western diet is rich in sodium and poor in potassium intake, kidneys were not adapted to this new dietary pattern. On contrary, prehistoric diets were rich in potassium and poor in sodium thus the kidneys were poised to conserved sodium and to eliminate potassium. This new diet interacts with the kidneys, resulting in an excess of sodium and in a deficit of potassium in the body which increase peripheral resistant leading to hypertension (**Figure 9**) (15).

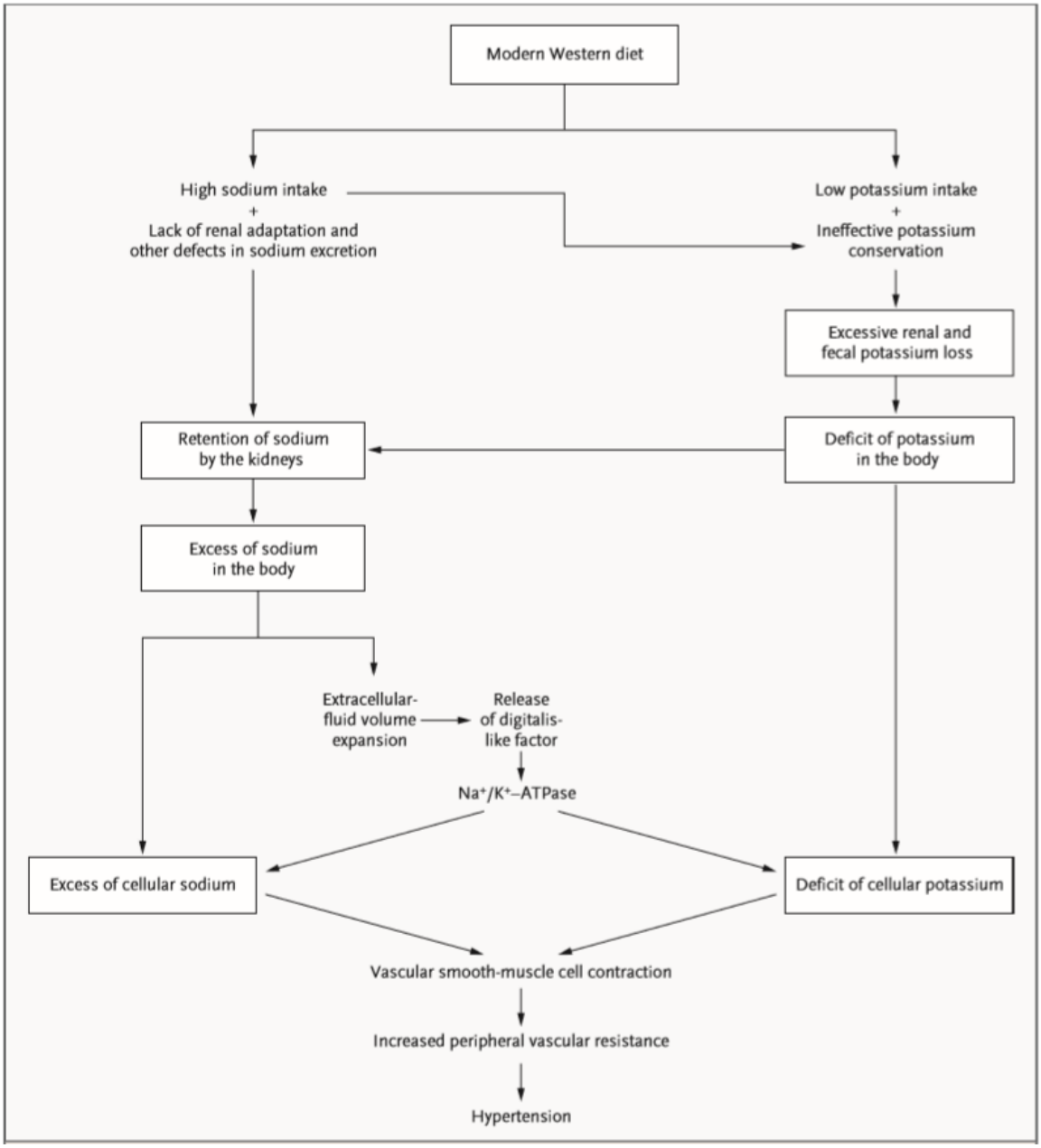


Figure 9. Interaction of the modern western diet and kidneys in the pathogenesis of hypertension.
Source : Adrogue HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. The New England journal of medicine. 2007;356 (19):1966-78.

2.3. Control of Blood pressure

Blood pressure increase due to cardiac output can occur in two ways. The first is a direct route, due to the increase in blood volume. This situation triggers a series of processes (increased circulatory filling, venous blood heart return), which increase cardiac output and therefore blood pressure (**Figure 10**). The second way is indirect, through self-regulation. As its name indicates, this is when the tissue that regulates the blood flow, due to an excess of blood flow, causes the vessels to constrict and reduce the passage of blood to normalize it. This mechanism increases the total peripheral resistance and thus increases the blood pressure (**Figure 10**) (9).

Many systems contribute to maintain blood pressure homeostasis, such as for short-term control, the sympathetic nervous system, and for long term, the kidneys. Faced with a drop-in pressure, the sympathetic nervous system secretes noradrenaline. This substance works as a vasoconstrictor and acts at the artery and small arteriole level, in this way it increases the peripheral resistance and consequently the arterial pressure (8).

The kidneys regulate blood pressure by controlling the extracellular fluid (8). In cases of excess extracellular fluid, the blood volume, and then, consequently, the blood pressure rises. This pressure elevation has a direct action on the kidneys, which excrete the exceeding extracellular fluid in order to normalize the blood pressure. The kidneys, in addition to regulating the pressure through the extracellular fluid, also have the renin-angiotensin system for this purpose (9).

Angiotensin II has two main effects at the circulatory level. Firstly, it causes vasoconstriction in the arterioles (and to a lesser degree, in the veins). The arteriole constriction increases the peripheral resistance, which in turn raises the blood pressure. Secondly, it increases blood pressure by decreasing the renal excretion of sodium and water. In this way, the volume of extracellular fluid increases progressively and consequently, the blood pressure, which is a slightly longer process, taking between hours and days (9).

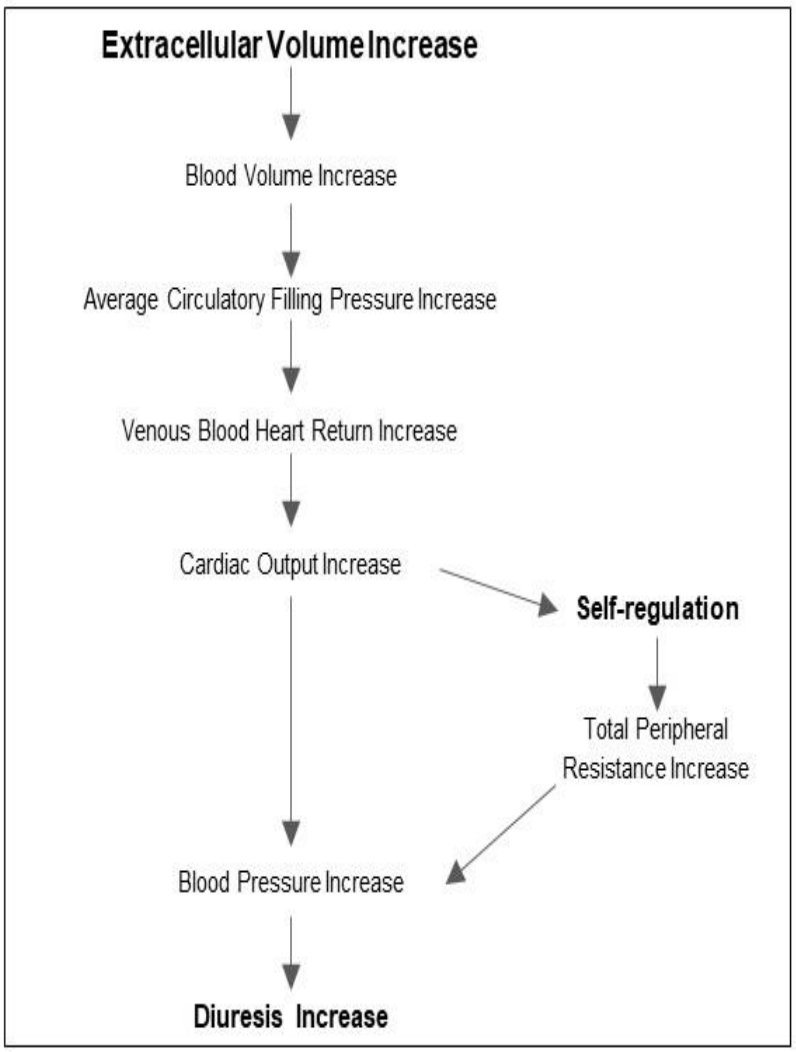


Figure 10. Mechanisms by which the increase in extracellular volume raises blood pressure. Source: Hall G. Treaty of Medical Physiology, 10th ed. Spain Graw Hill Interamericana, 2001.

2.4. Hypertension Risk Factors

The origin of hypertension is multifactorial, these factors can be classified as non-modifiable and modifiable. The first group refers to those factors in which an intervention is not possible, such as genetics, age, family history of hypertension, education and socioeconomic status. The second group includes lifestyle factors, which as the name implies, can be modified by changing behavior.

2.4.1. Non-Modifiable Factors

Hypertension can originate from the alteration of a single gene or a set of them. However, most cases of hypertension are of polygenetic origin, that is, two individuals may suffer from hypertension without having the same affected genes. In general, the altered genes are directly or indirectly related to the renal reabsorption of sodium and to the expression of the angiotensin renin system (16). Approximately 30% of the variability of blood pressure is attributed to genetic factors (17). Several studies have found an association of blood pressure between siblings and between parents and children (18). In addition, to specific genes there is evidence that family history hypertension increases its risk. Thus, the increase in the risk of hypertension has been consistently observed in those subjects who had a family history, due to hereditary factors, but also due to learning of lifestyle factors specific to the family (19). National screening programs have found that the prevalence of hypertension is twice in those who have a family history of hypertension compared to those who did not (19).

Age is a major risk factor for high blood pressure, as changes in the vascular system occur over time. The arteries harden as they lose elasticity, oxidative stress increases and, in general, the activity of the antioxidant system decreases, (20) thus favoring a blood pressure increase. In women, the prevalence of hypertension increases near their 50s and continues until their 80s (16), as we can observed previously in **Table 1** and **Figure 4** related to the prevalence of hypertension in France and Mexico. The Framingham study showed that the risk of a cardiovascular event among American aged between 50 and 60 years old was 37% for men and only 6% for women, however after 65 years, the risk is higher for women (21). In the near future, with aging of the population, hypertension will be a disease more common in women than in men (22).

Another important risk factor is socioeconomic status (SES). A meta-analysis concluded that SES was associated with an increase of hypertension risk. This association was particularly important with the level of education, participants with lower education doubled their risk of presenting hypertension (OR 2.02; 95% CI 1.55 - 2.63) (23). Furthermore, in other report, countries with lower income presented a greater number of habitants who were unaware of their disease (37.9% vs. 67.0%), treatment (29.0% vs. 55.6%) and hypertension's control (7.7% vs 28.4%) with respect to countries with higher income (3). Probably the difficulties to access to medical care, a weak health system, less capacity to confront the burden of the disease may explained the differences observed (3). Thus, the conditions of living and working delay the diagnostic and

treatment of hypertension which can contribute to the prevention of its complications (24).

2.4.2. Modifiable Factors

2.4.2.1. Tobacco

Tobacco consumption can increase oxidative stress, leading to an imbalance between oxidizing substances (endothelin, free radicals, etc.) and antioxidants (nitric oxide). The oxidative stress affects the basic functions of the endothelium such as vasodilation, anti-inflammatory and antithrombotic and thus predisposing to a blood pressure increase (25). Studies, have shown an acute blood pressure and heart rate increase after smoking, persisting even after 15 minutes of consumption (25). Besides, in the Women Health study (26), in multivariable models using never consumer as the category of reference, researchers observed that former smokers had 3% more risk of hypertension (HR 1.03; 95% CI 0.98 - 1.08), participants smoking 1 to 14 cigarettes/day had 2% more risk (HR 1.02; 95% CI 0.92 - 1.13), and those who smoked ≥ 15 cigarettes/day 11% more risk (HR 1.11; 95% CI 1.03 - 1.21). Participants in highest category of consumption (> 25 cigarettes/day) also had the highest risk of hypertension 21% (HR 1.21; 95% CI 1.06 -1.39).

2.4.2.2. Overweight and Obesity

A direct, consistent relation between body mass index and hypertension risk has been observed. In the Nurses´ Health study, using the WHO classification of nutritional status, assessed the relation between obesity and risk of hypertension (27). After 14 years of follow-up, women with overweight (HR 2.56; 95% CI 2.43 - 2.71) and obesity (HR 4.70; 95% CI 4.45 - 4.96) showed a higher risk of hypertension compared with normal weight women. Similar results have been found in the Southern Community Cohort study, as weight increased, participants showed more likelihood of hypertension compared to those with a normal weight (Overweight OR 1.60; 95% CI 1.52 - 1.68; obesity OR 2.54; 95% CI 2.42 - 2.67 and morbid obesity OR 4.03; 95% CI 3.74 - 4.33) (28).

2.4.2.3. Diabetes

Hypertension is a comorbidity that is frequently associated with diabetes. Approximately 20% - 60% of diabetics suffer from hypertension, this variation depends mainly on factors such as the degree of obesity, age and sex (29). Diabetes also increases the risk of a coronary event, in men it doubles, and in women it quadruples (29). The incidence of hypertension in type II diabetics is 1.5 to 3 times higher than in non-diabetics (30). Blood pressure increases in diabetics due to weight gain and insulin resistance, in addition, to the activation of the sympathetic nervous system, as well as the angiotensin-renin system and increased vascular resistance (31).

2.4.2.4. Hypercholesterolemia

Hypercholesterolemia is defined as a concentration greater than 200 mg/dl cholesterol in the blood (9), a known risk factor for cardiovascular disease. Fatty deposits called atheromatous plaques, located in the arteries walls, trigger a series of processes that end in atherosclerotic formation and reduce the arteries' diameter, increase peripheral resistance, and consequently, blood pressure (32). Several studies have shown an association between dyslipidemia and the risk of hypertension (33, 34). The Physicians' Health Study, after 18.6 years of follow-up, observed that participants in the highest quintile of total cholesterol had 23% higher risk of hypertension (RR 1.23; 95% CI 1.01 - 1.50) compared to those in the first quintile. The same behavior was observed in participants in the highest quintile of non-HDL cholesterol they had 39% (RR 1.39; 95% CI 1.13 - 1.70) higher risk of hypertension. In contrast, participants in the highest quintile of HDL cholesterol had less risk of hypertension (RR 0.68; 95% CI 0.56 - 0.84) compared to those in the first quintile (35).

2.4.2.5. Physical Activity

Physical activity is a well-established protective factor for hypertension. A meta-analysis of randomized clinical trials observed a decrease in systolic and diastolic blood pressure after endurance training. In hypertensives, the effect of endurance training was greater for SBP (-8.3 mmHg; 95% CI -10.7 to -6.0) and DBP (-5.2 mmHg; 95% CI -6.9 to -3.4 mmHg) compared with pre hypertensive (SBP -4.3 mmHg; 95% CI -7.7 to -0.90 ; DBP -1.7 mmHg; 95% CI -2.7 to -0.68 mmHg) and participants with normal pressure (SBP -0.75 mmHg; 95% CI -2.2 to -0.69 ; DBP -1.1; 95% CI -2.2 to -0.07 mmHg) (36). Cohort studies have observed a reduction of up to 20% in blood pressure obtained by performing

exercise of less intensity and shorter duration (37). In another meta-analysis Hu et al. (38) studied the impact of aerobic exercises in adults observing a net changed of 5.3 mmHg and 3.7 mmHg in SBP and DBP, respectively.

Beside the effect on blood pressure, physical activity also positively influences determinants of ischemic heart disease, as it favours decreased weight, cholesterol and triglyceride levels, as well as platelet aggregation. It also increases glucose tolerance as well as the concentration of HDL (16). Some mechanisms has been proposed to explain this association, findings from animal studies showed that aerobic exercises may prevent hypertension through beneficial alterations in insulin sensitivity and autonomic nervous system function (39) and resistance training through beneficial alterations in the regulation of vasoconstriction (40).

2.4.2.6. Dietary Factors

2.4.2.6.1. Sodium intake

The most researched nutrient in the literature regarding hypertension is sodium. Randomized controlled trials (RCTs), observational studies, meta-analysis and intervention studies have assessed this relationship. A meta-analysis of randomised trials (41) assessed a modest reduction of salt (5.1 g of salt/day), 17 trials were conducted in hypertensive patients and 11 in participants with normal blood pressure. In hypertensive patients, the excretion of sodium in 24h urine (equivalent to 4.6 g of salt), decreased by 4.96 mmHg and 2.73 mmHg SBP and DBP, respectively. In healthy participants, the increase of sodium excretion had a similar effect, in average a decrease of 2.03 mmHg SBP and 0.97 mmHg DBP was observed. A meta-analysis (42) composed of 13 observational studies, involving a total of 177 025 individuals, concluded that there is a direct relation between high salt intake and the risk of stroke (RR 1.23; 95% CI 1.06 - 1.43; p = 0.007) and cardiovascular disease (RR 1.14; 95% CI 0.99 - 1.32; p = 0.07). The mechanisms that underlie the effect of sodium on blood pressure were explained previously in this chapter.

2.4.2.6.2. Potassium

The large international INTERSALT study, observed that potassium intake measured by 24-hour urinary potassium excretion was an important and independent determinant of

blood pressure. An increase of potassium intake of 30-40 mmol was associated with a reduction of 2 - 3 mmHg in average (43). In this study, it is important to mention that the ratio between sodium and potassium had also a significant inverse association with blood pressure having a stronger statistical association than sodium and potassium individually. Moreover, in a meta-analysis of RCTs (44), potassium supplementation was associated with a decrease on blood pressure. In average they observed a significant reduction on SBP and DBP of -3.11 mmHg (95% CI -1.91 to -4.31 mmHg) and -1.97 mmHg (95% CI -0.52 to -3.42 mmHg), respectively. The effect was greater in participants exposed to a high consumption of sodium. Previous studies suggested that the balanced between sodium and potassium intake seems to be more important than the individual intake of both of them. A probable explanation is a possible additive effect when potassium intake is increased and sodium intake is reduced (12).

A diet rich in potassium increase plasma potassium as well as provoke endothelium-dependent vasodilatation stimulating the sodium pump and opening potassium channels (45). Additionally, potassium can influence blood pressure by natriuresis, modulation of baroreceptor sensitivity, reduced vasoconstrictive sensitivity to norepinephrine and angiotensin II, increased serum and urinary kallikrein, increased sodium/potassium ATPase activity, alter the synthesis of DNA, and the proliferation in vascular smooth muscle and sympathetic nervous system cells (46, 47). Furthermore, the homeostasis of both sodium and potassium plays a critical role in endothelium-dependent vasodilatation (48). The synthesis of nitric oxide decreases due to sodium retention, which can also cause an arteriolar vasodilator elaborated by endothelial cells, and increases the plasma level of asymmetric dimethyl-L-arginine, an endogenous inhibitor of nitric oxide production (49, 50).

2.4.2.6.3. Magnesium

Observational studies supported a role of magnesium intake in development of hypertension. A meta-analysis (51) of nine cohorts' studies including 180 566 participants and 20 119 cases of hypertension found an inverse relation between dietary magnesium and risk of hypertension. They reported 8% less risk of hypertension when they compared the participants in highest with lowest quintiles of consumption (RR 0.92; 95% CI 0.86 - 0.98). Also, a 5% reduction in the risk of hypertension (RR 0.95; 95% CI 0.90 - 1.00) was observed for an increase of 100 mg/day of magnesium intake. However,

the results of 4 meta-analysis of RCTs evaluating magnesium supplementation were not consistent. A meta-analysis (52) including 20 studies of hypertensive and normotensive individuals, observed a little reduction in blood pressure but it was not-significant. In contrast, Dickinson et al. (53), found a small beneficial effect on blood pressure due to the magnesium supplementation. Kass et al. (54), (n = 22 RCTs) reported a reduction of 3 - 4 mmHg on SBP and 2 - 3 mmHg on DBP with oral magnesium supplementation. Finally, Rosanoff et al. (55), reported a more important reduction of 18.7 mmHg on SBP and 10.9 mmHg on DBP in participants with high blood pressure (SBP > 155 mmHg).

Magnesium can act like a natural blocker of calcium channels in the cells which is a possible mechanism to explain the reduction on blood pressure. Moreover, sodium and magnesium compete to bind sides on vascular smooth muscle cells. Magnesium increases the prostaglandin E, binds to potassium in a cooperative manner, induces endothelial vasodilation, improves endothelial dysfunction and decreases intracellular calcium and sodium thus reduces blood pressure (56).

2.4.2.6.4. Calcium and Vitamin D

The consumption of calcium and hypertension were inversely associated in a meta-analysis of observational studies (n = 23). However, the effect size was relatively small (57). In the Women Health Study including 28 886 participants, dietary intake of calcium but not calcium from supplementation, was associated with a decrease of hypertension risk (58). There is no consistency in the results regarding the relationship between hypertension and vitamin D. One meta-analysis found that vitamin D supplementation significantly decreased systolic but not diastolic blood pressure (59). In another, more recent meta-analysis, a SBP reduction of 1.96 mmHg (95% CI 0.36 to 3.57 mmHg) and DBP reduction (-0.09; 95% CI -0.21 to - 0.03 mmHg) were observed. However, they were not significant when compared with the placebo (60). In 2017, a meta-analysis of RCTs evaluated the effect of the supplementation of calcium plus vitamin D on blood pressure. The follow-up time ranged from 15 weeks to 7 years and included 36 806 participants. The study showed no significant effect on DBP reduction, and in the pooled weighted mean differences was -0.22 mmHg (95% CI -0.89 to 0.46; p = 0.53) However there was evidence of significant heterogeneity, which means there was variability in the studies considered in the meta-analysis due to differences in participants, interventions or outcomes, in the study design, risk of bias as well as variation in intervention effects or results (61).

Vitamin D is critically for calcium absorption and homeostasis, both nutrients are often administrated together. According to a number of studies in human and animals, dietary calcium which main source is dairy products, forms insoluble calcium soaps with fatty acids (FAs) or bind of bile acids. In this way, calcium interferes with the absorption of fat in the intestine, resulting in the decrease of the digestible energy from diet through a higher excretion of fecal fat (62).

2.4.2.6.5. Saturated Fatty acids

Saturated fatty acids (SFAs) and cholesterol are the main dietary determinants of hypercholesterolemia, which is a cardiovascular risk factor mainly due to its role in the development of atherosclerosis. Saturated fat intake has been reported to increase levels of low-density lipoprotein-cholesterol (LDL) (63) being the target of oxidation by free radicals. Experimental studies with animals fed SFAs, observed impaired in the endothelial function (64) and enhanced sympathetic nervous system activity (65), which can elevate blood pressure. Additionally, diets with less than 10% kcal from saturated fat and less than 300 mg/d of cholesterol can lower total cholesterol and LDL cholesterol, which is a risk factor for hypertension (66).

The results regarding the consumption of saturated fat and risk of hypertension are not consistent. In the Women Health study (67), a prospective cohort study including 28 100, aged ≥ 39 years evaluated the relation between specific intake of saturated FAs (SFAs), monounsaturated FAs (MUFAs) and trans-unsaturated FAs (trans FAs) with risk of hypertension. They observed a direct relation when they compared the highest to the lowest quintile of intake of each fatty acids, they reported 12% (RR 1.12; 95% CI 1.05 - 1.20), 11% (RR 1.11; 95% CI 1.04 - 1.18) and 15% (RR 1.15; 95% CI 1.08 - 1.22) more risk of hypertension for intake of SFAs, MUFAs and trans FAs, respectively.

Nonetheless, the reduction of saturated fat alone did not affect blood pressure in randomized trials (68). Moreover, it seems that food rich in saturated fat are not the same. A randomized controlled cross-over study (69) evaluated the effect of SFAs, they compared the consumption of cheddar cheese versus a vegan meal. They observed a decrease of postprandial inflammation in overweight and obese individuals after consumption of SFAs in form of cheese matrix.

2.4.2.6.6. Alcohol Consumption

The evidence supports the association between elevated alcohol consumption and the risk of hypertension. In healthy adults, a low-moderate daily consumption of alcohol had no substantial impact on blood pressure (70). Nonetheless, the evidence showed that binge drinking defined as “more than 5 standard drinks in a single sitting” was associated with acute increased of blood pressure ranging from 4 to 7 mmHg for SBP and 4 to 6 mmHg for DBP (70). Further, Briasoulis et al. (71), in a systematic review and meta-analysis including 16 prospective studies on the relation of alcohol consumption on the risk of hypertension (SBP ≥ 140 mmHg; DBP ≥90 mmHg), observed an increase of blood pressure in women when the consumption was more than 20 g ethanol/day (around 1 to 2 drinks/day) (RR 1.19; 95% CI 1.07 - 1.32; $p = 0.002$) as well as in men (RR 1.77; 95% CI 1.39 - 2.26; $p < 0.001$) when the consumption was higher 31 to 40 g ethanol/day. In this study, the relation between alcohol consumption and risk of hypertension had a J-shape for women, whereas for men it was more a linear shape. Another meta-analysis of cohort studies ($n = 12$) found similar results, a dose-response relation between alcohol consumption and hypertension in men and the same J-shape relation for women showing a protective effect when the consumption was ≤ 15 g/day (72).

Several mechanisms may explain the underlying relation between alcohol consumption and hypertension risk. These include damages in the cells leading to the production of plaque in the arteries altering endothelial function and nitric oxide availability (70). Also, it leads to disruptions in the arterial vascular functions through myogenic mechanism and changes in baroreceptor function. Further, the imbalance on the hormones controlling fluids in the body and blood pressure regulation through the renin angiotensin system (RAS) appears after alcohol consumption (70, 73).

2.4.2.6.7. Fruits and Vegetables

Consumption of fruits and vegetables has been consistently associated with cardiovascular disease and hypertension, as protector factor. In a meta-analysis of 9 prospective cohort studies, including 185 676 with follow-up ranging from 3.8 to 28 years, evidenced an inverse association between the consumption of fruit and vegetables and

the risk of hypertension. The consumption of fruit and vegetables was evaluated individually, when they compared the highest with the lowest quintile of consumption, they found a 13% (RR 0.87; 95% CI 0.79 - 0.95) and 12% (RR 0.88; 95% CI 0.79 - 0.99) lower risk, respectively. Together, consumers of fruit and vegetables had 10% (RR 0.90; 95% CI 0.84 - 0.98) lower risk of hypertension (74). Fruits and vegetables are food groups source of antioxidants, which could neutralize the effect of oxidative stress and improve endothelial function. It is estimated that 1.7 million lives could be prevented each year if there was adequate consumption of these foods (75).

2.5. Oxidative Stress and Hypertension

2.5.1. Definition of oxidative stress

Oxygen free radicals are unstable molecules, containing one or more unpaired electrons in their last orbital (76). In cells, free radicals can be generated by the loss or acceptance of a single electron. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are reactive radicals formed from oxygen and nitrogen, respectively (77). Reactive oxygen and nitrogen species (RONS), when seeking to attack healthy cells, have an important role in aging and in several diseases (78). RONS are also associated with the immune defense signaling process and extraction of energy from organic molecules (77). Oxidative stress can be defined as “the imbalance between the formation and the removal of RONS because of an overproduction and/or an impaired ability to neutralize them or to repair the resulting damage” (77).

Some factors can produce free radicals: air and water pollution, aging, alcohol consumption, smoking, industrial solvents, heavy or transition metals**,** some drugs (bleomycin, gentamycin, cyclosporine and tacrolimus), cooking (fat, smoked meat, and waste oil) and radiation (77) (**Figure 11**).

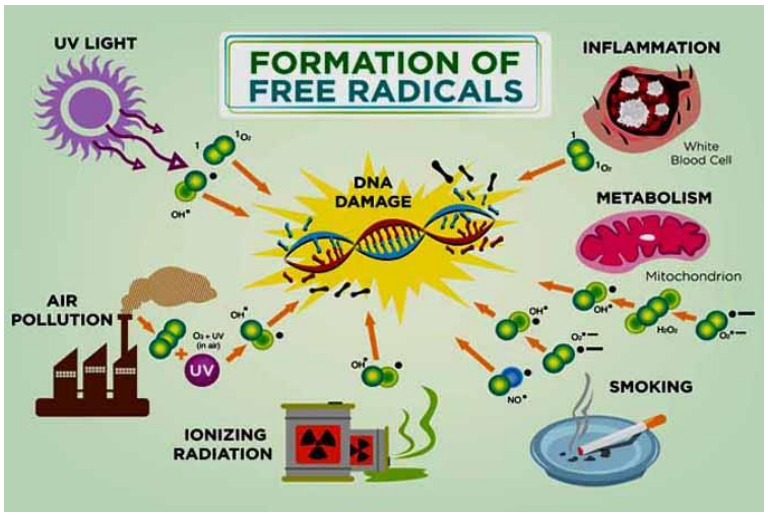


Figure 11. Formation of free radical.
Source: Kring L. Foodal. Easy way to increment your antioxidant intake. Available: https://foodal.com/knowledge/paleo/easy-antioxidant-tips/

2.5.2. The relation between oxidative stress and hypertension

The endothelium is an organ that lines the inside of veins, vessels and arteries. The cells in the vascular endothelial produce vasoactive agents that play a key role in cardiovascular regulation. The endothelium has various functions related to the substances produced by this organ. Thus, the endothelium relaxes the smooth muscle wall and inhibits the proliferation of this tissue. It also depresses the activation of the coagulation system, inhibits adhesion and platelet aggregation, promotes fibrinolysis, and depresses the coagulation system. In addition, it regulates the exchange of nutrients, decreases capillary permeability and inhibits the adhesion and migration of neutrophils and macrophages caused by inflammation (79).

There are several and complex mechanisms that may explain the relation between oxidative stress and hypertension. However, in this section I will explain some of them in a simplify way. The alteration of endothelium function is named endothelial dysfunction and can be caused by oxidative stress. This condition has been accepted as an early determinant of hypertension (80). Oxidative stress and inflammation are interrelated, oxidative stress can produce inflammation, which in turn can cause oxidative stress (**Figure 12**)(81). Thus, both oxidative stress and inflammation can damage cells including those of the endothelium leading to endothelium dysfunction. In consequence

this causes imbalance between the endothelium-derived relaxing (nitric oxide a vasodilator molecule) and contracting factors (endothelin) (82) inducing hypertension.

Furthermore, endothelium dysfunction can provoke atherosclerosis, leading to a pro-inflammatory environment by increasing endothelial expression of adhesion molecules and the imbalance of arachidonic acid metabolites (76). Also, it induces impaired in the vascular tone regulation and increase susceptibility to formation of foam cells and vascular remodeling (76). Accumulation of lipids and inflammatory cells (foam cells) in the arterial wall is a characteristic of atherosclerosis. The oxidation of low-density lipoproteins (LDL) plays a major role in the initiation and progression of atheromatous plaque (83). Biomolecules such as lipids are also attacked by free radicals, particularly the phospholipids found in the cell membrane. A lesion in the endothelium allows the entry of LDL into the vascular intima. LDL can then be oxidized, inducing an inflammatory process which generates the production of adhesion proteins and cytokines allowing monocytes to migrate to the site of the lesion and become macrophages and then foam cells. This process originates in the fat line, that is, the earliest lesion of atherosclerosis (**Figure 12**) (79, 84).

Another mechanism between oxidative stress and hypertension, is the role of endothelin and angiotensin II in the oxidative process. This vasoconstrictor has prooxidant and proinflammatory properties associated to endothelial dysfunction (85). In endothelial cells, the expression and production of endothelin is increased by stimulation of angiotensin II (86), ageing and oxidised LDL (87). The overexpression of endothelin induces ROS production by raising NADPH oxidase activity leading to oxidative stress (88), provoking a positive feedback loop of oxidative stress mediating endothelial oxidative injury and dysfunction (76).

The endothelium becomes a key objective to treat hypertension and reduce the production of free radicals, a means by which endothelial dysfunction can be combated. In this context antioxidant intake could be a good strategy to prevent hypertension (76). In the following section (2.6), antioxidants and its relation with hypertension is going to be explained deeply.

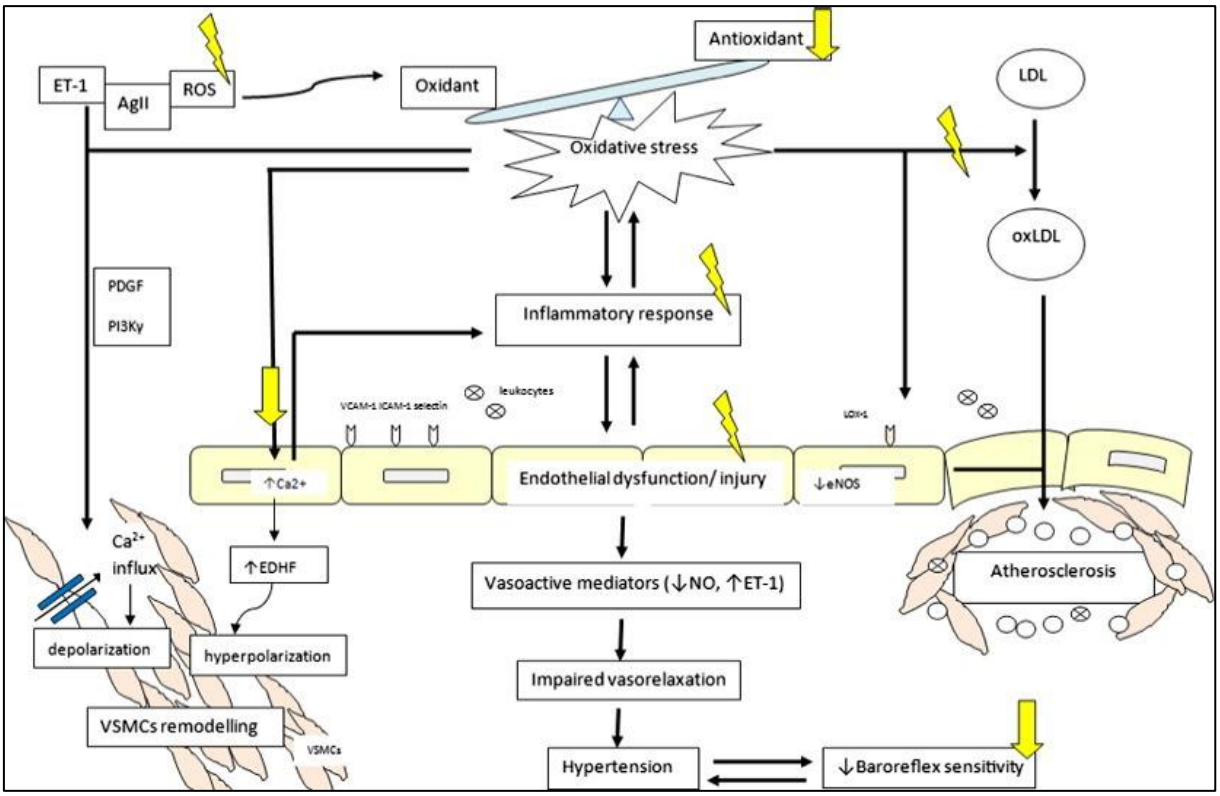


Figure 12. Proposal of the participation of oxidative stress, inflammation and antioxidants at vascular level.
Source: Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease, Vascul Pharmacol., 2015; 71: 40-56.

2.6. Antioxidants and Hypertension

2.6.1. Definition of antioxidants

Antioxidants are any substance that, in a low concentration, compared with an oxidizable substrate, retards or prevents the oxidation of that substrate (89). This definition only takes into account antioxidants with a direct ability to reduce or inhibit oxidants, and also implies that once the substance is oxidized it is not able to reduce another molecule. Besides, in a broader sense, an antioxidant could also be a substance that potentiates the action of another antioxidant (90). The antioxidant defense system considered obviously the direct antioxidant as well as the substances which enhance them.

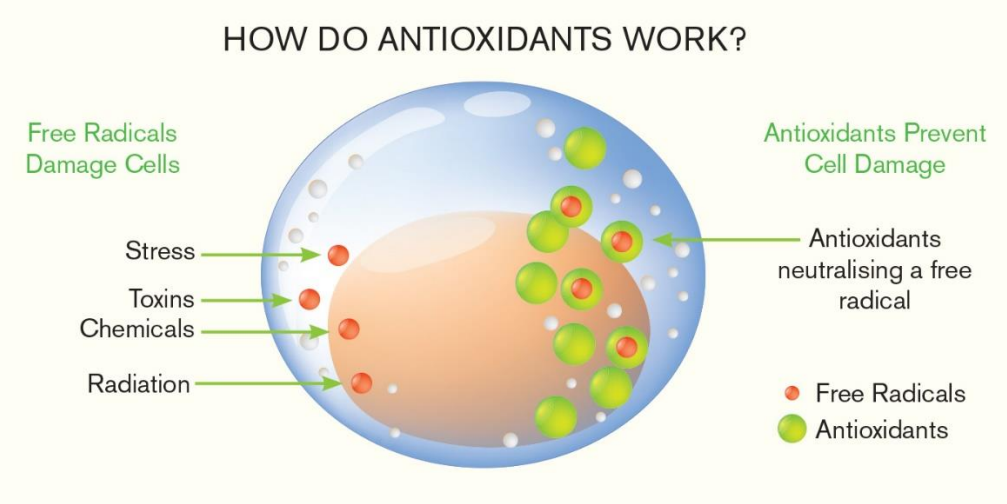


Figure 13. Antioxidants. How they work?
Source: Immune Health Basics. Available: http://immunehealthbasics.com/antioxidants-how-they-work/.

The antioxidant system is capable of adapting to the changes of antioxidant levels to maintain the balance between oxidant and antioxidants agents (76). The antioxidant system has two parts, an endogenous and an exogenous component. The endogenous component considered the enzymes synthesized in the presence of oxidants. These include enzymes and coenzymes such as superoxide dismutase, catalase, and glutathione peroxidase, all involved in the transformation of free radicals into less reactive molecules (76). The exogenous component come from the diet including: vitamin C, tocopherols, carotenoids, selenium, zinc and some polyunsaturated fats. Of these, only vitamin C, alpha-tocopherol, carotenoids and flavonoids have a direct antioxidant capacity (76). Antioxidants have been the subject of investigation due to their possible protective role against several diseases. In hypertension, part of the pathophysiology includes an increase in oxidative stress. Therefore, a diet rich in antioxidants could be an alternative to combat both oxidative stress and hypertension (91).

2.6.2. Antioxidants

2.6.2.1. Vitamin C

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin which acts as an antioxidant (92). Vitamin C recycles vitamin E, improves endothelial dysfunction, produces diuresis and protects low-density lipoproteins (LDL) from oxidative stress, thus

helping to prevent atherosclerosis (93). In a case-control study, an inverse association was observed between plasma vitamin C concentration and lipid oxidation levels, and this association was stronger in smokers (94).

In a meta-analysis (95) of 29 controlled clinical trials, the effect of vitamin C supplementation was evaluated and an overall decrease in systolic and diastolic blood pressure was observed. The median intervention time was 8 weeks, the sample size varied from 10 to 120 participants, and the median dose of vitamin C was 500 mg/d. The decrease in systolic blood pressure was -3.84 mmHg (95% CI -5.29 to -2.38 mmHg) and the decrease in diastolic pressure was -1.48 mmHg (95% CI -2.86 to -0.10 mmHg). Long-term vitamin C supplementation trials on blood pressure are needed.

2.6.2.2. Vitamin E

Vitamin E is the main fat-soluble cell antioxidant, it is found in the cell membrane and fat-rich tissues. This vitamin protects phospholipids and the low-density lipoproteins (LDL) from oxidation (8). Studies regarding the relationship between vitamin E, cardiovascular disease and hypertension are not consistent. This relation has been addressed by cohort studies, some of these studies have reported an inverse relationship (96), although the result of supplementation in clinical trials is controversial (97).

In the Nurses´ Health Study, after 8 years of follow-up, in 87 245 participants with no history of cardiovascular disease between 34 and 59 years, a 34% reduction (RR 0.66; 95% CI 0.50 - 0.87) of cardiovascular disease risk was observed in women in the upper quartile of vitamin E consumption compared with the lowest quartile. Further analyses in this study attributed the inverse relation exclusively to vitamin E consumption from supplements (96). However, the results of controlled clinical trials are less consistent. When 8 171 women were supplemented with 600 IU of vitamin E daily (98) during 9.4 years, no effect was reported on cardiovascular disease. In the Physicians Study (n = 14 641), after 8 years of supplementation with 400 IU of vitamin E daily similar results were found (99, 100).

In relation to blood pressure, in a double-blind controlled clinical trial, subjects received a dose of 500 mg/d of tocopherols for 6 weeks. An increase in systolic blood pressure (7.0 mmHg; 95% CI 5.2 - 8.8 mmHg) and diastolic blood pressure (5.3 mmHg; 95% CI 4.0 - 6.5 mmHg) was observed when supplemented with alpha tocopherol. The same trend was evidenced when it was supplemented with a mixture of tocopherols for both

systolic blood pressure (6.8 mmHg; 95% CI 4.9 - 8.6 mmHg) and diastolic blood pressure (3.6 mmHg; 95% CI 2.3 - 4.9 mmHg) (101). According to the evidence it appears that tocopherols supplementation had a negative effect on blood pressure.

2.6.2.3. Polyphenols and Flavonoids

Polyphenols are widely distributed in the diet, mainly in foods of plant origin (fruits, vegetables, seeds, nuts, tea, wine, and chocolate). Studies suggested that flavonoids may have protective effects against the oxidation of molecules such as lipids, lipoproteins and DNA (102).

A meta-analysis of controlled clinical trials included foods rich in polyphenols such as chocolate, soy, wine or grapes and black tea and examined their relation with hypertension (103). According to their results, long-term consumption of chocolate and soy products had a beneficial effect on blood pressure. The consumption of chocolate reduced the SBP (5.88 mmHg; 95% CI 9.55 - 2.21 mmHg; n = 5 studies) and DPB (3.30 mmHg; 95% CI 5.77 - 0.80 mmHg; n = 4 studies) significantly. On the other hand, the source of soy varied the effect on blood pressure, so that isolated soy protein reduced blood pressure (1.99 mmHg; 95% CI 2.86 - 1.12 mmHg; n = 9 studies) while soy products did not show the same effect. In relation to black tea, acute consumption increased blood pressure (SBP: 5.69 mmHg; 95% CI 1.52 - 9.86 mmHg; n = 4 studies and DBP: 2.56 mmHg; 95% CI 1.03 - 4.10 mmHg; n = 4 studies). No association was found between prolonged consumption of black tea, wine or grapes or other polyphenols and blood pressure (103).

Subsequently, in the United States the relation between the type of polyphenols and blood pressure was addressed (104). It was observed that the highest quintile of anthocyanin consumption had an 8% lower risk of hypertension (RR 0.92; 95% CI 0.86 - 0.98; $p < 0.03$) compared to the lowest quintile, however, no association was observed with other polyphenols. In participants younger than 60 years old, the hypertension risk reduction was higher 12% (RR 0.88; 95% CI 0.84 - 0.93; $p < 0.001$), in addition, in this group the flavan-3-ol was also associated with a hypertension risk reduction (RR 0.94; 95% CI 0.88 - 0.97; $p = 0.002$). Moreover, in the French E3N study, results were consistent with the American study. A lower risk of hypertension was observed in the highest quintile of flavonol (HR 0.90; 95% CI 0.84 - 0.97; $p = 0.03$), anthocyanins (HR

0.91; 95% CI 0.84 - 0.97; p = 0.01) and proanthocyandins (HR 0.91; 95% CI 0.85 - 0.97; p = 0.01) compared to the lowest quintile (105).

2.6.2.4. Vitamin A and Carotenes

Vitamin A is water soluble, regulating proliferation, differentiation and cellular apoptosis as well as being part of the immune function (106). Vitamin A is found in its preformed form in food. Within the vitamin A group are carotenoids, which have vitamin A action after being metabolized in the organism (106).

There are few studies evaluating the relation between vitamin A intake and hypertension risk and no association was found (107). However, observational studies have associated the risk of cardiovascular disease with plasma carotenoid levels. In the Women's Health Study (108), in a prospective, nested, case-control study, participants with a higher lycopene plasma concentration had a lower risk of cardiovascular disease (RR 0.66; 95% CI 0.47 - 0.95) compared to the lowest level of lycopene plasma concentrations. Similarly, in Europe, after a 10-year follow-up, an inverse relation was observed between carotenoid concentration and the risk of mortality due to cardiovascular disease (RR 0.83; 95% CI 0.70 - 1.00), this association was limited to participants with a BMI < 25 (RR 0.67; 95% CI 0.49 - 0.94) (109). Likewise, in the Nurses' Health study, after twelve years of follow-up, compared to the highest quintile of alpha and beta carotene consumption, those in the lowest quintile presented 26% (RR 0.74; 95% CI 0.59 - 0.93) and 20% (RR 0.80; 95% CI 0.65 - 0.99) decreased risk of coronary artery disease (110). Tobacco consumption may modify this effect, since in another cohort study, male smokers in the highest quintile of carotenoid consumption had a 70% lower risk compared to those in the lowest quintile. This relation was also observed in former smokers, however, in non-smokers this association was not evident (111).

There is little evidence between the relation of carotenoids and hypertension, in observational studies dietary carotenoids seems to protect against cardiovascular disease. Nonetheless, further studies are needed to assess the potential factors which can modify the relation, such as smoking or BMI.

3. TOTAL ANTIOXIDANT CAPACITY

3.1. Definition of total antioxidant capacity

Antioxidant capacity is defined as "the bulk of antioxidants neutralized by one liter of plasma, food extracts or individual molecules". The total antioxidant capacity (TAC) of food only gives us information about the *in vitro* capacity of a specific food to inhibit or reduce an oxidant (91), it does not provide information about its capacity *in vivo*. Thus, the dietary TAC is therefore a marker of the antioxidant potential of the diet. Dietary TAC is a new method that aims to reflect the totality of antioxidants in a meal, considering only direct antioxidants (vitamin A, C, E and flavonoids) but not nutrients that contribute to the antioxidant system indirectly (zinc, selenium) (91).

Dietary TAC represents a global estimate of antioxidants from the diet. However, the ability of diet to increase plasma TAC is a matter of debate. The consumption of antioxidants seems to affect plasma antioxidant capacity in the short term (91), however no long-term changes have been documented in clinical trials with high dietary intakes of antioxidants (112). Nonetheless several questions about its absorption, distribution and cellular role still remain unanswered.

3.2. Total Antioxidant Capacity Measure Methods

Due to the synergy between antioxidants, there has recently been greater interest to measure them globally in the diet or in foods rather than individually. However, in view of the complexity of the oxidation process and the diversity of antioxidants (water-soluble and lipo-soluble) there is no universal method to measure the antioxidant capacity. It is for this reason that the application of at least two methods is recommended (113). The methods vary in the substrates used and, in the technique to measure antioxidants. There are two main methods (113): the first measures the transfer of hydrogen atoms (HAT, Hydrogen atom transfer) and the second quantifies electrons (SET, Single electron transfer) (114). Both reactions lead to the same result, the inhibition of radical action (115).

The HAT measures the antioxidant's ability to inhibit radicals through the transfer of a hydrogen atom to stabilize the free radical (115), as a result, the antioxidant becomes a

free radical. However, the antioxidant that became radical is less reactive than the radical of origin and can be recycled to its initial form. Within this method, there are two types of analyses: the ORAC (Oxygen radical absorbance capacity) and the TRAP (Total radical absorbance parameter). The TRAP analysis focuses on the time the antioxidant takes to inhibit the decrease in fluorescence (oxidant substance) (116). This analysis begins when the antioxidant is added to the fluorescent solution and ends when the fluorescence begins to decrease (116).

The SET method is based on the antioxidants' ability to donate electrons and thus stabilize free radicals (115). There are two analyses, the FRAP (Ferric Reducing-Antioxidant Power) and the TEAC (Trolox equivalent antioxidant capacity). The FRAP is based on the ability of an antioxidant to reduce an iron ion (Fe^{+3} to Fe^{+2})(117). Iron forms a complex with a tripyridyltriazine molecule and this reaction produces coloration. In this way, the antioxidant capacity can be measured with a spectrometer comparing the absorbance produced at the beginning to the one produced at the end. The result is given in moles of iron produced by the reaction (117). The TEAC (91) assay is based on the formation of ferrylmyoglobin radical which may react with ABTS•+ (2,2′-azinobis-3-ethylbenzothiazoline-6-sulphonate) radical cation. The excess of this radical can be inhibited to an extent proportional to the total antioxidant capacity.

3.3. Total Antioxidant Capacity Food Contribution

The antioxidant capacity of foods is influenced by the content of flavonoids and vitamin C (118), while vitamin E contributes less. The food groups which provide the most important contributions to the TAC when the portion size is taken into account are chocolate, coffee, tea and nuts (118, 119). However, if the portion size is ignored, herbs and berries are the foods with the greatest contribution to the content of the TAC (115).

Despite the challenge of comparing TAC values in different studies, when analyzing TAC contributors at the population level, some generalizations can be made (120). It has been observed that the main contributors of antioxidant capacity of the diet vary by culture. For example, in Asian populations, green tea is the main contributor to the TAC, whereas in Europe coffee, red wine and chocolate are considered the main contributors (120, 121).

Coffee is one of the main dietary contributor to the TAC in diet in Western populations (122, 123) through phenolic substances. The end products from the Maillard reaction, are the main antioxidant compounds in coffee, which are produced during the roasting coffee beans processed (124). These polyphenols are too large to be absorbed in the intestine, so that their role in the antioxidant defense in the cell has been questioned (125). Furthermore, coffee also has other effects particularly through caffeine, studies have shown increased vascular resistance after acute intake of coffee or caffeine, which suggested a vasoconstriction effect (126). Additionally, coffee consumption has been associated with unhealthy behaviors (Western diet, sedentary lifestyle and overweight), leading to residual confounding. Finally, the contribution of its antioxidant capacity is important, which could lead to masking the action of other antioxidants with systemic action (127). In view of these arguments, many studies have decided not to take into account the contribution of coffee when estimating the TAC in diet (120, 128).

3.4. Total Antioxidant Capacity and Hypertension

Fruits and vegetables have been consistently and inversely associated with risk of hypertension (129). Nonetheless, the use of long-term individual antioxidants supplements was not supported according to the evidence reported from randomized controlled trials. In some studies no association was found with CVD or, on the contrary, an adverse effect was observed (130). Foods are usually consumed together in a meal. The total antioxidant capacity from diet represents a global estimate of antioxidants, this could be a better approach to evaluate the antioxidant power, to measure the synergistic effect of antioxidants (122) their relation with diseases such as hypertension.

Diets rich in TAC have been associated with decreased levels of inflammation and increased levels of circulating blood antioxidants in cross-sectional studies and controlled clinical trials (131, 132). Several studies reported an inverse association between the antioxidant capacity of the diet and C-reactive protein (CRP) (132), biomarkers of oxidative stress (133), diabetes (134), and metabolism (133, 134). In Italy, two intervention studies found that consumption of diets high in antioxidant capacity for two weeks significantly decreased biomarkers of inflammation and improved endothelial function (131). According to a review on antioxidants and cardiovascular disease risk, the evidence suggests that the TAC is associated with decreased risk of cardiovascular disease, however, the evidence is still limited (131).

3.5. Background: Dietary TAC and Hypertension

To my best knowledge, no prospective study has evaluated the relation between dietary TAC and hypertension. The TAC has been used in prospective studies and inverse relation with myocardial infarction (ORAC: HR 0.80; 95% CI 0.67 - 0.97; p = 0.02) (135), stroke (NEAC: HR 0.73; 95% CI 0.53 - 0.99; p = 0.03) (136) and global mortality (TRAP: HR 0.75; 95% CI 0.67 - 0.80; p < 0.0001) have been found (127).

However, one case-control study has addressed the relation between TAC and hypertension. The concentration of antioxidants, free radicals and cholesterol was measured in a blood sample. These measurements were compared between the hypertensive and normotensive group. It was observed that hypertensive patients had lower concentrations of high-density lipoproteins (HDL), vitamin A, vitamin C and nitric oxide. The concentration of TAC in blood was significantly lower for hypertensive participants (mean $\pm$ SD: 6.2 $\pm$ 0.4 vs. 10.9 $\pm$ 0.3) (137).

4. DAIRY PRODUCTS

The alimentary codex considers a dairy product as a "product obtained through any elaboration of milk, which may contain food additives and other ingredients functionally necessary for the elaboration".

4.1. Milk

Milk is a natural product of great interest due to its nutritional composition. This food make an important contribution to meeting the body's requirements of minerals and vitamins like calcium, magnesium, selenium, riboflavin, vitamin B12 and pantothenic acid (138). The main component of milk is water varying from 83% to 91% depending on the type of milk (139), it contains 3.5% of protein, 4.6% of carbohydrate and 3.3% of lipids (140). Nonetheless, the nutritional composition can vary between milk of different animal species (138). Lactose is the main carbohydrate, involved in the absorption of magnesium, calcium, phosphorus as well as the use of vitamin D (138).

Further, milk includes all the essential amino acids and for this reason its protein content is considered as high-quality (138). Casein and whey are the major proteins (141), casein accounts around 78% of the protein of cow milk and whey accounting 17% (142). Recently the evidence has shown that milk proteins are precursors of bioactive peptides. These amino acids are inactive within the protein however they can be released by the action of proteolytic enzymes or digestive proteases as occurs in the fermentation processed (138). It seems that the amino acids depending of the sequence, could exert a range of biological activities. However, the physiological properties in human's health are not completely elucidated (138).

The fat of the milk contains approximately 400 different types of fatty acids, making it the most complex of all-natural fat, which are carriers of fat-soluble vitamins (138). The majority of fatty acids in milk are saturated fatty acids (SFAs) (69.4%), among them palmitic, which is the most abundant (30%) followed by stearic and myristic acid. Milk also contains unsaturated fatty acids, monounsaturated fatty acids account for 25% and polyunsaturated for 2.3%. The most abundant acids are oleic acid and linoleic fatty acids, respectively monounsaturated and polyunsaturated. Trans-fat represents 2.7% and 0.4% are conjugated linoleic acid (CLA) (143).

Further, the term milk is almost considered a synonym of cow milk which is the most consumed worldwide, even if milk from other species as goat are also consumed. Cow and goat milk are similar in macronutrients content. However, the content of lactose is more important in goat milk (144) and despite the differences in proportion of SFAs of goat and cow milk are comparable, goat milk is rich in short- and medium-chain fatty acids almost up to twice as much as cow milk (145). Thus, caproic, caprylic and capric acids are named due to the origin of the milk. Also, goat milk contains branched-chain FAs which are almost not found in milk cow, giving this milk characteristics of “goaty and muttony flavours” (145). Goat milk compared with cow milk has been reported to have more oligosaccharide sialic acid than cow milk (four more times) (144) and retinol but less vitamin B12 (146).

4.2. Yogurt

Yogurt is a pasteurized coagulated milk obtained by fermentation of the lactic acid of two cultures Streptococcus Thermophilus and Lactobacillus Bulgaricus. Yogurt can be classified according to its fat content: low-fat yogurt (< 1% fat), half-fat (at least 1% fat) and whole-fat (at least 3.5% fat). As well as for its flavor: natural yogurt (without added sugar), sweetened yogurt (with added sugar), fruity yogurt (fruit and fruit syrup are added), flavored yogurt (in addition to sugar, contains flavorings) and yogurt with sweetener (based on skimmed-milk and sweetener added) (147).

4.3. Cheese and Cottage Cheese

According to FAO, cheese " is a solid or semi-solid product, ripe or unmatured, in which the proportion of casein whey and serum proteins is not higher than those of milk, obtained from the coagulation of milk " (148). Additionally, in France according to the Decree of November 12, 2013 (Decree No. 2013 - 1010), defined the use of the term "cheese" as: " a fermented or non-fermented product, repined or not, obtained from the following exclusively dairy-based ingredients: milk, partially or totally skimmed milk, cream, fat, buttermilk, used alone or in mixture and coagulated in all or in part before draining or after partial removal of the aqueous portion. [...] The minimum dry matter content of the product thus defined must be 23 grams per 100 grams of cheese " (149).

There are three general steps to make cheese (**Figure 14**)(138). The first, is curdling which is a required step in cheesemaking in order to separate the milk into solid curds and the liquid whey. This is a process usually done through the acidification of milk for which rennet (or vegetable/microbial enzyme) is added to cause the coagulation of milk. Secondly, the curd processing, at this stage the cheese turns into a very moist gel. In the case of some soft cheeses, after being drained, salted and packaged, their process is completed. For the other cheeses, the curd is cut in small pieces which allow the water to drain. Then, the curd is heated to temperatures ranging between 35 to 55 °C or higher, allowing the elimination of more water and making harder the cheese. Afterwards salt is adding to cheese to confer the flavor but also is required for preservation and texture. To obtain their final shape the curd is pressed in mold. More pressure is required to achieve a harder cheese. Finally, in the ripening and aging, the cheese is stored (for days or years) under controlled conditions and additional bacteria or molds are introduced before or during this stage.

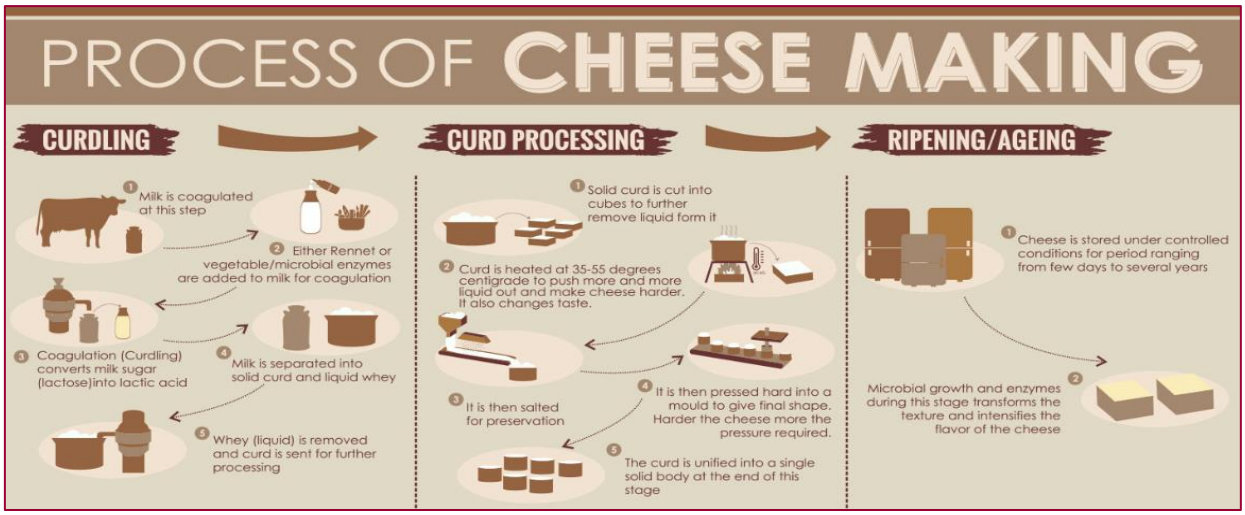


Figure 14. Process of cheese making.
Source: Healthonics. Available: http://www.healthonics.healthcare/ cheese-veg-non-veg-part-1-what-cheese/

Several types of cheeses are produced around the world, their different characteristics, flavors and textures depend on the type of milk (cow, goat), pasteurization process, the content of fat in the milk, aging, the type of bacteria or mold (138). Thus, there are a number of ways to classified cheeses. It can be classified by the origin of milk as goat, sheep, or cow cheeses. The CODEX also classified cheese according to firmness (extra-hard, hard, semi-hard and soft cheese), or by their ripening characteristics in two groups:

unripened (soft and cottage cheeses) and ripened cheeses (extra-hard, hard, semi-hard) (138) (**Figure 15**).

4.3.1. Types of cheese

- Soft-cheese. Cow's or goat's milk, raw or pasteurized, is used for its elaboration. The coagulation is of mixed type: enzymatic or lactic. The cheese is characterized by not being cured, neither cooked, nor unctuous and as its name indicates it is of soft texture.
- Semi-hard cheese. It is characterized by having a quick draining, has little acidity which gives it a mild flavor. No carbon dioxide is produced hence no holes are observed.
- Hard cheese. In this group the curd is cooked, between 30 to 60 minutes which favors the drainage of the curd. In some of them, fermentation can cause the production of carbon dioxide causing perforations (holes).
- Processed cheese. It is constituted by a mixture of cheeses and soft texture. These cheeses are made by melting one or more pressed cheeses cooked with other ingredients like milk, cream, butter and sugar (149).
- Blue cheese (green). These cheeses are characterized by the presence of blue mold. This mold called "Penicillium Roqueforti", can originate spontaneously or during the production process in the stage of the curd. To favor air circulation and its development, it can be perforated with needles.
- Goat cheese. On contrary to the first group, these cheeses are made from goat milk, which nutritional content is different compared to cow milk, they are not classified according to the manufacturing process and they are mostly soft cheese type moldy rind (147).
- Cottage cheese. It is a soft, rindless, unripen cheese, where lactic fermentation is the only one allowed and its solids content is less than 23 grams per 100 grams of cheese (148). However, in France it is considered as another kind of dairy product because of it amount of dry matter content that is under the threshold specified in the Decree No. 2013 - 1010. Furthermore, the nutritional content of this dairy product is different when compared with other types of cheeses. Cottage cheese is lower in energy, protein and total fat as we can observe in **Table 2**.

Cheeses
Soft cheese
 
Semi-hard cheese
 
Hard cheese
 

Processed cheese

Blue cheese

Goat cheese

Cottage cheese

Figure 15. Different types of cheese.

Table 2. Main nutrient composition in common cheeses (nutrients g per 100 g).

Cheeses		Water (g)	Energy (kcal)	Protein (g)	Total, fat (g)	Lactose (g)
Cottage cheese	average	**79.3**	**99**	**12.4**	**4.4**	**2.2**
	range	**78.6–79.8**	**94–103**	**11.1–13.7**	**3.5–5.4**	**1.0–3.1**
Blue cheese*	average	43.5	356	21	29.9	0.4
	range	38.0–50.8	324–410	19.1–23.7	27.1–35.0	0.1–1.0
Brie	average	48.8	331	20	27.9	0.3
	range	48.42–49.3	319–343	19.3–20.8	26.9–29.1	0.1–0.45
Camembert	average	51.9	297	20.9	23.7	0.2
	range	50.5–54.4	286–312	19.6–22.6	21.7–26.2	0.1–0.5
Cheddar	average	36.5	406	25.1	33.7	0.3
	range	34.0–38.5	381–427	24.2–26.2	31.0–36.6	0.1–0.5
Gouda	average	46.1	338	23	26.6	2.2
	range	41.5–50.8	320–356	21.1–24.9	25.8–27.4	2.2–2.2
Edam	average	41.5	353	26.6	27.1	0.8
	range	39.0–43.8	341–360	25.0–28.1	26.0–27.8	0.1–1.4
Feta	average	56.1	254	16.1	20.2	1.8
	range	54.9–57.1	249–264	14.2–19.4	19.2–21.3	0.5–4.1
Mozzarella **	average	53.9	275	22.1	20.3	0.5
	range	49.7–58.8	253–300	16.7–28.9	17.7–24.4	0.1–1.0
Parmesan	average	27.3	402	37.6	27.2	0.5
	range	16.0–36.4	356–444	33.6–44.9	24.1–29.7	0.1–0.9
Goat cheese, soft	average	55.8	294	19.8	23.4	0.9
	range	60.8–50.8	268–320	18.5–21.1	21.1–25.8	0.9–0.9

Source: FAO. 2013. Milk and dairy products in human nutrition, by Muehlhoff E, Bennett A and McMahon D. Rome. Available at: http://www.fao.org/3/i3396e/i3396e.pdf.

The data were obtained (where available) from the following databases: USDA, Food Standards Agency/McCance and Widdowson, Danish Food Composition Databank, New Zealand food composition tables, Italian Food Composition database. The number of data points varied. * Blue cheese includes Roquefort (sheep milk), Stilton, Gorgonzola and Danish Blue. ** Includes milk from cow and buffalo.

4.4. Other milk-based products

Butter and cream, both are milk products characterized by their high content of fat and low content of calcium (**Table 3**)(138). The alimentary codex defines butter as “a fatty product derived exclusively from milk and/or products obtained from milk, principally in the form of an emulsion of the type water-in-oil” around 81% of this product consist on fat (148). Cream is “the portion of milk which is rich in milk fat and is separated by skimming or centrifuging” also is “the fluid milk product comparatively rich in fat, in the form of an emulsion of fat-in-skimmed milk, obtained by physical separation from milk” (148). Ice cream rich in fat and carbohydrates (**Table 3**) (150) “means edible ices prepared from milk and milk products and which contain as fat only milk fat and as protein only milk protein” and edible ices (150) “mean the food preparations obtained either from an emulsion of fat and protein with or without the addition of other ingredients and substances, or from a mixture of water, sugars and other ingredients and substances which have been treated by freezing and are intended for storage, sale and human consumption in the frozen or partially frozen state. For those edible ices containing milk ingredients, the ice mix shall be pasteurised (or undergo an equivalent treatment)”

Table 3. Composition of milk products excluding cheese (per 100 g of product).

USDA food name	Energy (kcal)	Protein (g)	Total, fat (g)	Lactose (g)
Cow milk, whole, fresh	61	**3.2**	**3.3**	5.1
Cow milk, Skimmed	34	3.4	0.1	5.1
Yogurt	61	3.5	3.3	4.7
Cottage cheese	99	**12.4**	4.4	2.2
Cream, fresh	195	2.7	**19.3**	0.1
Butter of cow milk	717	0.9	**81.1**	0.1
Ice cream, vanilla	207	3.5	**11**	**23.6***

Source: FAO. 2013. Milk and dairy products in human nutrition, by Muehlhoff E, Bennett A and McMahon D. Rome. Available at: http://www.fao.org/3/i3396e/i3396e.pdf. * Carbohydrates

4.5. Importance of Dairy Product Consumption

Milk and its derivatives are considered of important nutritional value. They are the main source of bioavailable calcium because milk does not contain phytates and oxalates which are substances that inhibit mineral bioavailability (138). Almost all the calcium in the body (99%) is stored in the teeth and bones, although the body can only use calcium from the bones in a context of low consumption (106).

Calcium is important due to its physiological functions since it participates in the coagulation of the blood, in the muscular contraction, the production of hormones and in the preservation of bone health. Furthermore, the main dietary factors that influence bone mass are calcium and vitamin D along with other nutrients as potassium, zinc, vitamins A, C and K and protein, as well as energy, also play a role. The most important minerals related to bone health are calcium, phosphorus and magnesium (138).

In women, dairy consumption is recommended due to its calcium and vitamin D content, mainly to prevent osteoporosis (138). This is the most frequent bone disease; it has a multifactorial origin that is characterized by a decrease in bone mass which can lead to fractures. Postmenopausal women are more at risk, since osteoporosis is associated with the production of estrogen. Controlled clinical studies have shown that consumption of calcium and vitamin D supplements can decrease the risk of fractures (151). To avoid osteoporosis, it is necessary to have an adequate supply of calcium and vitamin D. The recommendation is 1200 mg of calcium in women over 50 years and for all adults over 70 years, equivalent to 3 - 4 servings of daily dairy depending of the size of the portion (106).

4.5.1. Dairy Product Consumption

4.5.2. Dairy Product consumption in France

The French National Nutritional and Health Program (PNNS) created to improve the health status, recommended the daily consumption of three dairy products for adults aged 18 to 54 years, and 3 or 4 for adults of 55 years an older. This program considered milk, yogurt, cottage cheese and cheese as dairy products (152). According to the National ENNS study (French National Nutritional and Health) (153), 29% of French population followed the daily dairy recommendation, this percentage increased with age for both sexes. For example, in women over 54 years, about half (46.5%) consumed at least three servings per day. The 28.4% of women's dairy products consumption could be considered as low (< 1.5 portions).

In France the annual consumption per capita of milk was 52.6 kg and for cheese was 26.7 kg (148), being the first consumers of cheese in the world (154). According to the National Survey (INCA 2), on average the daily intake of milk was 75.3 $\pm$ 144.5 g, of yogurt and cottage cheese was 76.7 $\pm$ 78.7 g and 30.9 $\pm$ 31.3 g of cheese. Daily consumption among adults, was 43.7% milk, 68.6% yogurt and cottage cheese and 80.4% cheese. Milk consumption was mainly at breakfast whereas yogurt, cottage cheese and cheese consumption were at lunch and dinner (155).

Dairy products consumption varied slightly according to age, sex and educational level. Men consumed more cheese than women (84% vs. 77%); while, women consumed more yogurt and cottage cheese (82 g/d vs. 72 g/d). Adults aged 65-79 years were the highest consumers of cheese 37.5 $\pm$ 38.4 g/d than the rest of the population (18 - 44 years: 28.4 $\pm$ 28.2 g/d; 45-64 years: 31.0 $\pm$ 30.8 g/d). No differences were observed in the yogurt, cottage cheese and milk consumption according to age. Educational level was associated in a direct way with dairy products consumption in contrast the socioeconomic category was little associated with nutrition in general (155).

4.5.3. Dairy Products consumption in Mexico

In Mexico, the Official Mexican Standard (Norma Mexicana) defined dairy product as " the product made from milk ingredients, such as casein, fat, whey, water for human consumption and use, with a minimum of 22 g/L of milk protein and, of this, 80 % of

casein, may contain fats of vegetable origin in the quantities necessary to adjust it to the specifications established in this standard" (156). The Official Mexican Food Guidance Norm (157) promotes the intake of food source of calcium such as milk and dairy product, but it recommends low-fat milk. In 2016, the National Health and Nutrition Survey (ENSANUT)(158), categorized food groups according to their positively or negatively association with overweight and obesity. Dairy products were categorized in two groups: recommended (cheese, yogurt, milk without added sugar) and no recommended for commonly consumption (milk with sugar or chocolate, yogurt to drink, atole with milk and sugar).

In Mexico, the annual consumption of liquid milk per capita was 29.9 and 3.7 for cheeses (kg)(139). According to ENSANUT 2016 (158), 61.7% of the adult population reported consuming at least one dairy product (unsweetened milk, yogurt and cheese) the previous week to the survey. However, the consumption was not homogenous throughout the country, it varied according to the location area and the region. The percentage of consumers was higher in the urban area (64.8%) than in the rural area (52.3%). The southern region had the lowest percentage of consumers (54.1%) compared to other regions of the country (North 65.6%, Center 63.9% and Mexico City 66.4%).

Regarding the specific consumption of different types of dairy products throughout the country, it was reported that 24.1% of adults consumed sweetened dairy drinks (milk with sugar or chocolate, drinking yogurt, atole with milk and sugar). A lower consumption of this product was observed in the rural area (24.8%) compared to the urban area (22.1%) as well as in the north of the country (18.1%) compared with center (25.4%), Mexico City (28.3%) and the South (24.1%).

Whole-milk is commonly consumed in Mexican population (47.3%) and only 6.6% consumed low-fat milk (skimmed and semi-skimmed milk). Together, cream, cheese, fermented dairy products and butter represented 39.6% and yogurt 8.5%. The daily average of energy consumption from dairy products was 167.5 kcal whereas in consumers was higher 238.4 kcal (13% of the total energy of the diet).

Regarding women, 69% consumed dairy products, their consumption represents on average 202.4 kcal. According to the type of dairy product, the average milk consumption was 257.3 ml, whole-milk 254 ml, non-fat milk 204.5 ml, yogurt 199 g and other dairy products 40.3%. The consumption of yogurt represented a little more than a quarter

(28.3%) of the sweetened dairy products consumption showing that the sugar content in this product is high. The reduction of sugar content at the same time decreases the caloric intake contributes directly to weight loss, a major problem in Mexico (6).

4.6. Nutrients in Dairy Products and Hypertension

For decades, milk has been widely recommended, because of its high content of bioavailable calcium and also due to their beneficial effect on health. Nonetheless, in recent years the role of milk and dairy products has been increasingly questioned in human health. This food group which have a complex nutritional content and most of their nutrients do not work in isolation rather their components interact among them (138). Furthermore, their nutrients are involved in various biological process even with conflicting effects on health such as the high content of saturated fat and sodium, which are known factors for CVD (159).

Dairy products nutritional content, includes minerals (calcium, sodium, potassium and magnesium), vitamins (A, C and D), proteins of high quality and a rich matrix of fat content (160). Different mechanisms have been proposed to explain the relation between dairy products consumption and hypertension however it is not completely elucidated. One possible mechanism is the vasodilator action of potassium and magnesium which inhibits the contraction of the smooth muscle avoiding vasoconstriction (9). Vitamins A, E and C act as antioxidants which neutralize the action of free radicals and prevent the lipid peroxidation of lipoproteins particularly LDL, which is a major mechanism of atherogenesis. These vitamins maintain the balance between oxidants and antioxidants in the endothelium as well as maintaining its proper functioning (66).

Vitamin D could be associated with hypertension under several mechanisms. Some studies suggest that it could have a role in the renin angiotensin system regulation. Vaidya et al, observed after supplementation with vitamin D, a decreased in the concentration of angiotensin and renin as well as blood pressure (141). In addition, vitamin D could lower blood pressure through the reduction of parathyroid hormone having a direct effect on vascular tissue (161). Moreover, vitamin D and calcium are interdependent in the human body. When levels of ionized calcium decrease in blood,

parathyroid hormone is secreted to stimulate the conversion of vitamin D to its active form (calcitriol) and in consequence depleting vitamin D status. In the intestine calcitriol influences the absorption of calcium, an inadequate status of vitamin D is associated with a decrease of the absorption of calcium from the diet (148, 162).

Further, calcium decreases fat absorption; this mineral can bind with fatty acid producing insoluble soap which reduces the absorption of fat in the gastrointestinal track and increase the excretion faecal fat (163). In addition, calcium and vitamin D, work together in vascular smooth cells regulating the concentration of intracellular calcium (163). The increase in serum of 1, 25-OH^2-vitD due to a low concentration of calcium, lead to an increase of calcium into the cells provoking constriction and increasing of the pressure (140). Increasing the consumption of calcium from dairy products, the 1, 25-OH^2-vitD concentration could decrease preventing vasoconstriction (141).

Perhaps the most important mechanism of the potential role of dairy products in lowering blood pressure is the inhibition of angiotensin-converting enzyme. Dairy products contain two proteins, casokinin and lactokine, both of which contain peptides with inhibitory properties of the converting enzyme (164). When the angiotensin II occurs, blood pressure increases, causes vasoconstriction, increases the release of the antidiuretic hormone through the release of vasopressin, and thus produces the reabsorption of water at the level of the kidneys, and triggers the release of the aldosterone of the adrenal cortex inducing the sodium reabsorption by the kidney (9). In one trial (165), men and women were supplemented with 27 g of whey or casein as part of their usual diet for 12 weeks. A significant reduction in systolic blood pressure was observed in 4.0 and 4.2% in the group supplemented with serum and casein, respectively. The diastolic pressure decreased by 3% for both treatments compared to the start of the study, there was no difference between the types of protein.

Sodium is the only causal dietary factor associated to hypertension. This element increases blood pressure through the increase of blood volume and in consequence the increase of cardiac output (9). Finally, saturated fat is a possible factor involved in the increase of hypertension risk. Besides the appreciable content of saturated fat in dairy fat, it contains nearly 400 fatty acids and many of them are only found in this food (159). These unique fatty acids have a biological importance (166), the evidence suggest that conjugated linoleic acids were associated with anticarcinogenic and antiatherogenic effects (167-169), while branched chain fatty acids are resistant to oxidation (170). The relation between sodium saturated fat and hypertension was explained deeply previously

in this chapter. In summary, for fermented products it is possible that the main mechanism related to hypertension are the peptides with inhibitory properties of the converting enzyme. Globally, dairy products contain a high amount of calcium along with the potassium which were inversely associated with hypertension. Probably they may be the main nutrients in the studied relation.

4.7. Background: Dairy Product Consumption and Hypertension

In this section, previous cohort studies which evaluated the association studied were summarized to understand their strengths and limitations (**Appendix 2**). All the studies (n = 9) were conducted in developed countries: United States (n = 3) (58, 171, 172), France (n = 1) (173), Spain (174) (n = 3), Holland (175, 176) (n = 2) and England (177) (n = 1), among them, four found a significant inverse relation between dairy or at least one type of dairy product and hypertension.

Summary of studies which found a significant association between dairy and hypertension

These studies were characterized by having an important statistical power, the sample size varied from 2 245 to 28 886, the follow-up time varied from 2 to 10 years, all of them used a semi-quantitative food frequency questionnaire to evaluate dairy intake. Dairy products were evaluated according to their fat content classified as whole and skimmed, some studies evaluated the relationship between each dairy type and hypertension. The evaluation of hypertension in two of the studies was conducted through self-report (diagnosis, treatment or blood pressure values) and clinical examination.

The SUN cohort (174) followed former students graduated from the University of Navarra, after 2 years, a lower risk of hypertension was observed among those who were located in the extreme quintiles of consumption of semi-skimmed milk (HR 0.46; 95% CI 0.26 - 0.84), however, no inverse relationship was found with the consumption of whole milk products. The American study ARIC (171), estimated the risk of hypertension stratified by race (Caucasian and Afro American). Over 9 years, the systolic pressure increased 2.7 mmHg (95% CI -0.3 to - 0.6; p = 0.01) less in participants who consumed

3 or more servings of skimmed milk compared to those who consumed less than 1 serving per week. This association was observed only in Caucasian participants. The estimation of the risk of hypertension by type of dairy product was only possible with whole milk, no significant association was found, this analysis was not possible with other dairy products due to the small variability in their consumption. In the Women's Health Study (58), after 10 years of follow-up, a significant inverse association was found between hypertension and skimmed dairy consumption, but this was attenuated when adjusted for calcium intake.

The Rotterdam Study (175) evaluated this relationship in two follow-up times after 2 and 6 years. After 2 years, a significant inverse relationship (Q4 vs. Q1; HR 0.69; 95% CI 0.56 - 0.86) between the consumption of skimmed dairy products and the risk of hypertension was observed, but not with whole milk products (p = 0.77). In addition, in the analyses by type of dairy product, neither the fermented products nor the cheese showed a significant association. After 6 years, the association with skimmed dairy products was no longer significant (HR 0.84; 95% CI 0.70 - 1.01; p = 0.07).

Summary of studies which did not find a significant association between dairy and hypertension

Five studies conducted in different countries (England, Holland, United States and France) (173) did not find a significant association between dairy products and hypertension. These studies had a smaller sample size than the previous group (from 755 to 4 304 participants) and a longer follow-up from 5 to 15 years. To evaluate hypertension all the studies used the physical examination, hypertension was defined as pressure values were ≥ 140/90 mmHg, apart the CARDIA study (172) which used the cut-off point of ≥ 130/85 mmHg. Dairy product consumption was evaluated by two methods, the frequency of consumption (n = 2) and the records (n = 3). In addition, three of them did not classify the dairy products as whole and skimmed, which could explain the non-association since fat content may be associated with hypertension.

In the other two studies, dairy products were classified according to their fat content and they had some limitations. The study National Birth Cohort 1946 (177), used several classifications of dairy: total, with and without cheese, whole, skimmed and fermented. This study recruited children born in 1946 to participate in order to collect information during childhood and adulthood. The diet and covariates were evaluated at the age of

43 years and the outcome at 53 years. During follow-up, diet and covariate information were not updated. In England, during that period there was a drastic change in dietary habits and probably in lifestyle. The average intake of skimmed dairy increased (from 142 g/d to 245 g/d) whereas the intake of whole dairy decreased (from 138 g/d to 52 g/d) leading to a misclassification of the exposure. The status of the covariates also did not have an update and could undergo modifications. In addition, residual confusion cannot be rule out certain variables such as diabetes, family hypertension history and cardiovascular disease were not taken into account in the analyses.

On the other hand, the Morgan Study (176), showed an inverse association between the consumption of skimmed dairy products and the hypertension risk, however this association was not significant. It is possible that it did not have enough power to show statistical significance. Furthermore, in this study, not all participants had physical activity information as an important risk factor for the development of hypertension.

Finally, SU.VI.MAX (173) is the only prospective French study that evaluated the relation between dairy products intake and the hypertension risk. Despite having a follow-up of 5 years, the researchers did not find an association its main limitation was they did not classify dairy products by fat content or by type of dairy.

OBJECTIVES

CHAPTER II: SUMMARY AND OBJECTIVES

Hypertension is a preventable disease which is a major cause of disease burden and expected to rise in the future. It is considered the first risk factor for cardiovascular disease which are the first cause of death worldwide. It has been associated with several cardiovascular and renal outcomes such as ischemic heart disease, cerebrovascular disease and chronic kidney disease. Modifiable risk factors, such as use of alcohol, lack of physical activity, overweight, obesity and diet, have been identified for hypertension. However, among dietary factors there are some nutrients and foods for which their role in hypertension risk remains unclear.

Antioxidants are one of those dietary factors. Oxidative stress is associated to hypertension. However, results from clinical trials evaluating antioxidant supplementation and hypertension are inconsistent. Nonetheless, evidence from observational studies supports a potential protective effect of dietary antioxidants against cardiovascular risk thus hypertension.

Dairy is a food group that has been widely studied as a potentially important risk factor for hypertension (and subsequent cardiovascular disease). These products are largely consumed worldwide because of its content of calcium. The nutritional content of milk is complex. The health benefits of dairy consumption have been questioned because of the high content of saturated fat and sodium in these foods. However, some dairy, specifically milk contain nutrients known to be protect against hypertension. Observational prospective studies were not consistent, this could be partly explained due to the methods (statistical methods, diet measurements and confounding), but also because of the differences in the nutritional content of each type of dairy.

This thesis explores the influence of dietary factors and the risk of hypertension, particularly antioxidants and dairy products. **Therefore, the first specific objective** was to assess the relation between the dietary total antioxidant capacity (TAC) and the risk of hypertension in the E3N French prospective cohort of women. Using dietary TAC as an exposure is an alternative and innovative method that may more appropriately represent the total impact of antioxidants on hypertension risk because it considers the possible synergy between different antioxidants in the diet. This analysis would be the first occasion in which TAC is used to determine the impact of antioxidants on the risk of hypertension.

The second specific objective was to evaluate the relation between total dairy consumption and different types of dairy (milk, yogurt, cottage cheese and cheese) and risk of hypertension in French adult women of the E3N study. Additionally, in secondary analyses the relation between whole-fat, low-fat and various types of cheeses with hypertension was also evaluated. In France, there are a large diversity of dairy which is the ideal place to study this relation. Only two studies have previously evaluated the relation between blood pressure and total dairy consumption, but not hypertension. There is no information on the relation of each type of dairy or various types of cheeses and hypertension risk.

Similarly, but in a different population, the third specific objective was to evaluate total dairy products and subtypes of dairy (milk, yogurt, cheese and sugared dairy products) as they relate to risk of hypertension in the Mexican Teacher´s Cohort. In secondary analyses, we evaluated also the relationship between whole-milk, skimmed-milk products, high-fat milk-based products, and sugar-sweetened dairy products consumption.

Evaluating the relation between dairy product consumption and hypertension in two different populations has important advantages. First, observations made in two independent populations with a different distribution of hypertension risk factors. Second, having populations with a different distribution of dairy product may provide information on the impact of different areas of the distribution and hypertension risk.

MATERIALS AND METHODS

CHAPTER III: MATERIALS AND METHODS

This chapter will provide details the materials and methods used to achieve the objectives of the thesis. First, the French E3N cohort study will be described, which was the basis for the analyses on dietary total antioxidant capacity, dairy products and hypertension, followed by a description of the MTC cohort study, in which the relation of dairy products and hypertension were assessed. Finally, the statistical analyses used will be described.

1. THE E3N COHORT STUDY

1.1. Presentation of the cohort

The E3N study or **E**tude **E**pidemiologique auprès de femmes de la Mutuelle Générale de l'**E**ducation **N**ationale (MGEN), is an ongoing prospective cohort started in 1990, consisting of 98 995 female volunteers between 40 and 65 years old, living in metropolitan France at the time of its inclusion (1989 - 1990). The primary objective of this study was to investigate lifestyle, nutritional, hormonal, and genetic factors associated with cancer and other non-communicable diseases in women (178). All the participants were members of MGEN (Mutuelle Générale de l'Education Nationale) a national health scheme mostly covering teachers. The French National Commission for Computed Data and Individual Freedom (Commission Nationale Informatique et Libertés, CNIL) gave their ethical approval for the investigation. In addition, the participants signed an informed consent, allowing the research team to access regular information on the reimbursement of their medical expenses, vital status and address changes. This cohort has a very low loss to follow-up rate (3%) and the vital status is unknown for only a minimum proportion (0.75%) of participants (178). In 1993, E3N became the French component of the European EPIC study (European Prospective Investigation into Cancer and Nutrition) (179) conformed by 10 European countries, with the objective of studying risk factors for cancer, among men and women.

1.2. Data Collection

The primary information collected in the questionnaires were related to lifestyle, anthropometry, and health status. The data was updated approximately every 2 years through questionnaires sent via postal mail. To date, 12 questionnaires have been sent to participants (**Figure 16**). At baseline in 1991, sociodemographic characteristics, medical history, reproductive life, tobacco consumption, anthropometry, physical activity and family cancer history were evaluated. The second questionnaire (Q2, 1992) was mainly focused on reproductive history and hormonal treatments. Health status and medical treatments received by the participants were updated throughout follow-up (Q2 to Q11). The third (Q3, 1993) and eighth (Q8, 2005) questionnaire evaluated food intake. (178). The questionnaires were processed internally and anonymously by the research team. Once the questionnaires are received, they are scanned. The data management team proceeded with the data cleaning, harmonization and verification of the coherence of the information. Systematic validation of self-reported diseases was performed using the information of the MGEN health insurance plan drug reimbursement claims database.

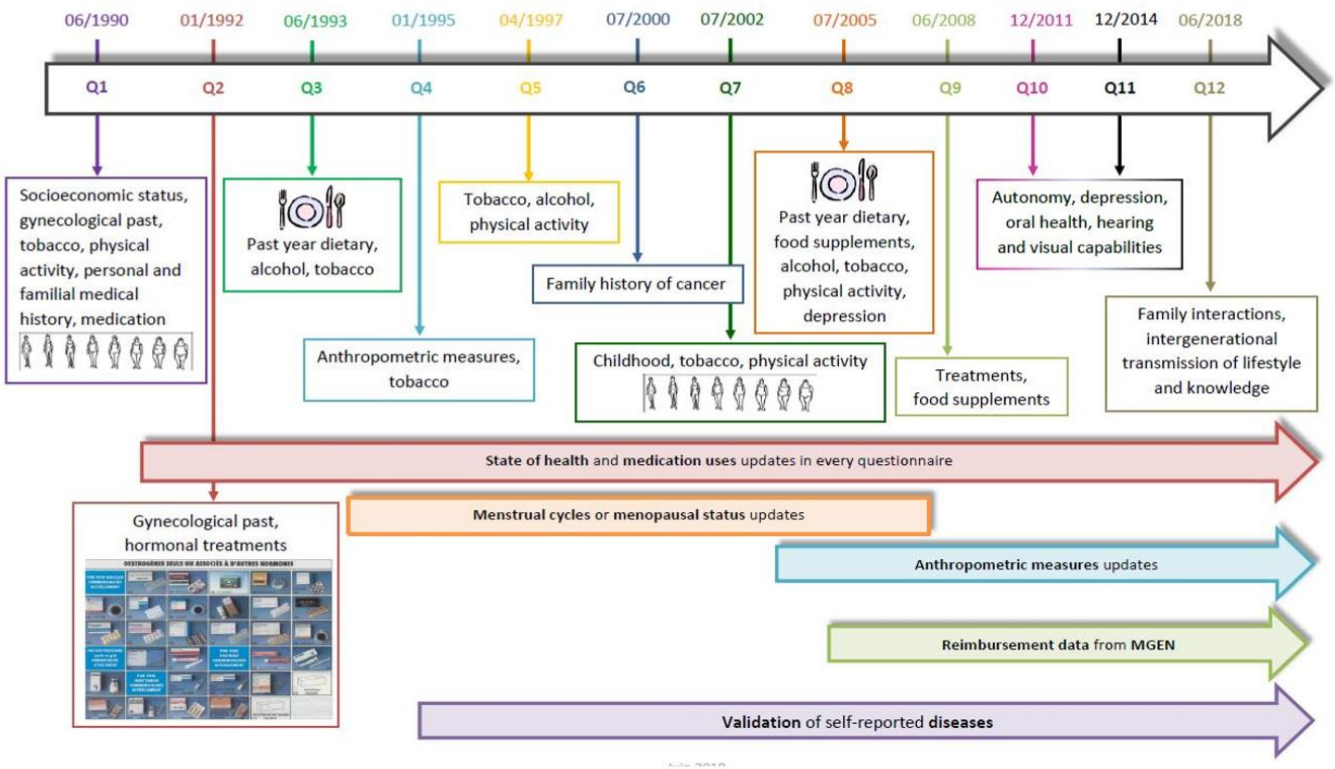


Figure 16. The E3N Cohort study enrolment and calendar of self-administrated follow-up questionnaire.

1.3. Dietary questionnaire

A self-administered dietary history questionnaire was sent to all cohort participants in 1993. The questionnaire was designed to assess the habitual diet of the previous year. Participants were asked to report their usual daily intake of foods and drinks. The questionnaire was designed to take into consideration typical French meal and dietary patterns. With the aid of a clock face and photo album, participants recorded the habitual frequency of consumption and the portion size for commonly consumed food groups, foods, and drinks for each of the following 8 meals: breakfast (7 a.m.), mid-morning snack (10 a.m.), lunch appetizer (11:45 a.m.), lunch (12:00 p.m.), mid-afternoon meal (4:00 p.m.), dinner appetizer (7:45 p.m.), dinner (8:00 p.m.), late night snack (10:00 p.m.)

The questionnaire is divided into two parts, the first (**Figure 17**) contains quantitative information on the frequency of consumption and the portion size of 66 items, grouped by meal. To quantify the frequency of consumption eleven categories were available: never or less than once a month, once a month, twice a month, three times a month, once a week, twice a week, three times a week, four times a week, five times a week, six times a week and seven times a week (180). The quantity consumed was estimated using standard units or portions size which were indicated with the aid of photo album (181). Portion sizes were established by nutritionists and team researchers, based on their knowledge of standardized portions of the collective catering from which they were adapted after a validation examination. All pictures were taken by a professional photographer. For each item of the questionnaire, the album had 3 options of portions size: small (A) medium (B) and large (C). However, participants could choose up to 7 response options, the sizes of portions A, B, C, smaller than A, between A and B, between B and C, and larger than C.

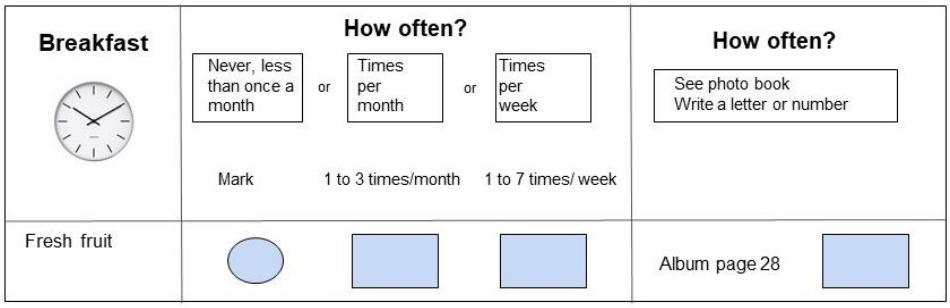


Figure 17. First section of the E3N dietary questionnaire (fruit consumption during breakfast).

The second part (**Figure 18**) includes qualitative questions which allows to detail the consumption within the generic food groups in the first part (cooked vegetables, raw vegetables, fruits, meat, fish and dairy products) as well as the frequency of its consumption with the following categories: never or less than once a month (0), occasionally (+), regularly (++) and very often (+++). For example, if in the first part asks about fruit consumption, the second part includes a list of fruits. Then, for each fruit on the list, participants must characterize their consumption frequency. By combining the first and second parts it is possible to estimate the usual consumption of 238 meals (153).

Fruits: Do you usually consume fruits?										
No, Never										
Yes, Which?										
	0	+	++	+++			0	+	++	+++
Orange						Strawberries and raspberries				
Grapefruit						Cherries				
Tangerine						Peach				
Apple						Melon				
Pear						Apricot				
Banana						Plum				
Kiwi						Grapes				
Pineapple						Other (precise)				

Figure 18. Second section of the E3N dietary questionnaire.

1.3.1. Daily consumption and nutrient estimation

The estimation of the energy and nutrient intakes were obtained by multiplying the quantity of daily consumption of each food by their nutrient content of the food according to the French food composition table (182). To estimate the daily consumption of fruits, the daily frequency was estimated first (**Figure 19**), dividing the number of times declared by 30 if the consumption was monthly and by 7 if it was weekly. The amount obtained was multiplied by the reported portion in grams. For example, if a participant reported a consumption of 200 g of fruit 6 times a week. Six was divided by 7 obtaining a consumption of 0.86 servings of fruit daily at breakfast. The value obtained (0.86) was multiplied by the reported amount 200 grams, obtaining a consumption of 172 grams of fruit per day at breakfast (180). To estimate a specific fruit as daily orange consumption (or any fruit) in grams, the total fruit consumption obtained in the first part of the questionnaire (172 grams per day) was multiplied with the orange's weighting factor

(0.375), obtaining an orange consumption of 64.5 grams daily at breakfast. The process to estimate the weighting factor for each food is described in **Figure 19**. In this example, firstly the participants characterized their frequency of consumption of fruits in four categories "0", "+", "++" and "+++" supposed to represent: never or less than once a month (zero), occasionally (1 cross), regularly (2 crosses) and very often (3 crosses). Then, the sum of crosses was conducted and equaled to 100% (because it represents the total fruit consumption) permitting to obtained an attributed weight (X= 0.125). This value was used to be replaced in each attributed weight in order to estimate the weighting factor in order to obtain a weighted consumption for each fruit (**Figure 19**).

The French nutrient composition table created by the CIQUAL (Centre d'Information sur la Qualité des Aliments) (183) was used to estimate the nutrient intake. In this table the nutritional information for each 100 grams of food is specified. For example, to estimate the energy provided by the orange, the process is explained in **Figure 19**. The information provided by the CIQUAL table was used, in which the amount of energy in 100 grams of orange is 42 calories, with this information and with the amount of daily consumed fruit (172 grams) we made a cross-multiplication. In the E3N study, the weighting factor was added to the multiplication in order to take into account the consumption frequency of each fruit in the energy estimation.

Fruits	0	+	++	+++	**Attributed Weight**	**Weighting Factor**	**Daily Consumption (g)**	**CIQUAL Energy 100g**	**Estimated energy for each fruit**
Orange				X	3X	3(0.125)= **0.375**	172	42	(172x42/100)x **0.375** = 27
Tangerine			X		2X	2(0.125)= **0.250**	172	45	(172x45/100)x **0.250** = 14.8
Apple			X		2X	2(0.125)= **0.250**	172	54	(172x45/100)x **0.250** = 14.8
Pear		X			1X	1(0.125)= **0.125**	172	55	(172x55/100)x **0.125** = 9
Total					8X=100% X=0.125	1			

Figure 19. Estimation of the weighting and weighted energy.

1.3.2. Validity and reproducibility

In 1990, the validity and reproducibility of the questionnaire was evaluated in a subsample of 119 female workers of the Gustave Roussy Institute. Participants in that study were similar in age to E3N study participants (180). Women in that study answered

a dietary history questionnaire at the beginning and at the end of a one-year period. Information from both questionnaires was compared with 12 24-hour recalls applied monthly during the study duration. The 24-hour recall is a method that consists in remembering the food items consumed 24 hours before answering the survey that is usually conducted through an interview by trained nutritionists. Estimates derived from the 12 24hr recalls were considered the reference. By repeating the recall on a monthly-basis dietary intake variation during the week (weekdays vs. weekends) and season (e.g. summer) are taken into account. Reproducibility was evaluated by comparing the results obtained by the two dietary history questionnaires. The correlation coefficients comparing estimated food intake from the second questionnaire and the average of the 12 24-hour recalls ranged from 0.12 (seasoning and sauces) to 0.71 (alcoholic beverages). The correlation coefficients for macronutrients were relatively high (r = 0.67 for proteins, r = 0.74 for carbohydrates, r = 0.60 for fat, and r = 0.86 for alcohol). Regarding reproducibility, the coefficients ranged from 0.40 (seasoning and sauces) to 0.74 (fats) for food groups and for nutrients from 0.54 (vitamin E) to 0.75 (calcium). This study showed that the diet history questionnaire created by the E3N team is adequate to classify the usual consumption of food and nutrients (180).

1.4. Exposures

1.4.1. Dietary total antioxidant Capacity (TAC)

In the E3N study, the total antioxidant capacity (TAC) of the diet was previously determined for all individuals with dietary information in 1993. The TAC was estimated with the FRAP (Ferric reducing ability of plasma) and TRAP (Total Radical Absorbance Parameter) methods, both based on determinations made in Italy (91), with which a table of food composition that included TAC was generated. The values reported by this table were considered the most relevant to food consumption in France. For each food of the 238, the antioxidant amount (mmol) per 100 grams is counted. For each food item in the diet history questionnaire, an equivalent food in the TAC database was identified. For four items (apple, melon, beer, and vinegar), more than two values were available and an average of the available values were calculated. When a direct match was not found, values for a similar food were used, based on the similarity in botanical group and vitamins C and E, and polyphenol contents. In this way, based on the daily consumption of each food, the antioxidant capacity per food was estimated. By adding the antioxidant capacity of all foods, the total antioxidant capacity of the diet was obtained for each study

participant (122). In the E3N study, the FRAP and TRAP measures were strongly correlated (0.97). FRAP method is usually used when the research is focused in diseases related with iron consumption which was not the interest of this thesis. For this reason, TRAP method was used to evaluate the total antioxidant power of the diet with hypertension.

The main contributor to TRAP were TRAP from coffee represented 75% of overall TRAP, 6% for fruit, 5% for wine, 5% for tea, 4% for vegetables, 3% for chocolate, and 3% for other sources. For non-coffee TRAP, major providers were fruit (22%), wine (20%), tea (18%), vegetables (16%), chocolate (12%), and other miscellaneous sources (12%) (127). As well as in this study, the main contributor to diet TAC in western populations is coffee (122, 123). However, because of the dominant participation of coffee, and the doubts about the proportion of polyphenols from coffee to be absorbed and play an actual systemic role (127, 184), the TAC of coffee was not considered in the main analyses of this study. Nonetheless, models with a partition of TRAP into coffee-TRAP and non-coffee TRAP with mutual adjustment were performed. Besides, a fully partitioned model, simultaneously considering coffee TAC, TAC from fruit and vegetables, TAC from wine, TAC from chocolate, TAC from tea, and TAC from miscellaneous other sources was conducted.

In addition, the diet´s antioxidant capacity can be influenced by the antioxidant supplement consumption and generate an interaction between them. Thus, analyses were conducted removing antioxidant supplements consumers. The data of dietary TAC was available only for the 1993 dietary questionnaire for this reason the 2005 dietary questionnaire was not used. The TAC estimation in E3N has proven to be useful for evaluating relation between diet and health outcomes. In a recent E3N study, an inverse association was observed between the consumption of TAC and mortality (127).

1.4.2. Dairy Products

Dietary information was evaluated twice in E3N study (1993 and 2005 questionnaires). However, only the 1993 dietary questionnaire was used for this thesis to evaluate the relation between dairy products and hypertension, because the questions assessed dairy products consumption were not the same in both questionnaires. Of the 238 foods evaluated in the1993 dietary questionnaire, there were 23 dairy foods items including butter, cream, and ice cream. We excluded these three items from the estimation of dairy

intake because according to French National Programme of Nutrition and Health butter and cream are considered to be a type of fat (and very often used for cooking) whereas ice cream is a sugary product. The other dairy items included in the questionnaire were milk, yogurt, cottage cheese and cheese. Items were included to differentiate the products according to their content in fat, sugar and artificial sweetener in some of them (**Table 4**). The yogurt with artificial sweetener in France is made with skimmed milk. The cheeses were classified into six groups according to the manufacturing process: soft, processed, semi-hard, hard, and goat cheese.

For the main analysis in this study total dairy and the consumption of four types of dairy products (milk, yogurt, cottage cheese and cheese) were considered (**Table 4**). From the daily consumption in milliliters or grams as the case may be, portions were estimated according to those established in French national surveys (185). To obtain the total of dairy products consumption, the number of daily servings for each type of dairy product (milk, yogurt, cheese and cottage cheese) were added. For secondary analyses, whole-fat dairy, low-fat dairy, and types of cheeses individually were taken in consideration and the characteristics of each food group are listed in **Table 5**.

Table 4. Dairy Products in the E3N study.

Dairy Products	**Characteristics**		
Milk			
	Whole, semi-skimmed, skimmed, concentrated, powder		
Yogurt			
Unsweetened	Whole	skimmed	with added sugar
Scented or fruited	Whole	skimmed	with sweetener (light)
Cottage cheese			
Unsweetened	0% fat	10-20% fat	30-40% fat
Scented or fruited	0% fat	10-20% fat	30-40% fat
Cheese			
	Soft, processed, blue, semi-hard, hard and goat cheeses		

Table 5. Dairy Products in secondary analyses in the E3N study.

Dairy Products	Characteristics
Whole-fat	
Milk	Whole milk, concentrated milk or powder
Yogurt	Unsweetened whole, scented or fruited whole, unsweetened whole with added sugar
Cottage cheese	Unsweetened and scented or fruited of 0% and 10-20% fat
Low-fat	
Milk	Semi-skimmed, skimmed
Yogurt	Unsweetened skimmed, scented or fruited skimmed, scented or fruited skimmed with sweetener
Cottage cheese	Unsweetened and scented or fruited of 30-40% fat
Types of cheeses	
Soft cheese	Camembert, St Marcelin, Brie, Munster, Vacherin, Pont l´Eveque
Processed cheese	Vache qui rit types
Blue cheese	Bleus, Roquefort
Semi-hard cheese	Cantal, Gouda, Port-Salut, Babybel, Tommes, Morbier, St Nectaire
Hard cheese	Gruyère, Comté
Goat cheese	Goat Cheeses

1.5. Outcome: Hypertension

Study participants reported hypertension diagnosis, date of diagnosis, blood pressure values, and antihypertensive treatment, at baseline (1993) and in all successive questionnaires (1994, 1997, 2000, 2005 and 2008). The validity of self-reported hypertension in E3N was previously evaluated in 46 254 participants (105). Therefore, the information obtained from the Medical Insurance (MGEN) about antihypertensive drugs (diuretics, beta-blockers, calcium inhibitors and drugs that act on the renin-angiotensin system; Anatomical Therapeutic Chemical Classification System codes C02, C03, C07, C08, and C09, respectively) was compared with the information declared by the questionnaires participants. Almost all (97.6%) of the participants in the E3N study were members of the MGEN. Different definitions of hypertension were evaluated: diagnosed hypertension, antihypertensive treatment, high blood pressure values, diagnosed hypertension under antihypertensive treatment, diagnosed hypertension under antihypertensive treatment and self-reports of high blood pressure values. The definition for hypertension that yielded the highest positive and negative predictive values (82% and 84%, respectively) was hypertension under antihypertensive treatment.

Sixty-nine percent of validation study participants reported a complete date of diagnosis (month and year). Fourteen percent did not report month of the diagnosis. For participants without a month of diagnosis the month was imputed to June. For women without a date of diagnosis, the median time between the date of diagnosis and the date of response of the first questionnaire on which the hypertension diagnosis was declared (among the participants who had the information) was 12 months. Thus, for the remaining 17% of cases without a date of diagnosis we imputed to12 months before the questionnaire date on which hypertension was first reported (105).

For the current analysis, one participant was considered hypertensive when she declared having hypertension diagnosis and receiving antihypertensive treatment at the same time, blood pressure values were not used as part of the definition since antihypertensive treatment could falsify the values. Thus, hypertension was operationalized as a dichotomous variable (yes / no).

1.6. Covariates

For statistical analyses we used the information on recognized risk factors for hypertension of the questionnaire from 1992 whenever possible to ensure that the covariate preceded the exposure.

1.6.1. Age

The date of birth was reported at the beginning of the study (Q1, 1990). The age of response to the dietary (baseline) questionnaire was estimated by subtracting the date of questionnaire response and the date of birth. In case the date of birth was not available, the age declared by the participant in the first questionnaire that was available was used. This variable was used as time scale as a continuous variable.

1.6.2. Education

In the first questionnaire (1990) the participants reported their education level. Five categories of their highest attained educational degree were available: assistant, technical diploma, bachelor's degree, master's degree and doctorate. This information was used to categorize participants in women with and without a high school diploma.

1.6.3. Family History of Hypertension

In the questionnaire (2005) participants were asked to state whether their father or mother had been diagnosed with hypertension and the age of diagnosis. For the purposes of this study, it was considered that a participant had a family history if at least one of their parents was diagnosed with hypertension.

1.6.4. Tobacco Consumption

This information was reported in each questionnaire. For the current analysis, the information reported in the second questionnaire (1992) was used. Five categories were available: non-smoker, regular former smoker, occasional former smoker, regular current smoker and occasional current smoker. This variable was categorized in three groups: nonsmoker, current smoker and former smoker.

1.6.5. Hypercholesterolemia

The participants were asked if they had received a hypercholesterolemia diagnosis or treatment at baseline and in the follow-up questionnaires. To consider a participant with hypercholesterolemia, the treatment report of this disease was taken into account in the second questionnaire (1992). Participants were considered to have hypercholesterolemia when they declared having the diagnosis and treatment at the same time.

1.6.6. Diabetes

The cases were identified through questionnaires, participants reported diabetes, diet adapted to diabetics, diabetes drugs and hospitalization for diabetes. Women who reported a diagnosis of diabetes were then contacted to validate their condition. They were asked to answer a specific questionnaire including questions related to the diagnosis (year of diagnosis, symptoms, biological exams and fasting or random glucose concentration at diagnosis) diabetes treatment (prescription of diet or physical activity, list of glucose-lowering drugs taken) as well as the last concentrations of fasting glucose and Hb1Ac (186). A self-reported case to be validated had to self-report at least one of the following criteria: fasting plasma glucose ≥ 7.0 mmol/L or random glucose ≥ 11.1 mmol/L at diagnosis and/or use of glucose-lowering medication and/or last values of fasting glucose ≥ 7.0 mmol/L or HbA1c concentrations ≥ 7% (186). In addition, the MGEN data provides access to reimbursed drugs, which also validated diabetes cases and obtained a date of diagnosis. The diagnosis of diabetes for this study was obtained from the 1992 questionnaire, a participant was considered diabetic when she reported a diagnosis of diabetes and receiving treatment at the same time.

1.6.7. Anthropometric Measurements

The body mass index (BMI) was estimated using the weight and height reported in the Q2 questionnaire, in order to evaluate the nutritional status. The BMI was defined as weight (kg) between the sizes squared (m^2). This variable was categorized according to the WHO criteria (187) (low weight < 19, normal weight 20 - 24.9, overweight 25 - 29.9 and obesity ≥ 30). The self-report of the anthropometry can be considered reliable since a validation study was carried out in 152 teachers of the study obtaining a correlation of 0.89 for the height and 0.94 for the weight (188).

1.6.8. Physical Activity

The information on physical activity was selected from the 1993 questionnaire, which included items on the number of hours that the participants performed activities such as: hiking, cycling, light and moderate tasks at home, recreational activities (example: swimming) and the daily number of steps up. The participants reported the average number of hours per week of each activity carried out during the winter and summer. The metabolic index (metabolic equivalents) per week was estimated by multiplying the annual average of MET for each item based on the values of the Physical Activities compendium (189) for the duration of the activity reported.

1.6.9. Dietary Information

Based on the dietary questionnaire applied in 1993 (Q3), energy (kcal/day), alcohol (g/day), sodium (mg/day), potassium (mg/day), magnesium (mg/day), coffee (ml/day), omega-3 fatty acids (g/day), fruits (g/day), vegetables (g/day), processed meat (g/day) were estimated. All were used in continuous and were those that have previously been associated with hypertension in the literature.

1.6.10. Antioxidant supplement

Antioxidant supplement intake was assessed through the 1995, 2000, 2002, and 2005 questionnaires. Participants were asked about their intakes of different vitamins and minerals, including vitamin E, vitamin C, and beta-carotene if consumed at least three times per week. A participant was considered as consumer of supplements if in any of the questionnaires (1995, 2000, 2002, and 2005) answered positively. The assumption was that participants who consumed antioxidant during the follow-up was a consumer at baseline.

2. THE MTC COHORT STUDY

2.1. Presentation of the cohort

The Mexican Teacher's Cohort (MTC) (190), is a prospective study conducted by the National Institute of Public Health of Mexico (INSP). The objective of the study was to identify risk factors for incidence of breast cancer and other chronic diseases. This study was approved by the Ethics Committee of the INSP. The study began in 2006, with a pilot phase in the Jalisco and Veracruz states. A questionnaire was sent to 44 542 teachers along with a recruitment package (including an invitation letter, an informed consent, a promotional brochure and a measure tape), obtaining a 63% response rate (27 986). In 2008, using the same methods, the study expanded, incorporating 10 additional states, Baja California, Chiapas, Mexico City, Durango, State of Mexico, Guanajuato, Hidalgo, Nuevo León, Sonora and Yucatán, adding 87 336 teachers to the study (**Figure 20**). Finally, the study was formed by 115 314 teachers, obtaining an overall response rate of 64% (ranging from 42 to 89% for each state). In addition, the study has a clinical sub-cohort with detailed information on exposures and outcomes of 6 834 participants, being very useful to validate self-reported exposures and outcomes (190).

The recruited participants were women of 25 years and older, active members of the Federal and State-level Ministry of Education's Program, called TIP (Teachers' Incentives Program), this facilitated the recruitment due to the partnership between the study and the Mexico's Education System. The TIP is a voluntary program to improve the quality of education through training and assessments, which are part of the public education teachers. Thus, teachers are accustomed to answer self-administered questionnaires as part of their evaluations. In addition, thanks to job stability and its membership in the TIP, it facilitates access to information for long-term follow-up, as well as the vital status of the participants.

2.2. Data Collection

To collect data about risk factors and medical conditions, a self-administered questionnaire was sent to participants approximately every 3 years. In addition, annually through the TIP, the study receives information about the membership of this program, as well as the participants' vital status, which is also verified with the database of pension management organizations (PMO). At baseline, different kind of data were collected such as reproductive history, physical activity, smoking, family history of chronic diseases, anthropometry, screening for chronic diseases, medicine use and medical conditions. Besides, information on socioeconomic status, diet, supplement use, adolescent physical activity and sun exposure. During follow-up cycle 1, the information obtained in baseline was updated. Further, new exposures related to diet, alcohol during adolescence, sleep quality, restless legs and depression were assessed (follow-up rate of 83%) (190).

Once the questionnaires were received, they were processed internally in the MTC team. This was a process that began with the scanning of the questionnaires, this stage was done anonymously. They were then cleaned and verified for the information consistency by the Data Entry and Reading Center.

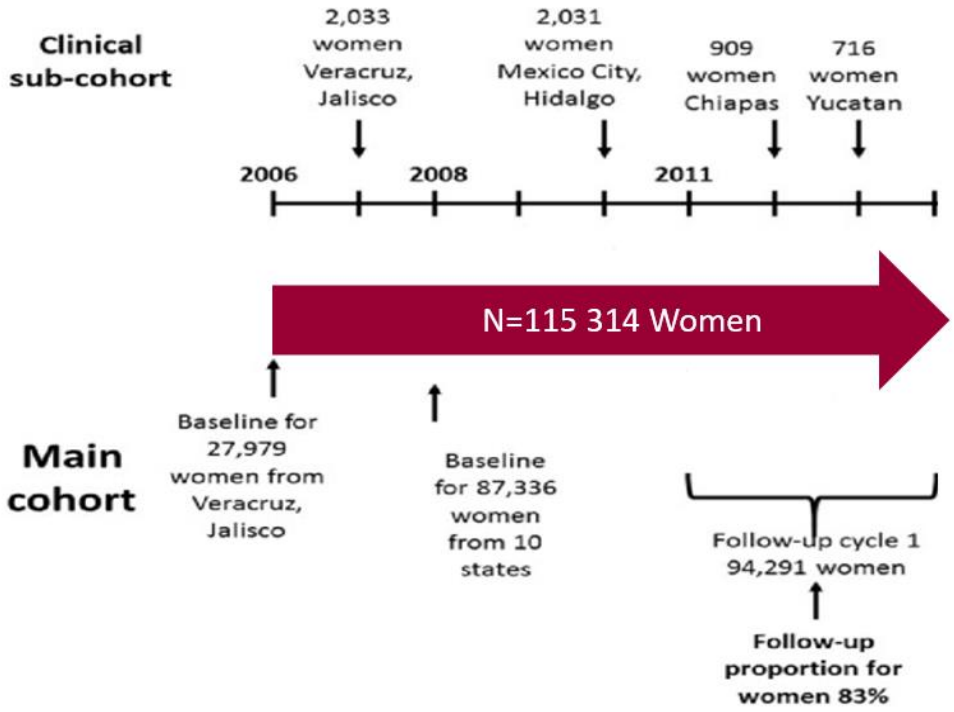


Figure 20. The Mexican Teacher´s Cohort enrolment, follow-up and clinical sub-cohort.
Source : Lajous M et al. Cohort Profile: The Mexican Teachers' Cohort (MTC). Int J Epidemiol. 2017;46(2):10.

2.3. Dietary questionnaire

In 2006 and 2008, a validated semi-quantitative food frequency questionnaire (FFQ) consisting of 141 items (191) was sent to all participants. The questionnaire aimed to evaluate the teachers' habitual dietary consumption. For each item, the participants were asked about the average consumption frequency for each food during the last year, they could answer for standardized portions and a frequency of ten categories (never, once a month or less, 2 - 3 times per month, once a week 5 - 6 times a week, once a day, 2 - 3 times a day, 4 - 5 times a day and 6 or more times a day). The participants could only mark one of the alternatives. Each item was accompanied by a standardized portion, for example: a glass of milk, a slice of cheese. (**Figure 21**).

AVERAGE CONSUMPTION DURING LAST YEAR										
1. DAIRY PRODUCTS	Select one option per line									
	Never	Once a month or less	2-3 times per month	Once a week	2-4 times per week	5-6 times per week	Once a day	2-3 times a day	4-5 times a day	6 or more times a day
One glass of whole milk (240 ml)					X					

Figure 21. MTC´s semi-quantitative food frequency questionnaire.

2.3.1. Estimation of daily nutrient consumption

Daily consumption was calculated by multiplying the consumption frequency by the nutrient content of a standard portion pre-defined in the questionnaire. The USDA food-composition database (192) and the local food-composition database in the National Health and Nutrition Survey of Mexico (193) were used to estimate nutrient and energy intake and to define servings.

2.3.2. Validity and reproducibility

The validity and reproducibility of the dietary questionnaire were previously evaluated. In 1998, 134 Mexican women residing in Mexico City were asked to complete two food frequency questionnaires at the beginning and end of the study. Both questionnaires were compared with four 4-day 24hour recalls were taken during the year of study. The correlation coefficients for energy, carbohydrates, proteins and total fat between the food frequency questionnaire and the 24-hour recall were 0.52, 0.57, 0.32 and 0.63

respectively (191). This questionnaire has been previously used in Mexico to assess diet-disease relations and been shown to perform well.

2.4. Exposure

2.4.1. Dairy Products

The dairy products section included 13 dairy items: whole milk, semi-skimmed milk, skimmed milk, yogurt or milk kefir, five types of cheese (Cream, Oaxaca, Manchego, Chihuahua, and Fresh), sugar-sweetened fresh cheese "Petit Suisse/Danonino" (Danonino® a register brand of a fermented product with added sugar), sugar-sweetened probiotic fermented milk beverage "Yakult" (Yakult® a drink which contains added sugar and lactobacillus) cream, butter, and ice cream.

For this study dairy products were defined as milk, yogurt or milk kefir and cheese consumption (**Table 6**). Dairy products intake was estimated in servings by week and the total dairy consumption was the sum of servings of milk, yogurt and cheese. The main analyses included total dairy, milk, yogurt or milk kefir and cheese consumption. Due to the high content of fat and sugar; butter, cream, Petit Suisse/Danonino, sugar-sweetened probiotic fermented milk beverage and ice cream were not taken into account for the main analysis. We conducted secondary analyses to explore the relation between whole-milk, skimmed-milk, fresh cheese, other cheeses, milk-based products with added sugar, high-fat milk-based products (**Table 6**) and hypertension.

Table 6. Dairy products and milk-based products in the MTC study.

Dairy Products	Characteristics
Main Analyses	
Milk	Whole, semi-skimmed, skimmed
Yogurt	Whole yogurt or milk kefir
Cheese	Cream cheese, Oaxacan string cheese, Manchego cheese, Chihuahua semi-soft cured cheese and Fresh cheese curd
Secondary Analyses	
Whole-milk	Whole-milk
Skimmed-milk	Semi-skimmed and skimmed
Fresh cheese	Fresh cheese curd
Other cheeses	Cream cheese, Oaxacan string cheese, Manchego cheese, Chihuahua semi-soft cured cheese
Milk-based products with added sugar	Sugar-sweetened probiotic fermented milk beverage, Petit Suisse/danonino and ice cream
High-fat milk-based products	Butter and cream

2.5. Outcome: Hypertension

At baseline and in follow-up questionnaires, data on health status and treatments received was collected. In 2006 and 2008, the teachers were asked if a doctor had diagnosed them with high blood pressure, whether they had received treatment and the years' quantity since their diagnosis. In 2011, the question about diagnosis and treatment was repeated and it was asked whether the year of diagnosis was 2009 or 2010. For women which started their participation to this study on 2006 two updated of hypertension status were available (2008 - 2011), whereas only one updated of hypertension status for those who started the study on 2008.

For this study the high blood pressure diagnostic report was considered hypertension. A participant was considered hypertensive if she reported at the same time having a hypertension diagnosis and receiving antihypertensive treatment. Previously, in a validation study of self-reported hypertension in MTC study, a structured telephone interview was applied in a random subsample of 101 participants. The standardized interviewers asked seven questions: 1. Can you confirm that you were diagnosed with high blood pressure or hypertension? 2. How old were you when you were diagnosed? 3. Who made the diagnosis: a doctor, a nurse, or another health worker? 4. How many times have you been told that you have hypertension? 5. What was your blood pressure when you were diagnosed with hypertension (systolic / diastolic)? 6. Has a health professional provided you with lifestyle recommendations to control your blood pressure? And 7. Do you use medications to control your blood pressure? The answers were reviewed by a physician who classified as hypertensive 89% of participants who reported having hypertension and being under treatment before the interview (194). While 72% of people who reported having hypertension without treatment, were considered hypertensive.

2.6. Covariates

The covariates were reported at the beginning of the study. For certain participants this information was taken from the year 2006 or 2008 this depends on the year in which the participants entered to the study.

2.6.1. Age

Age is an important hypertension risk factor, being a confounding factor. This variable was estimated from the current date's subtraction (beginning of the study in 2008 or 2006) and the date of birth declared in 2006 or 2008.

2.6.2. Family History of Hypertension

In the questionnaire the teachers were asked if any of their parents or siblings had suffered from hypertension. For this study, a participant was considered with a family history of hypertension if she answered affirmatively to this question.

2.6.3. Socioeconomic status

For several years the relation between the socioeconomic status (SES) and hypertension has been evidenced, therefore this variable must be included in the analysis. In MTC study the SES was evaluated based on several indicators, a score was created based on the sum of home assets (mobile, landline, microwave oven, car, vacuum cleaner, computer, and internet access) and this variable was categorized in quartiles, the greater the number of assets, the greater the socioeconomic status.

2.6.4. Regions

According to Mexico's National Nutrition Survey (6) the dairy product consumption is different across the regions in Mexico. Based on the state of residence, participants were classified in the four regions used in that survey: North, South, Center, and Mexico City and the surrounding metropolitan area.

2.6.5. Tobacco consumption

According to evidence presented in the first chapter of this thesis, tobacco consumption is well-documented risk factor for hypertension. In the baseline questionnaire teachers answered if they were currently smoking, the number of cigarettes, having the following alternatives; never, yes (currently) and not because they stopped smoking. This variable was categorized as non-smoker, current smoker and former smoker.

2.6.6. Diabetes and Hypercholesterolemia

In each questionnaire participants were asked if they had been diagnosed with diabetes or high cholesterol by a doctor, if they received treatment and how long ago, they were diagnosed. To consider a woman with diabetes or hypercholesterolemia, the participant reported the diagnosis and treatment at the same time for any of these diseases. In MTC study, a validation of self-reported diabetes was conducted (195) using a subsample of 3 140 women who reported a diagnosis of diabetes at baseline and additionally answered a supplementary questionnaire with questions related to the diagnosis, treatment, and complications of diabetes. Even if there was not a perfect gold standard an algorithm was developed using information on whether the participant confirmed the diagnosis of diabetes, the use of pharmacological treatment and/or control of diabetes (diet and exercise). According to the algorithm, 89% (95% CI 87.5 - 90.0) of self-reported cases, were confirmed through the diagnosis or treatment in the supplementary questionnaire. The definition chosen for diabetes for the analyses is the one which had the higher positive predictive value. Diabetes and hypercholesterolemia were used as dichotomous variables.

2.6.7. Body Mass Index

Obesity is a major risk factor for hypertension, which was assessed through the body mass index (BMI) defined as the weight (kg) between the squared sizes (m^2). The self-reported weight and size was used to calculate this indicator. This variable was used in categorical based on the classification of the World Health Organization. Previously, in MTC cohort the reproducibility and validity of self-reported anthropometry were assessed in a sample of 3 413 women (196). The correlation coefficients between standardized technician measurements and self-reported for weight, height and waist circumference were 0.92, 0.86 and 0.78 respectively showing a good correlation.

2.6.8. Physical Activity

Physical activity was evaluated through self-reported questionnaires. In 2006, participants reported the amount of time spending on walking and in recreational physical activities during the previous year. In 2008, the questionnaire was expanded including the amount of time spending in work or recreation activities, including sports, walking and household cleaning activities. Total metabolic equivalent hours were calculated per week in 2006 and 2008 (189).The physical activity and inactivity cohort's questionnaire is a reduced version of the questionnaire of the International Physical Activity

Questionnaire (IPAQ) (189). Based on the report of the intensity and amount of physical activity, this variable was classified into 3 categories, (low, medium, and high). This definition has been used before in the MTC study (195).

2.6.9. Dietary Information

The dietary variables were estimated from the consumption frequency in grams or milligrams. The variables included were the habitual energy (kcal/d, alcohol (g/day), fruits (g/day), vegetables (g/day), processed meat (g/day), coffee (ml/day), magnesium (mg/day), potassium (mg/day), sodium (mg/day), omega-3 fatty acids (mg/day) consumption. All the variables mentioned before were continuous according to their behavior and distribution, their categorization was used.

3. STATISTICAL ANALYSES

3.1. Descriptive Analyses

Firstly, an exploratory analysis of the data was conducted to evaluate the distributions of the variables in order to understand their behavior. Allowing me to identify the association patterns between the outcome variable and the adjustment variables, as well as the patterns between the adjustment variables. This analysis was important to identify and understand the behavior of the outcome variable. The exploratory analysis was focused on the behavior of the Kaplan-Meier estimator of the survival function and the overall survival function was estimated.

For the three analyses conducted for this thesis, the characteristics of the participants were described using basic statistics such as frequency, mean, standard deviation (SD), and median. At the time of inclusion, the characteristics of the participants also the potential confounders were described according to the outcome variable (hypertension) and the main exposures (total antioxidant capacity of the diet and dairy products).

3.2. Association measures

3.2.1. Survival analyses: The Cox Proportional Hazard model

Theoretical elements on these models are presented in this section. The survival analysis focuses on the examination of the time of the occurrence of an event for one or several groups. The outcome variable is the time until an event occurs. Time, also called survival time, can be expressed in years, months or days, since the individual begins the follow-up procedure until the event is presented, it can also refer to the age at which the individual presents the event (197).

In this thesis, in order to perform the survival analysis, the semi parametric Cox model was used. The Cox model expresses the instantaneous risk for a given event (hypertension) as a function of time and a group of variables, taking into account the censored data. Censorship occurs when you do not have accurate information about survival time. There are three main mechanisms of censorship: when the individual does

not present the event before the end of the study, losses in the follow-up or if the participant leaves the study.

The equation of the model is as follows:

$$h(t,Z) = h_0(t) \cdot \exp(\beta 1 Z_1 + \ldots + \beta_p Z_p)$$

In the equation, the hazard function h (t, Z) is dependent on a group of p independent variables (Zi). The effect of these, is measured through the size of their regression coefficients, which are estimated by the maximum likelihood method. The term h0 (t) represents the basic risk of suffering the event, when all the variables are equal to zero. This part is the only one that depends on time, the rest depends on the variables. Since this part does not assume a form is the so-called non-parametric part of the model. The association measure resulting from the Cox model is the hazard ratio (that is to say the ratio of two instantaneous hazard functions). An HR above 1 is interpreted as a positive association between the event of interest and the study variable, on the contrary, if it is less than 1, it shows an inverse association.

3.2.2. Model assumptions

The Cox model has two hypotheses that must be verified, the first is the risks proportionality, which implies that the risk functions for the different categories of a variable are proportional and their relation is independent of time. (197). The second is the log-linear assumption and implies that, having a quantitative variable, the increase in relative risk is constant due to the increase of one unit of the variable, whatever the measured unit is. (197).

The first assumption was verified through graphic methods, on which this assumption is fulfilled, only if the functions are parallel and do not cross over time. To test the second assumption, the risk associated with the interest variable can be modeled, categorizing it into percentiles (tertiles or quartiles) depending of the distribution of the variable. When plotting the risks based on the median of each quartile, the hypothesis is verified if a line is obtained. If the hypothesis is not met, the continuous variables should be used categorically. This assumption is important and when was not properly suited to the variables explored in this thesis, thus the decision was to transform all continuous variables into categorical variables when was necessary.

3.3. Time Scale

The Cox model was originally used to analyze clinical data, in this context the most intuitive time scale was the treatment follow-up duration and age was taken as an adjustment variable (198). However, in prospective cohort studies, events are the occurrence of diseases, for which age can be an important factor. In most cohort studies, inclusion in the study does not coincide with the onset of exposure to risk factors. This is one of the reasons, why it is recommended in this type of studies to use age as a time scale instead of time on study (199). Another reason is that age is a risk factor very associated with the disease of study.

3.4. Statistical Modelling

The adjustment variables were chosen based on a literature review, on which the recognized risk factors for hypertension and the diet variables previously associated with hypertension were selected, these associations were confirmed in our sample during the exploratory. Based on the findings of the exploratory data analysis and based on the theoretical framework, the relevant statistical models were defined. The Cox Regression model was used and the assumptions of the model were verified.

For this, the study event was defined as a hypertension diagnosis with treatment. The response variable was constructed taking into account the time elapsed from the moment the participant entered the study until she was diagnosed with hypertension. The censorship variable includes all women who did not have a hypertension diagnosis until the end of the study. The mechanisms of censorship were: loss to follow-up and death. The construction of this variable was of a dichotomous form, with all the women mentioned above being the reference variable, and women who are diagnosed with hypertension as the study variable. All analyses were performed with the SAS 9.3 program.

3.5. Spline regression curves

For objective 1 to better characterize the shape of the association, the analysis on dietary TAC and hypertension were also performed using spline regression. This method is used when an explanatory variable is continuous, it provides an easy way to create, test and model nonlinear relations in regression models (200). To create splines the values of the predictor (here dietary TAC intake in mmol/day) have to be divided by a number of knots, for the first analyses four knots were selected (20th, 40th, 60th, and 80th percentiles of the distribution). In spline regression curves, the number of knots is more important than the location of them. Harrell et al. affirmed that “for many datasets, k = 4 offers an adequate fit of the model and is a good compromise between flexibility and loss of pocesion caused by overfitting a small sample” (201).

3.6. Missing data

The missing data were imputed by the median, for the quantitative variables, when the percentage was less than 5% and for the qualitative variables, fashion was imputed, that is, the category with the highest frequency. If the percentage was greater than 5%, a category of missing data was created. This is a pre-established procedure in both studies for the treatment of these data.

RESULTS AND DISCUSSION

CHAPTER IV: DIETARY TOTAL ANTIOXIDANT CAPACITY AND HYPERTENSION

1. Background

As previously described in depth in Chapter I, oxidative stress, can lead to potential alterations in endothelial cells, it has been suggested to be a potentially important mechanism in the development of hypertension (202, 203). Antioxidants can neutralize the negative effects of free radicals (131). Results from cohort studies related to dietary antioxidant intake support a protective effect of dietary vitamin C (95), carotenoids (108), and polyphenols (104, 105) on cardiovascular risk. However, results from clinical trials of single antioxidant supplements have been inconsistent. They reported null (98, 204) or even adverse effects on major cardiovascular events including hypertension (130).

The individual evaluation of antioxidants may not reflect the total antioxidant power from diets and the possible synergistic effects of antioxidants (205). The dietary total antioxidant capacity (TAC) is a new method which represents the global measure of antioxidants in a meal (91). This measurement provides information about the in vitro capacity of food to inhibit or reduce an oxidant, being a marker of the antioxidant potential of the diet (91). The consumption of antioxidants seems to affect plasma antioxidant capacity immediately. However, no long-term changes have been documented in clinical trials when the intake of antioxidants from the diet is high.(91)

Since diet is based on different foods consumed together, assessing the dietary TAC could be a good alternative to studying individual antioxidants when exploring the impact of antioxidants on various conditions, including hypertension. High TAC diets have been associated with reduced inflammation and high circulating antioxidant concentrations in cross sectional and randomized studies (131, 132). To my knowledge, no study examined the association between dietary TAC and the risk of hypertension. The current work prospectively assessed the relation between dietary TAC and the risk of hypertension in French women.

2. Methods

2.1. Study Population

This analysis was based on the E3N study, among 74 520 women with dietary data available (180). Women were excluded if they had an unrealistic energy consumption defined as extreme values for the ratio between energy intake and required energy (the 1st and 99th percentiles of the distribution in the population, n = 1 381) (206), with no follow-up after 1993 (n = 846), with no information on risk factors prior to 1993 (n = 2 793), and women who reported a prevalent cancer (n = 4 253), hypertension (n = 24 222), or cardiovascular disease (n = 449) before or at the 1993 questionnaire. The final study population included 40 576 women.

2.2. Statistical analysis

Participants were categorized according to the dietary TAC intake in quintiles with the lowest category as the reference. Time at entry was the age at the beginning of follow-up (1993), exit time was the age when participants were diagnosed with hypertension, died (dates of death were obtained from the participants' medical insurance records), were lost to follow-up, or were censored at the end of the follow-up period (June 25, 2008), whichever occurred first. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated from Cox regression models with age as the time scale. In the E3N study, age was used as time scale because this population was older population with a long follow-up. Therefore, no parametric assumption had to be made on this variable since it is placed in the no parametric part of the hazard function. Thus, it was no necessary to verified the proportional hazards and log-linear assumptions for this variable, avoiding potential invalid estimations (207).

In multivariable models were first adjusted for energy (Model 1), then for family history of hypertension (yes/no), BMI (< 25, 25 - 29.9, ≥ 30), physical activity (Met-h/week, continuous), smoking (as never, former, and current), education (no high school diploma, high school diploma), diabetes (yes/no), and hypercholesterolemia (yes/no) (Model 2). In model 3, the main model, was further adjusted for intakes of alcohol, coffee, magnesium, potassium, omega-3 fatty acids (all as continuous variables); in an additional model (Model 4, not shown) was further adjusted for dietary patterns (Western

and Healthy pattern scores, continuous variables) (208). For all the models, linear trends across categories were estimated with a semi-quantitative variable based on the median values of exposure categories. The treatment for missing data was explained in Chapter III.

Further, sensitivity analyses were performed to evaluate TAC of coffee and the TAC of the main contributors to global TAC. A partition model considering TAC from coffee and TAC from other sources (non-coffee TAC) was conducted. Then, finally in a fully partitioned model, simultaneously considering coffee TAC, TAC from fruit and vegetables, TAC from wine, TAC from chocolate, TAC from tea, and TAC from miscellaneous other sources was performed. Spline regression curves, explained in depth in the previous chapter, were designed to better characterize the shape of the association between dietary TAC and hypertension. The minimum TRAP value was chosen as the reference for estimating HRs and 95% CI, and four knots were used (20th, 40th, 60th, and 80th percentiles of the distribution).

The potential effect modification of BMI (25< vs ≥ 25 kg/m^2), and age (divided in < median, ≥ median) on the association between dietary TAC consumption and risk of hypertension was evaluated. In addition, tobacco smoking (ever/never) was evaluated as an effect modifier, the evidence showed that smokers have elevated concentrations of oxidative stress biomarkers and compromised antioxidant status (209). Statistical significance of an interaction term between dietary TAC and the potential effect modifiers was tested.

Further, sensitivity analyses were performed to test reverse causation; models excluded cases that occurred in the five first years of follow-up. The impact of excluding women with any antioxidant supplement intake (vitamin E, vitamin C, or beta-carotene) was also evaluated, during baseline or the follow-up.

3. Results

After an average 12.7 years of follow-up and 493 895 person-years, 9 350 cases of incident hypertension were identified (18.9 cases per 1 000 person-years). The incidence of hypertension in participants in the fifth quintile of dietary TAC was 18.4 per 1 000 person-years, whereas it was 19.9 per 1 000 person-years in those in the first quintile. The mean age at baseline was 51.6 $\pm$ 6.2 years, and the mean dietary TAC consumption was 4.9 $\pm$ 2.4 mmol/d; it was 2.2 $\pm$ 0.5 mmol/d in the first quintile, and 8.6 $\pm$ 1.8 mmol/d in the fifth quintile.

Table 7, presents the baseline characteristics of the study population according to hypertension status. Hypertensive women compared with women without a diagnosis of hypertension, were slightly older, they were more often obese and overweight, and had a diagnosis of diabetes or hypercholesterolemia and history of family hypertension. However, they were less frequently smokers and had a lower level of education. In addition, they had a higher consumption of coffee, sodium, potassium and magnesium.

Baseline characteristics of participants according to quintiles of dietary TAC are listed in **Table 8**. Compared with those in the lowest quintile, women in the highest quintile of TAC were more likely to have a higher education level and a normal weight, and to be more physically active but were more often smokers. Women with a high dietary TAC also consumed more magnesium, potassium, omega 3 fatty acids, coffee, and alcohol.

Dietary TAC intake was inversely associated with hypertension in all models (**Table 9**). When extreme quintiles were compared, there was an inverse relation between dietary TAC and risk of hypertension, with a 15% lower rate of hypertension in the fifth vs. first quintile of TAC consumption (HR 0.85; 95% CI 0.79 - 0.92; p-trend = 0.0002) in the multivariable model (Model 3).

Dietary TAC was partitioned by TAC into coffee and non-coffee TAC (**Table 10**), non-coffee TAC was associated with reduced risk of hypertension from the second quintile on, and an inverse dose-effect relation (M3: $HR_{5vs1quintile}$: 0.85; 95% CI 0.79 - 0.92; p-trend < 0.0001). Regarding coffee TAC, the association was weaker, with an inverse association only with the fifth quintile (M3: $HR_{5vs1quintile}$: 0.86; 95% CI 0.75 - 0.97; p-trend = 0.03). Further the associations between dietary TAC from major TAC providers and risk of hypertension were evaluated, using a fully partitioned model. Only dietary TAC

from wine, from fruit and vegetables, and from miscellaneous other sources remained inversely associated with the risk of hypertension, while TAC from coffee, tea, or chocolate was not (**Table 11**).

The shape of the association between non-coffee dietary TAC and the risk of hypertension is presented in **Figure 22**. There was a steep inverse dose-effect relation between dietary TAC and risk of hypertension up to a TAC value of 5.0 mmol/day, then a leveling off of the association. The risk of hypertension associated with TAC consumption remained similar when excluding cases diagnosed during the first 5 years of follow-up (**Table 12**) (n = 38 445; HR 0.84; 95% CI 0.76 - 0.92; p-trend < 0.0001), or participants with supplement intake of antioxidants (**Table 13**) (n = 28 648; HR 0.83; 95% CI 0.75 - 0.91; p-trend = 0.0002). There was no statistically significant interaction between dietary TAC and age, BMI, or smoking, regarding the risk of hypertension.

Additionally, the relation between dietary TAC and risk of hypertension was evaluated in women with low fruit and vegetables consumption (below the median population value) (n=20 288). In low-fruit and vegetable consumers, dietary TAC remained inversely associated with risk of incident hypertension (HR 0.85; 95% CI 0.76 - 0.95; p = 0.03; model 3) (**Appendix 4**).

Because there is no universal method to measure the antioxidant capacity, it is recommended to evaluate TAC with at least two methods. To evaluate dietary TAC and hypertension, the main analyses were also conducted with FRAP method which is strong correlated (r = 0.97) with TRAP method in the E3N study. The results did not change in terms of statistical signification but is slightly attenuated (HR 0.87; 95% CI 0.79 - 0.97; p-trend = 0.01; model 3) (**Appendix 5**).

4. Discussion

In the present study, a high antioxidant capacity was associated with a reduced risk of hypertension in a large cohort of French women, especially a high antioxidant capacity from other sources than coffee. Results appeared to be independent of the major risk factors of hypertension, including anthropometry and lifestyle. The spline regression curve demonstrated a steep inverse dose-effect relation between dietary TAC and risk of hypertension, then a leveling off of the association, suggesting that the maximal action of TAC could be associated with a TAC intake around 5.0 mmol/day.

To the best of my knowledge, this is the first time that an inverse association between the dietary TAC and the risk of hypertension has been shown. Dietary TAC has been previously inversely associated with several outcomes such as stroke (136), myocardial infarction (210), cancer (120, 211), diabetes (212), metabolic disorders (213), and mortality (127). When hypertensive and normal subjects were compared regarding antioxidant and free radical levels, hypertensive subjects had significantly lower concentrations of HDL-cholesterol, antioxidant enzymes, and ferric reducing antioxidant power but higher total cholesterol and LDL cholesterol concentrations, and higher lipid peroxidation (137).

Previous studies reported inverse associations between intake of antioxidant-rich foods and the risk of hypertension. The DASH diet (Dietary Approaches to Stop Hypertension) (214), based on fruit and vegetables, low-fat dairy products, and whole grains, demonstrated a reduction in blood pressure in both healthy and hypertensive individuals, as well as a reduction in cardiovascular disease associated with hypertension such as stroke (215). However, the effect of antioxidant supplementation on blood pressure has not been consistent, especially across genders. The Linxian trial showed a reduced risk of hypertension among men but not among women after six years of follow-up (216). In contrast, the SUVIMAX trial did not find any association between antioxidant supplementation and incident hypertension (217). This suggests that the natural balance between dietary antioxidants could be more efficient for preventing hypertension than specific supplements which may lead to an excess of a given antioxidant and thus to an imbalance of the complex antioxidative system.

Oxidative stress results from the excessive production of oxygen free radicals or the decrease of the concentration of antioxidants in the body. It has been suggested that hypertension could indirectly result from a state of imbalance between antioxidants and free radicals (76). Several mechanisms associated with free radical damage have been suggested, including endothelium dysfunction that would reduce its ability to quench the vasodilator nitric oxide, damage to endothelial cells and to vascular smooth muscle cells, increase in endothelial permeability and intracellular free calcium concentration, collagen deposits leading to the thickening of the vascular media and the narrowing of the vascular lumen, and oxidation of biomolecules such as LDL-cholesterol, a well-known risk factor for atherosclerosis and hypertension (75). Since antioxidants can stabilize free radicals, they could thereby prevent hypertension by avoiding cell damage.

Dietary TAC represents a global estimate of antioxidants from the diet. However, the ability of diet to increase plasma TAC is a matter of debate. Previous studies reported the ability of various foods including fruit juice (218), wine (219), chocolate (220), onions (221), lettuce (222), or tomato products with extra virgin olive oil (223), to increase plasma TAC. However, a 3-week intervention with fruit juice and vegetable burgers in male smokers failed to modify biomarkers of oxidative stress (224), while another intervention in male smokers of the same duration was shown to increase the plasma oxidative stability, assessed by the oxygen radical absorbance capacity (ORAC) assay (225). Altogether, intervention studies were of short duration and cannot easily be extrapolated to real-life long-term TAC intake.

In the main analyses the TAC of coffee when studying the effect of dietary TAC on hypertension was not included. Coffee is complex, as it contains over 1 000 compounds (126). The absorption of coffee antioxidants remained uncertain. These compounds have to be absorbed through the gastrointestinal wall to exert systemic in vivo effects; because of their size, the absorption of these molecules is unclear and their systemic antioxidant action is questioned (120). Moreover, a number of epidemiological studies have shown that high coffee consumption was often associated with smoking and other unhealthy habits such as lack of physical activity and alcohol use (226).

In these analyses considering the antioxidant capacity of specific food groups, dietary TAC of fruit and vegetables, of wine, and of other miscellaneous foods were inversely associated with hypertension. Fruit and vegetables have been consistently inversely associated with a lower risk of hypertension (227) or coronary heart disease (228) , which has been attributed to their antioxidant content. However, high fruit and vegetable intake is a well-known marker of a healthy lifestyle, so that we cannot exclude that the observed association could be a proxy for healthy life choices. However, we also reported an inverse association with the highest quintile of coffee TAC, with TAC from wine, and with TAC for more minor sources. This is more in favor of a true effect of antioxidants on the risk of hypertension. Furthermore, in additional analyses, dietary TAC stayed inversely associated with hypertension even for women with lower consumption of fruits and vegetables (below the median population value) (**Appendix 4**).

It is of interest to compare the TAC levels from coffee and those from other sources. While non-coffee TAC was inversely associated with risk from the second quintile on, from a TAC value above 2.95, an inverse association of a similar magnitude was only

observed for coffee TAC from a value of 25, thus nearly ten times higher. This is in line with previously reported questioning about the bioavailability of the various antioxidants from coffee, especially those produced by the Maillard reaction of rather large size (229). Several studies already reported that coffee TAC was unrelated to the risk of hypertension, possibly due to a balance between favorable antioxidant effects, unfavorable vasoconstriction effects, and possible associations with negative lifestyle factors (226). Indeed, the effect of coffee on cardiovascular disease is not clear. The most investigated compound is caffeine; studies have shown increased vascular resistance after acute intake of coffee or caffeine, which suggests a vasoconstriction effect (126). The long-term effect has also been evaluated, and a meta-analysis of randomized controlled trials demonstrated a positive relation between the number of cups of coffee and changes in systolic pressure (230). Nonetheless, coffee is also an important source of antioxidants (226). By partitioning the antioxidant capacity of the diet into coffee and non-coffee components of TAC, we avoided the potential confounding effect of other components of coffee since TAC coffee was analysed individually but mutually adjusted for the other components of dietary TAC. The results with almost ten times weaker associations between coffee TAC and hypertension compared to other TAC sources suggest that the antioxidant effect of coffee on hypertension would be largely reduced by potentially lower bioavailability of coffee TAC and adverse cardiovascular effects of caffeine.

The findings that the association between dietary TAC of chocolate or tea and hypertension was of the same magnitude, but not statistically significant, suggest that in our population with a high proportion of non-consumers of tea or chocolate, consumptions were not high enough to be able to demonstrate any association. A previous study reported no association between tea consumption and hypertension, but an inverse association with chocolate or cocoa consumption (103).

The spline regression curve showed a steep inverse dose-effect relation between dietary TAC and risk of hypertension up to a TAC value of 5.0 mmol/day, then a leveling off of the association. These results are in line with previous studies. Cao et al. (231) reported a linear correlation between daily intake of antioxidants and fasting plasma oxygen radical absorbance capacity, a plateau was observed when plasma antioxidant capacity reached values above 3.0 mmol/day. In another study (212), an inverse association between dietary TAC and risk of diabetes was observed, reaching a plateau for values over 15 mmol/day. A possible explanation, as suggested previously is as a result of the

excess of antioxidants or vitamins, a saturation of the capacity of the organism to absorb this substance from the diet could be observed (212). However, more studies are necessary to understand the underlying mechanism.

In the E3N study, to evaluate dietary TAC, besides the TRAP method another method strongly correlated ($r = 0.97$; $p < 0.0001$) was available, the FRAP method. The associations found with TRAP were similar when the analyses with FRAP method were performed (**Appendix 5**). FRAP method is usually used when we are interested in diseases related with iron. In this study, the interest was the relation of hypertension and antioxidants, which is why TRAP method was used to evaluate the antioxidant power of the diet.

4.1. Strengths and limitations

Strengths of this study are its prospective design since it has been demonstrated that knowledge of hypertension influenced the answer to a dietary questionnaire (232), large sample size, long follow-up (15 years) with minimal loss to follow-up, large number of cases, and use of a validated diet history questionnaire to evaluate diet and dietary TAC. Our study also has some limitations. Dietary TAC intake was only assessed at baseline thus misclassification of exposure is possible since the dietary habits of participants may change over time. Because of the study design, the measurement error is likely to be non-differential and would tend to underestimate the association. In addition, dietary TAC values for French foods were not available, and most estimated values related to raw foods. The Italian TAC database was used, but the antioxidant content in foods can be affected by cooking, and by geographic location, climate, and growing conditions of the crop, which may lead to over or underestimate the TAC content of foods. This should again lead to non-differential misclassification of exposure, and thus reduce the associations, which may therefore be even stronger.

In this study, cases of hypertension were identified through follow-up questionnaires. The validity of cases of hypertension was assessed, observing an 82% positive predictive value between the self-reported information and the use of a drug reimbursement database. Some degree of misclassification is possible however since hypertension was diagnosed after dietary assessment, it should not be related to the exposure; therefore, this could again potentially attenuate the observed associations. Last, despite the fact

that the models were adjusted for all known risk factors for hypertension, residual confounding by some unmeasured or poorly measured factor cannot be totally ruled out.

5. Conclusion

These findings showed that a high TAC diet was associated with a reduced risk of incident hypertension in women, suggesting that promoting a diet naturally rich in antioxidants might help prevent the development of hypertension. These results have to be interpreted cautiously; there are still questions about the absorption, distribution and cellular role still unanswered. Additional studies are needed to further investigate the association of dietary TAC intake with changes in blood pressure levels over time in other settings.

Table 7. Population characteristics according to hypertension status (N=40 576). E3N Cohort, France 1993-2008.

Characteristics	Hypertension		
	Yes (N=9 350)	No (N=31 226)	All (N=40 576)
Dietary TAC Intake mmol/d (mean, SD)	4.9 (2.4)	5.0 (2.4)	4.9 (2.4)
Risk factors (%)			
Age at 1993: years (mean, SD)	52.6 (6.5)	51.3 (6.1)	51.6 (6.2)
Body mass index: kg/m^2			
Normal	79.7	88.7	86.6
Overweight	17.5	10.2	11.9
Obesity	2.8	1.1	1.5
Diabetes	0.9	0.3	0.5
Hypercholesterolemia	6.5	4.2	4.7
Smoking			
Never	53.1	51.8	52.1
Former	33.3	34	33.9
Current	13.6	14.2	14
Education			
With high school diploma	88.2	90.8	90.2
Family history of hypertension	41.3	24.9	28.7
Physical activity: METS/week (mean, SD)	54.9 (30.5)	54.0 (29.6)	54.2 (29.8)
Dietary factors (mean, SD)			
Energy without alcohol (kcal/day)	2128 (541)	2127 (535)	2127 (536)
Alcohol (g/day)	11.7 (14.1)	11.4 (13.4)	11.5 (13.6)
Coffee intake (ml/day)	295.7 (273.2)	291.8 (269.9)	292.7 (270.6)
Potassium (mg/day)	3871.9 (1042.6)	3842.3 (1023.2)	3849.1 (1027.8)
Magnesium (mg/day)	442.5 (144.0)	439.3 (141.5)	440.0 (142.1)
Omega-3 fatty acids (g /day)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)
Sodium (mg/day)	2847.6 (906.7)	2817.8 (895.0)	2824.7 (897.8)
Western pattern (%)			
Q1	32.5	33.6	33.3
Q2	33.0	33.4	33.3
Q3	34.5	33.0	33.3
Healthy pattern (%)			
Q1	32.8	33.5	33.3
Q2	32.1	33.7	33.3
Q3	35.1	32.8	33.3

Table 8. Population characteristics according to Dietary TAC intake without coffee (N=40 576). E3N Cohort, France 1993-2008.

Characteristics	Dietary total antioxidant capacity (TAC)				
	Q1(< 2.95) (N=8 115)	Q2 (2.95 – 3.99) (N=8 115)	Q3 (4.00 – 5.12) (N=8 116)	Q4 (5.13 – 6.69) (N=8 115)	Q5 (> 6.69) (N=8 115)
TAC Intake mmol/d (mean, SD)	2.2 (0.5)	3.5 (0.3)	4.5 (0.3)	5.8 (0.4)	8.6 (1.8)
Risk factors (n, %)					
Age in 1993: years (mean, SD)	51.3 (6.2)	51.6 (6.2)	51.8 (6.3)	51.8 (6.2)	51.6 (6.2)
Body mass index: kg/m^2					
Normal	86.5	85.6	87.1	87.1	87
Overweight	11.7	12.7	11.6	11.6	11.9
Obesity	1.8	1.7	1.3	1.4	1.1
Diabetes	0.5	0.5	0.5	0.4	0.5
Hypercholesterolemia	5	5	4.7	4.4	4.4
Smoking					
Never	59.5	55.7	52.3	49.4	43.8
Former	28.2	32	35	35.7	38.3
Current	12.3	12.3	12.7	15	18
Education					
With high school diploma	86	88.7	91	92.1	93.3
Family history of hypertension	28	29.5	29.2	29.2	27.6
Physical activity: METS/week (mean, SD)	51.5 (28.9)	53.8 (29.7)	53.9 (29.8)	55.0 (29.5)	56.6 (30.8)
Dietary factors (mean, SD)					
Energy without alcohol (kcal/day)	1879 (462)	2045 (477)	2137 (502)	2214 (531)	2362 (576)
Alcohol (g/day)	4 (5)	7 (7)	10 (9)	14 (12)	22 (20)
Coffee intake (ml/day)	338 (282)	319 (270)	293 (268)	271 (263)	242 (260)
Potassium (mg/day)	3367 (905)	3731 (915)	3878 (995)	3975 (989)	4294 (1094)

Magnesium (mg/day)	409 (132)	433 (133)	440 (141)	446 (143)	473 (154)
Omega-3 fatty acids (g/day)	1.3 (0.4)	1.4 (0.5)	1.5 (0.5)	1.6 (0.5)	1.7 (0.6)
Sodium (mg/day)	2565.4 (844.8)	2742.5 (850.9)	2837.2 (871.0)	2918.8 (895.8)	3059.6 (945.5)
Western pattern (%)					
Q1	41.7	35.8	33.2	30.2	25.8
Q2	34.7	35.2	34.0	32.4	30.3
Q3	23.7	29.0	32.8	37.4	43.8
Healthy pattern (%)					
Q1	53.7	35.2	31.6	26.2	20.1
Q2	31.7	36.1	34.6	34.8	29.6
Q3	14.6	28.7	33.9	39.1	50.4

Table 9. Hazard ratios of hypertension according to dietary total antioxidant capacity intake without coffee TAC (n=40 576). E3N Cohort, France 1993-2008.

Dietary TAC (mmol/day)	Cases		M1		M2		M3	
		Person-years	HR [95% CI]	p-trend	HR [95% CI]	p-trend	HR [95% CI]	p-trend
Q1 (< 2.95)	1 948	97 769	Reference	0.0002	Reference	0.01	Reference	0.0002
Q2 (2.95-3.99)	1 909	98 826	0.95 [0.89; 1.01]		0.93 [0.88; 1.00]		0.93 [0.87; 0.99]	
Q3 (4.00-5.12)	1 831	99 414	0.89 [0.84; 0.95]		0.89 [0.84; 0.95]		0.88 [0.82; 0.94]	
Q4 (5.13-6.69)	1 845	99 045	0.90 [0.84; 0.96]		0.90 [0.84; 0.96]		0.88 [0.82; 0.94]	
Q5 (> 6.69)	1 817	98 840	0.88 [0.83; 0.94]		0.90 [0.84; 0.96]		0.85 [0.79; 0.92]	

M1: Age as the time scale + energy excluding alcohol

M2: M1 + (Diabetes, treated hypercholesterolemia, education, family history of hypertension, smoking, physical activity, and body mass index)

M3: M2 + (Sodium, Potassium, Magnesium, omega-3 fatty acids, alcohol and coffee)

Table 10. Sensitivity analyses. Mutually adjusted analysis. Hazard ratios of hypertension according to dietary total antioxidant capacity intake, partitioned into TAC from coffee and TAC from all other sources. (N=40 576). E3N Cohort, France 1993-2008.

Dietary TAC (mmol/day)		M1		M2		M3	
	Cases	HR [95% CI]	p-trend	HR [95% CI]	p-trend	HR [95% CI]	p-trend
Non-coffee TAC							
Q1 (<2.95)	1 948	Reference	0.001	Reference	0.006	Reference	<0.0001
Q2 (2.95 - 3.99)	1 909	0.95 [0.89; 1.01]		0.94 [0.88; 1.00]		0.93 [0.87; 0.99]	
Q3 (3.99 - 5.52)	1 831	0.89 [0.84; 0.96]		0.90 [0.84; 0.96]		0.88 [0.82; 0.94]	
Q4 (5.52 – 6.69)	1 845	0.91 [0.85; 0.97]		0.91 [0.85; 0.97]		0.88 [0.82; 0.94]	
Q5 (>6.96)	1 817	0.90 [0.90; 0.83]		0.90 [0.84; 0.97]		0.85 [0.79; 0.92]	
Coffee TAC							
Q1 (<2.46)	1 820	Reference	0.01	Reference	0.70	Reference	0.03
Q2 (2.46 – 9.15)	1 861	1.00 [093; 1.06]		1.00 [0.93; 1.06]		0.97 [0.90; 1.03]	
Q3 (9.15 – 15.97)	1 898	1.05 [0.98; 1.11]		1.02 [0.96; 1.09]		0.96 [0.89; 1.03]	
Q4 (15.97 – 24.99)	1 923	1.07 [1.00; 1.15]		1.04 [0.98; 1.11]		0.95 [0.87; 1.03]	
Q5 (> 24.99)	1 848	1.06 [1.00; 1.14]		1.00 [0.94; 1.07]		0.86 [0.75; 0.97]	

M1: Age as the time scale + energy without alcohol

M2: M1 + (Diabetes, treated hypercholesterolemia, education, family history of hypertension, smoking, physical activity, body mass index)

M3: M2 + Na (mg), K (mg), Mg (mg), AGPIw3 (mg), alcohol (g)

Table 11. Sensitivity analyses. Hazard ratios of hypertension according to dietary total antioxidant capacity of main food groups (N=40 576). E3N Cohort, France 1993-2008.

Dietary TAC (mmol/day)			M1		M2		M3	
	Cases	Person- years	HR [95% CI]	p-trend	HR [95% CI]	p-trend	HR [95% CI]	p-trend
Coffee				0.01		0.13		0.93
Q1 (<3.78)	2 272	124 084	Reference		Reference		Reference	
Q2 (3.78-12.94)	2 332	124 593	1.03 [0.97; 1.09]		1.02 [0.96; 1.08]		1.00 [0.94; 1.07]	
Q3 (12.95-22.49)	2 416	122 864	1.09 [1.03; 1.16]		1.08 [1.01; 1.14]		1.05 [0.97; 1.13]	
Q4 (> 22.49)	2 330	122 355	1.08 [1.01; 1.14]		1.04 [0.98; 1.11]		0.98 [0.87; 1.11]	
Tea				0.04		0.42		0.47
Q1 (0)	3 814	192 963	Reference		Reference		Reference	
Q2 (0.002-0.19)	999	53 183	0.96 [0.90; 1.03]		0.97 [0.90; 1.04]		0.98 [0.91; 1.05]	
Q3 (0.20-1.50)	2 325	12 3243	0.97 [0.92; 1.02]		0.98 [0.93; 1.04]		0.99 [0.94; 1.04]	
Q4 (> 1.50)	2 212	12 4506	0.95 [0.89; 1.00]		0.98 [0.93; 1.04]		0.98 [0.93; 1.04]	
Chocolate				0.22		0.27		0.55
Q1 (0)	4 175	210 308	Reference		Reference		Reference	
Q2 (0-0.12)	668	36 846	0.97 [0.89; 1.05]		0.95 [0.87; 1.03]		0.95 [0.88; 1.04]	
Q3 (0.13-0.77)	2 102	118 467	0.93 [0.88; 0.98]		0.92 [0.87; 0.97]		0.93 [0.88; 0.98]	
Q4 (>0.77)	2 405	128 275	0.96 [0.91; 1.01]		0.96 [0.91; 1.01]		0.97 [0.92; 1.03]	
Fruits and vegetables				0.001		<0.0001		<0.0001
Q1 (< 1.09)	2 360	122 429	Reference		Reference		Reference	
Q2 (1.10-1.52)	2 337	123 437	0.96 [0.90; 1.01]		0.96 [0.90; 1.01]		0.96 [0.90; 1.02]	
Q3 (1.53-2.06)	2 274	124 930	0.89 [0.84; 0.95]		0.87 [0.82; 0.93]		0.87 [0.82; 0.93]	
Q4 (> 2.06)	2 379	123 100	0.91 [0.85; 0.96]		0.87 [0.82; 0.93]		0.87 [0.81; 0.93]	
Wine				0.54		0.89		0.001

Q1 (<0.03)	2 403	122 134	Reference		Reference		Reference	
Q2 (0.04-0.43)	2 285	124 581	0.96 [0.91; 1.02]		0.95 [0.90; 1.01]		0.94 [0.89; 1.00]	
Q3 (0.44-1.32)	2 303	124 560	0.95 [0.90; 1.01]		0.95 [0.90; 1.01]		0.91 [0.86; 0.97]	
Q4 (> 1.32)	2 359	122 620	0.96 [0.91; 1.02]		0.97 [0.92; 1.03]		0.85 [0.78; 0.93]	
Other sources				0.003		0.04		0.01
Q1 (0.01-0.50)	2 470	121 940	Reference		Reference		Reference	
Q2 (0.51-0.72)	2 374	123 829	0.96 [0.90; 1.02]		0.98 [0.92; 1.04]		0.98 [0.92; 1.04]	
Q3 (0.73-1.01)	2 218	124 715	0.89 [0.83; 0.94]		0.92 [0.86; 0.97]		0.91 [0.86; 0.97]	
Q4 (>1.01)	2 288	123 411	0.92 [0.86; 0.98]		0.95 [0.89; 1.02]		0.93 [0.87; 1.00]	

M1: Age as the time scale + energy excluding alcohol

M2: M1 + (Diabetes, treated hypercholesterolemia, education, family history of hypertension, smoking, physical activity, and body mass index)

M3: M2 + (Sodium, Potassium, Magnesium, omega-3 fatty acids, alcohol and coffee)

Table 12. Sensitivity analyses. Hazard ratios of hypertension according to dietary total antioxidant capacity intake, excluding cases diagnosed in the first 5 years of follow-up (N=38 445). E3N Cohort, France 1993-2008.

Dietary TAC (mmol/day)			M1		M2		M3	
	Cases	Person-years	HR [95% CI]	p-trend	HR [95% CI]	p-trend	HR [95% CI]	p-trend
Q1 (< 2.95)	1 478	96 922	Reference	<0.0001	Reference	0.0004	Reference	<0.0001
Q2 (2.95-3.99)	1 500	98 050	0.97 [0.90; 1.04]		0.95 [0.88; 1.02]		0.95 [0.88; 1.02]	
Q3 (4.00-5.12)	1 432	98 673	0.90 [0.83; 0.97]		0.89 [0.83; 0.96]		0.89 [0.82; 0.96]	
Q4 (5.13-6.69)	1 414	98 236	0.88 [0.82; 0.95]		0.87 [0.81; 0.94]		0.86 [0.79; 0.93]	
Q5 (> 6.69)	1 395	98 082	0.87 [0.80; 0.94]		0.87 [0.81; 0.94]		0.84 [0.76; 0.92]	

M1: Age as the time scale + energy excluding alcohol

M2: M1 + (Diabetes, treated hypercholesterolemia, education, family history of hypertension, smoking, physical activity, and body mass index)

M3: M2 + (Sodium, Potassium, Magnesium, omega-3 fatty acids, alcohol and coffee)

Table 13. Sensitivity analyses. Hazard ratios of hypertension according to dietary total antioxidant capacity intake, excluding participants with supplement intakes of antioxidants (N=28 648). E3N Cohort, France 1993-2008.

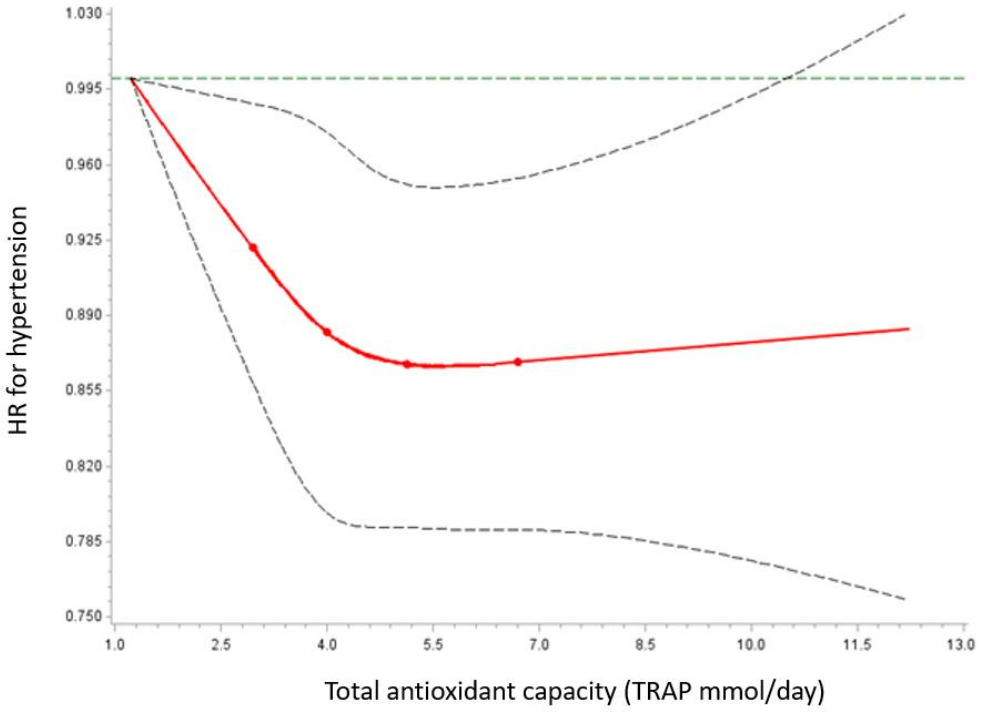
Dietary TAC (mmol/day)			M1		M2		M3	
	Cases	Person-years	HR [95% CI]	p-trend	HR [95% CI]	p-trend	HR [95% CI]	p-trend
Q1 (< 2.95)	1 486	72 721	Reference	0.001	Reference	0.01	Reference	0.0002
Q2 (2.95-3.99)	1 386	70 240	0.95 [0.88; 1.02]		0.93 [0.86; 1.00]		0.92 [0.85; 0.99]	
Q3 (4.00-5.12)	1 277	68 482	0.88 [0.82; 0.95]		0.88 [0.82; 0.95]		0.87 [0.80; 0.94]	
Q4 (5.13-6.69)	1 300	68 147	0.89 [0.83; 0.97]		0.90 [0.84; 0.98]		0.87 [0.80; 0.95]	
Q5 (> 6.69)	1 212	64 993	0.87 [0.81; 0.94]		0.89 [0.82; 0.96]		0.83 [0.75; 0.91]	

M1: Age as the time scale + energy excluding alcohol

M2: M1 + (Diabetes, treated hypercholesterolemia, education, family history of hypertension, smoking, physical activity, and body mass index)

M3: M2 + (Sodium, Potassium, Magnesium, omega-3 fatty acids, alcohol and coffee)

Figure 22. Cubic spline regression model between the total antioxidant capacity and HRs for hypertension (n=40 576). E3N cohort, 1993 - 2008.



Spline regression: the four knots were the 20th, 40th, 60th and 80th percentiles, the reference value was the minimum total antioxidant capacity. The model was adjusted for smoking status, physical activity, education level, diabetes, hypercholesterolemia, family history of hypertension, energy intake without alcohol, alcohol intake, and BMI. Solid line, HR; dashed lines, 95% CI.

CHAPTER V: DAIRY PRODUCTS AND HYPERTENSION IN THE E3N STUDY

1. Background

Dairy products are the main source of high bioavailable calcium and they are widely consumed across different populations (233). However, in the last years, their consumption has been questioned because of the saturated fat and sodium content, known risk factors for cardiovascular disease which are the first cause of mortality in the world (234, 235).

The relation between dairy products and hypertension risk still not clear. A clinical trial, showed a beneficial effect of low-fat dairy on blood pressure from a diet (DASH diet) that combined whole grains, fruit and vegetables, besides to decrease total fat. Nonetheless, this is a dietary healthy pattern and is difficult to isolate the effect of each component (214). Then, the role of different types of dairy products on the development of hypertension has been studied in observational studies (58, 172, 175) and results are inconsistent and vary importantly across populations. Studies conducted in the US found an inverse relation between yogurt (236) and milk (58) with hypertension. While in England no association was found between fermented dairy products and risk of hypertension (177) and in the Netherlands the relation between milk did and hypertension was null (175). This lack of consistency may be explained by methodological differences (statistical methods, diet measurements, confounding) or variation in the nutritional composition of dairy products. Milk has a complex nutritional composition that includes different types of fat, proteins of high biological value, minerals, and antioxidants (106). Fermented products contain biopeptides with angiotensin converting inhibitor effects (216) and cheese has an important sodium content, but also similar to milk has several vitamins and minerals with a potentially beneficial impact in cardiovascular health (237).

Dairy and specially cheese consumption are commonly consumed in France (the first consumer of cheese in the world) (106) and this country has probably the greatest diversity in milk-derived foods. In France, only two studies (173, 238) have previously evaluated total dairy consumption and changes in blood pressure. These studies were limited by the lack of information on different types of dairy products. The aim of this

study was to investigate the relation between each type of dairy product including different types of cheese and incident hypertension in French women.

2. Methods

2.1. Study Population

Participants were asked to complete a self-administered questionnaire, every 2-3 years in order to update medical events and lifestyle. Between 1993 and 1995, 74 520 participants answered a follow-up questionnaire and a validated self-administrated diet history questionnaire (180). Participants with an unrealistic energy consumption (n = 1 381), with no follow-up after 1993 (n = 846), without risk factor information before 1993 (n = 2 793), women with cancer (n = 4 253), cardiovascular disease (n = 449) or hypertension (n = 24 222) on the 1993 questionnaire and 50 participants without information on dairy product consumption were excluded. The final study population included 40 526 women.

2.2. Statistical analysis

Total dairy, yogurt and cottage cheese consumption were categorized in quintiles, milk in quartiles and the cheeses in tertiles. Cox models with age as the time scale were used to estimate hazards rations (HR) and 95% confidence intervals (95% CI). Time at entry was the age at baseline (1993), exit time was the age of diagnosis, death (dates of death were available from medical insurance), last follow-up, or the end of the follow-up period (June 25, 2008), whichever occurred first. The median value for each exposure category was used to estimate linear trend across categories and included as a continuous variable in statistical models.

For each type of dairy product, the adjustment was progressively for risk factors of hypertension that could be associated to dairy intake. The first model was adjusted only for age and energy without alcohol. The second model additionally included family history of hypertension (no/yes), diabetes (no/yes), treated hypercholesterolemia (no/yes), smoking status (never, former, current), education (without high school diploma, with high school diploma), body mass index (< 25, 25 - 24.9, ≥ 30) and physical activity (Mets-h/week, continuous). The third model was further adjusted for alcohol (g/d), fruits and vegetables (g/d), processed meat (g/d) as continuous variables.

The final model 4, all the dietary variables (intakes of alcohol (g/d), fruits and vegetables (g/d), processed meat (g/d), magnesium (g/d), potassium (g/d) and sodium (g/d)) were added to the second model. Additionally, an adjustment for diet, using dietary patterns (healthy and western) was conducted (model 5). In all the models, the adjustment was simultaneously for others dairy, for example milk models were controlled for yogurt, cottage cheese and cheese.

Secondary analyses were conducted in which an alternative classification for dairy products (whole and low-fat dairy) was used. Also, the impact of different types of cheese on the risk of hypertension was evaluated. Further, potential effect modification by age (divided in two categories according to the median value), family history of hypertension (yes/no) and BMI (25 < vs ≥ 25 kg/m^2) was assessed. Also, gut microbiota in people with obesity and normal weight appears to be different (239). Thus, we specifically assessed effect modification of BMI on the yogurt-hypertension relation. Statistical significance of an interaction term between dairy products and the potential effect modifiers was tested. However, these tests are usually underpowered for this reason even if the term was not significant the stratification was conducted.

Finally, in sensitivity analyses, cases of hypertension that occurred within the first five years of follow-up were excluded, as knowledge of borderline hypertension may have produced changes in participants' diets. To limit confounding, participants with diabetes, hypercholesterolemia, overweight or obesity at baseline were removed, they could change their diet during the follow-up.

3. Results

The mean age (± SD) of the participants was 51.6 (± 6.2), the mean servings/day of dairy products was 2.2 ± 1.1. The mean daily servings were 0.4 (± 0.7) for milk, 0.6 (± 0.5) for yogurt, 0.2 (± 0.2) for cottage cheese, and 1.1 (± 0.8) for cheese. The dairy with the highest consumption was cheese (99% of participants) and with the lowest milk (57% of participants). In relation to cheese consumers, 27.8% consume only one serving, 34% 2 servings, 21.2% 3 servings and 17% consumed at least four servings per day.

As shown in **Table 14**, a greater intake of dairy products was associated with a higher BMI but with less hypercholesterolemia at baseline. Women with the highest consumption category (Q5) compared with those with a lowest category (Q1) were more

physically activate but smoked less and were slightly more overweight/obese. Increasing intake of dairy products was associated with a higher consumption of energy, processed meat, alcohol, sodium, but also of potassium, magnesium or fruits and vegetables.

After an average 12.2 years of follow-up and 493 309 person-years, 9 340 cases of incident hypertension were identified. The incidence rate in participants in the first quintile of dairy products consumption was 19 per 1000 person-years, whereas in the fifth quintile it was 18.4 par 1 000 person-years. In multivariable analyses, there were no association between total dairy intake and hypertension. In the first model, adjusted for age and energy, no association between total dairy consumption and risk of hypertension was observed. Further adjustment for lifestyle factors (model 2) or for dietary factors (model 3), did not alter the relation. In the final model, adjusted for food groups and nutrients, there were no changes (model 4). Additional adjustment for dietary patterns (healthy or western diet) did not modify the results (model 5).

When the relation between each dairy product including milk, yogurt, cottage cheese and cheese and the risk of hypertension was evaluated no association between any of these products and hypertension was observed (in both univariate and multivariable models) (**Table 15**). The same models described previously were conducted, considering each specific type of cheese (**Table 16**), there was a significant direct association only with processed cheese (HR 1.11; 95% CI 1.05 - 1.18; p-trend < 0.0001). In addition, whole and low-fat dairy intake was analyzed, but no association was observed (**Table 17**). After the exclusion of participants diagnosed with diabetes, hypercholesterolemia, overweight or obesity (**Table 18**) or the cases developed during the first five years of follow-up (**Table 19**) or the results did not change. There was no statistically significant interaction between dairy products and age, BMI, or smoking, regarding the risk of hypertension. Thus, when the levels of the modifier's variables were explored no effect modification of age, family history of hypertension or BMI in the relation studied was observed (**Appendix 7 and 8**).

4. Discussion

In this large prospective French cohort of women, no association between total dairy, and different types of dairy (milk, yogurt, cottage cheese and cheese) and the risk of hypertension after adjustment with the main risk factors for hypertension was found. There is a suggestion that processed cheese consumption may be directly associated with hypertension.

Milk is a complex food, rich in a wide variety of nutrients like vitamins, minerals, proteins and approximately 400 different types of fatty acids (143). Thus, different mechanisms deeply explained in the first chapter, have been proposed to explain the relation between dairy products consumption and hypertension.

Results from previous studies on the relation between dairy consumption and hypertension were not conclusive (58, 172, 175). In US-based populations, (58, 172) an inverse association between milk and skimmed-milk and the risk of hypertension in middle-aged and older women was observed. In United States, the nutritional content of milk is different, is fortified with vitamin D being the main source of this vitamin in this country. This is particularly important because this vitamin regulates the calcium absorption from the intestinal tract and interact with parathyroid hormone maintaining the homeostasis of calcium (62). The deficiency of vitamin D might be associated with hypertension development through an inadequate stimulation of the renin-angiotensin system (240). Besides, the inverse association for milk and hypertension could be confounded by behaviors or dietary habits. In the studies in which a significant inverse association with low-fat dairy has been reported (58, 174), participants with a high consumption of milk were more likely to have a better lifestyle (for example they had more fruits and vegetable consumption and were less smokers), than those with a low consumption.

In agreement with previous reports (58, 176, 177), in the current study, participants with higher consumption of dairy had a higher consumption of fruits or vegetables and in general a better lifestyle. In this study, the impact of lifestyle and diet appeared to be limited. Since in this research all the statistical models were adjusted for fruit and vegetables intake and for a healthy dietary pattern, however no association was observed for any type of dairy product and risk of hypertension.

Previously, the DASH diet (214), based on fruit and vegetables, low-fat dairy products, and whole grains, demonstrated a reduction in blood pressure in both healthy and hypertensive individuals. However, this trial was not design to evaluate the individual effect of each of their components besides the duration of the intervention was short. Alonso et al, in a randomized controlled trial which evaluated the specific effect of whole and low-fat dairy on blood pressure, did not find an association (241).

Furthermore, previous studies as well as in this research, did not show an association with cottage cheese (58) or yogurt which are fermented products (242). A meta-analysis, of 5 prospective cohorts from United States and Netherlands, including 45 088 participants and 12 959 cases, did not find an association between yogurt and hypertension (242). However, the Nurses´ Health study showed an inverse association between yogurt and hypertension. In this population, participants who consumed more yogurt (and dairy), consumed less refined carbohydrates, sugar sweetened beverages and processed meat. Thus, the results observed could be partly explained because of a replacement effect (236). Another possible explanation is the difference in the nutritional content of the yogurt according to the countries. For example, according to USDA food-composition database (243), one yogurt serving size (245 g) provided 223 - 345 mg of calcium whereas in other countries the servings are smaller like England (150 g) providing 137 - 211 mg. The gut microbiota in people with obesity and normal weight is different (239), for this reason the modification effect of BMI on yogurt consumption was assessed, but the results stayed unchanged.

Besides, being rich in calcium, cheese could exert a paradoxical effect because of the amount of sodium and fat. Sodium, is the only dietary factor that is considered as causal for hypertension (234). Consistent with the results of this study, in the Rotterdam (175), the CARDIA study (172) and The Women's Health Study (58), participants with a high consumption of cheese did not have a higher risk of hypertension. In this research, only one type of cheese, processed cheese, was associated positively with risk of hypertension showing a modest dose-effect relation, however these analyses were exploratory. Processed cheeses are made by melting one or more pressed cheeses cooked with other ingredients like milk, cream, butter and sugar. Furthermore, processed cheeses are rich in lipids, sodium and sugar in contrast, a lower content in proteins, magnesium and calcium (182) which are potential protective nutrients against hypertension. Calcium can bind with fatty acids in the intestinal track to create insoluble soup which reduce the absorption of fat (62), possibly the high content of calcium in

cheese can neutralize the effect of fat in blood lipids (163, 244). Further, a randomized controlled cross-over study in overweight and obese individuals (69) reported that saturated fat in the form of a cheese matrix compared with plant sources of saturated fat, decreased postprandial inflammation, suggesting that maybe not all food rich in saturated fat are equivalent and a possible interaction among their nutrients. In addition, whey, a protein milk, has been associated to the reductions on weight gain and blood pressure, inflammation and oxidative stress markers (245). Further, vitamin K2 only synthesized by bacteria, can inhibit vascular calcification playing an important role to prevent CVD and T2DM (246-249). Nonetheless, these results on a possible increased risk related to processed cheeses have to be confirmed in other populations, these findings suggest to explore separately from the other types of dairy products the potential impact of processed cheese on cardiovascular markers. To the best of my knowledge this is the first-time cheeses are studied by types.

Participants with certain conditions like hypercholesterolemia, overweight or obesity could have changed their diet during the follow-up, leading to a misclassification on the covariates. For this reason, these participants were excluded from the analysis. The results remained the same, there were not significant changes in results.

In France, there are a wide variety of dairy products therefore the nutritional content specially calcium and fat, are not the same as in others countries. In this study 99 % of participants consumed cheese having an important variability (at least 1 servings/d – more than 4 servings/d). This results are similar with those of the Dutch study (176), this population is similar to the French as they are regular consumers of dairy products, limiting confounding.

4.1. Strengths and limitations

Several strengths deserve to be considered in this study. A prospective design, a long follow-up (12 years), a large sample size, an important number of cases which enabled us to have enough statistical power. The large variety of dairy products commonly consumed allowed us to evaluate the relation of different dairy products and hypertension over a wide range of intake.

However, there were some limitations. Misclassification of dairy intake is possible, dietary assessment was conducted once at the beginning of the study; thus, it is difficult

to know towards which direction is the estimate biased. However, we used a validated dietary questionnaire which was used successfully in previous studies (208, 250). Incident hypertension was identified by self-report; we did a validation study with the information provided by medical insurance. Nonetheless, a misclassification of the outcome is possible, it seems likely to be non-differential because the exposure was measured before the hypertension status. Despite we adjusted for the major factor risks for hypertension we cannot rule out confounding by unmeasured factors (dietary, behaviors and lifestyle) or poorly measured factors.

5. Conclusion

In this large prospective French cohort, no association between total dairy product consumption or any type of dairy (milk, yogurt, cottage cheese and cheese) and the risk of hypertension was observed. These findings suggest that intake of cheese (apart from processed cheese) may not be considered as deleterious in terms of development of hypertension in women. These results have to be confirmed in randomized control trials.

Table 14. Population characteristics according to total dairy consumption (N=40 526). E3N Cohort, France 1993 - 2008.

Characteristics	Dairy products consumption in quintiles (servings)				
	Q1 (N=8105)	Q2 (N=8105)	Q3 (N=8106)	Q4 (N=8105)	Q5 (N=8105)
Risk factors [1]					
Age, years [2]	51.9 (6.3)	51.7 (6.3)	51.6 (6.3)	51.4 (6.1)	51.5 (6.1)
Family history of hypertension	28.7	29	28.3	29.7	27.7
Body mass index (kg/m^2)					
Normal	88.1	87.5	87.2	85.6	84.7
Overweight	10.7	11.3	11.2	13	13.3
Obesity	1.2	1.2	1.6	1.4	2
Diabetes	0.4	0.5	0.6	0.4	0.5
Hypercholesterolemia	5.2	4.8	5	4.1	4.3
Smoking status					
Never	51.1	51.3	52.8	52.9	52.6
Former	32	34.4	34.5	34.3	34.1
Current	16.9	14.3	12.7	12.9	13.3
Physical activity (mets/d) [2]	53.1 (30.0)	54.0 (29.4)	53.8 (29.6)	54.7 (29.9)	55.3 (30.0)
With high school diploma	90	90.6	90.8	90.2	89.6
Dietary Factors [2]					
Energy without alcohol (kcal/d)	1840 (453)	1987 (458)	2109 (475)	2233 (504)	2471 (558)
Alcohol (g/d)	13 (15)	12(14)	11 (13)	11 (13)	11 (13)
Processed meat (g/d)	24 (18)	26 (19)	27 (19)	29 (20)	30 (23)
Fruits and vegetables (g/d)	592 (256)	626 (246)	651 (259)	677 (266)	720 (300)
Sodium (mg/d)	2359(756)	2595 (750)	2791 (798)	2995 (844)	3391 (960)
Potassium (mg/d)	3359 (884)	3589 (881)	3796 (895)	4027 (951)	4475 (1129)

Magnesium (mg/d)	398 (133)	417(130)	436 (134)	455(139)	495 (153)
Western pattern					
Q1	36.6	33.9	32.5	32	31.7
Q2	34.9	35.4	34	32.7	29.7
Q3	28.5	30.7	33.5	35.4	38.6
Healthy pattern					
Q1	46.5	38.4	33.5	27.6	20.7
Q2	31.2	35.9	34.8	34.4	30.2
Q3	22.3	25.7	31.7	38	49.1

[1] % [2] Mean (SD)

Table 15. **Dairy products and hypertension risk (N=40 526). E3N Cohort, France 1993 - 2008.**

Dairy product (servings)	Cases	Person-years	M1		M2		M3		M4		M5	
			HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Total												
Q1	1859	98258	Reference	0.41	Reference	0.82	Reference	0.50	Reference	0.96	Reference	0.34
Q2	1820	99380	0.97 [0.91; 1.04]		0.97 [0.91; 1.03]		0.97 [0.91; 1.04]		0.97 [0.91; 1.03]		0.98 [0.91; 1.04]	
Q3	1890	98624	1.02 [0.95; 1.08]		1.02 [0.95; 1.08]		1.02 [0.96; 1.09]		1.01 [0.95; 1.08]		1.03 [0.96; 1.10]	
Q4	1903	98791	1.03 [0.96; 1.10]		1.01 [0.94; 1.07]		1.02 [0.95; 1.08]		1.01 [0.94; 1.07]		1.03 [0.96; 1.10]	
Q5	1868	98257	1.01 [0.94; 1.08]		0.99 [0.93; 1.06]		1.01 [0.94; 1.08]		0.99 [0.92; 1.06]		1.02 [0.95; 1.09]	
Milk												
Q1	4042	210401	Reference	0.41	Reference	0.40	Reference	0.60	Reference	0.42	Reference	0.83
Q2	1511	85562	0.92 [0.86; 0.97]		0.91 [0.86; 0.97]		0.91 [0.86; 0.97]		0.91 [0.86; 0.97]		0.91 [0.86; 0.97]	
Q3	1925	98836	1.00 [0.95; 1.06]		0.98 [0.93; 1.04]		0.98 [0.93; 1.04]		0.98 [0.93; 1.04]		0.99 [0.94; 1.04]	
Q4	1862	98511	0.97 [0.92; 1.03]		0.97 [0.92; 1.03]		0.98 [0.93; 1.03]		0.97 [0.91; 1.03]		0.99 [0.93; 1.05]	
Yogurt												
Q1	1935	98427	Reference	0.14	Reference	0.27	Reference	0.09	Reference	0.19	Reference	0.11
Q2	1746	96538	0.95 [0.89; 1.02]		0.96 [0.90; 1.02]		0.96 [0.90; 1.02]		0.95 [0.89; 1.02]		0.96 [0.90; 1.02]	
Q3	2141	96538	0.99 [0.93; 1.06]		1.00 [0.94; 1.07]		1.00 [0.94; 1.07]		1.00 [0.94; 1.06]		1.00 [0.94; 1.07]	
Q4	1586	86231	0.95 [0.89; 1.02]		0.95 [0.89; 1.01]		0.96 [0.90; 1.03]		0.96 [0.89; 1.02]		0.96 [0.90; 1.03]	
Q5	1932	98333	1.04 [0.97; 1.11]		1.03 [0.96; 1.10]		1.05 [0.98; 1.12]		1.03 [0.97; 1.10]		1.04 [0.98; 1.11]	
Cottage cheese												
Q1	2463	131350	Reference	0.99	Reference	0.19	Reference	0.45	Reference	0.34	Reference	0.29
Q2	1252	68038	1.00 [0.93; 1.07]		0.99 [0.93; 1.06]		1.00 [0.93; 1.07]		1.00 [0.93; 1.07]		1.00 [0.93; 1.07]	
Q3	1836	96776	1.04 [0.98; 1.11]		1.02 [0.96; 1.09]		1.03 [0.97; 1.09]		1.03 [0.96; 1.09]		1.02 [0.96; 1.09]	
Q4	1929	100671	1.03 [0.97; 1.10]		1.02 [0.96; 1.09]		1.03 [0.96; 1.09]		1.02 [0.96; 1.09]		1.02 [0.96; 1.08]	

Q5	1860	96474	1.01 [0.95; 1.07]		0.97 [0.91; 1.03]		0.98 [0.92; 1.05]		0.98 [0.92; 1.04]		0.97 [0.92; 1.04]	
Cheese												
Q1	1856	97937	Reference	0.55	Reference	0.58	Reference	0.39	Reference	0.20	Reference	0.59
Q2	1862	98905	1.01 [0.94; 1.07]		1.02 [0.95; 1.08]		1.01 [0.95; 1.08]		1.01 [0.94; 1.08]		1.01 [0.95; 1.08]	
Q3	1901	98754	1.04 [0.97; 1.11]		1.05 [0.98; 1.12]		1.04 [0.97; 1.11]		1.03 [0.97; 1.11]		1.05 [0.98; 1.12]	
Q4	1913	98646	1.04 [0.97; 1.11]		1.04 [0.98; 1.11]		1.03 [0.97; 1.10]		1.02 [0.96; 1.09]		1.04 [0.97; 1.11]	
Q5	1808	99067	0.98 [0.91; 1.05]		0.98 [0.92; 1.05]		0.97 [0.91; 1.04]		0.96 [0.89; 1.03]		0.98 [0.92; 1.05]	

M1: Adjusted for energy (energy without alcohol (kcal/d),

M2: M1+ smoking status (never, former, current), education (without high school diploma, with high school diploma), family history of hypertension (no, yes), and physical activity (Mets/d)

M3: M2+ alcohol (g/d), processed meat (g/d), and fruits and vegetables (g/d)

M4: M2+ alcohol (g/d), processed meat (g/d), fruits and vegetables (g/d), sodium (mg/d), potassium (mg/d), and magnesium (mg/d)

M5: M2+ dietary patterns (western and healthy)

Table 16. **Types of cheeses and hypertension risk (N= 40 526). E3N Cohort, France 1993 - 2008.**

Cheeses (servings)	Cases	Person-years	M1		M2		M3		M4		M5	
			HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Soft												
Q1	2330	122759	Reference	0.40	Reference	0.85	Reference	0.69	Reference	0.59	Reference	0.74
Q2	2319	123613	1.00 [0.93; 1.07]		0.98 [0.91; 1.05]		0.97 [0.91; 1.04]		0.97 [0.91; 1.04]		0.98 [0.91; 1.05]	
Q3	2372	122459	1.06 [0.99; 1.14]		1.04 [0.97; 1.12]		1.03 [0.96; 1.11]		1.03 [0.96; 1.11]		1.04 [0.96; 1.11]	
Q4	2319	124478	1.03 [0.96; 1.11]		0.99 [0.92; 1.07]		0.98 [0.91; 1.06]		0.98 [0.90; 1.06]		0.99 [0.91; 1.07]	
Processed												
Q1	3982	223391	Reference	<0.0001	Reference	<0.0001	Reference	<0.0001	Reference	<0.0001	Reference	<0.0001
Q2	529	27229	1.08 [0.97; 1.19]		1.07 [0.96; 1.18]		1.06 [0.96; 1.17]		1.06 [0.96; 1.17]		1.05 [0.95; 1.17]	
Q3	2363	119582	1.10 [1.04; 1.17]		1.10 [1.04; 1.16]		1.10 [1.04; 1.16]		1.10 [1.04; 1.16]		1.09 [1.03; 1.16]	
Q4	2466	123107	1.14 [1.08; 1.20]		1.11 [1.06; 1.18]		1.12 [1.06; 1.18]		1.11 [1.05; 1.17]		1.11 [1.05; 1.17]	
Blue												
Q1	2371	124255	Reference	0.62	Reference	0.33	Reference	0.31	Reference	0.36	Reference	0.26
Q2	2290	122223	0.96 [0.90; 1.03]		0.98 [0.91; 1.04]		0.97 [0.91; 1.04]		0.97 [0.91; 1.04]		0.97 [0.91; 1.04]	
Q3	2367	124194	1.00 [0.94; 1.07]		1.01 [0.94; 1.08]		1.01 [0.94; 1.08]		1.01 [0.94; 1.08]		1.01 [0.95; 1.08]	
Q4	2312	122637	1.01 [0.94; 1.08]		1.03 [0.96; 1.10]		1.03 [0.96; 1.11]		1.03 [0.96; 1.10]		1.03 [0.96; 1.11]	
Semi-hard												
Q1	2385	123455	Reference	0.08	Reference	0.17	Reference	0.19	Reference	0.16	Reference	0.18
Q2	2373	122593	0.99 [0.92; 1.05]		1.00 [0.93; 1.07]		1.00 [0.93; 1.07]		1.00 [0.93; 1.07]		1.00 [0.93; 1.07]	
Q3	2273	123473	0.91 [0.84; 0.97]		0.92 [0.85; 0.98]		0.92 [0.85; 0.98]		0.92 [0.85; 0.98]		0.92 [0.85; 0.98]	
Q4	2309	123789	0.94 [0.87; 1.01]		0.95 [0.89; 1.03]		0.95 [0.89; 1.03]		0.95 [0.88; 1.02]		0.95 [0.89; 1.03]	
Hard												
Q1	2314	122959	Reference	0.82	Reference	0.92	Reference	0.62	Reference	0.57	Reference	0.74
Q2	2338	123572	1.04 [0.97; 1.11]		1.05 [0.98; 1.12]		1.04 [0.97; 1.11]		1.04 [0.97; 1.11]		1.04 [0.97; 1.11]	

Q3	2431	122831	1.11 [1.03; 1.19]		1.11 [1.04; 1.19]		1.10 [1.02; 1.18]		1.10 [1.02; 1.18]		1.10 [1.02; 1.18]	
Q4	2257	123948	1.00 [0.93; 1.09]		1.01 [0.94; 1.10]		1.00 [0.92; 1.08]		0.99 [0.92; 1.08]		1.00 [0.93; 1.09]	
Goat												
Q1	2407	123340	Reference	0.05	Reference	0.17	Reference	0.28	Reference	0.28	Reference	0.28
Q2	2390	123660	1.00 [0.93; 1.07]		1.01 [0.94; 1.08]		1.01 [0.94; 1.08]		1.01 [0.94; 1.08]		1.01 [0.94; 1.08]	
Q3	2235	122097	0.91 [0.85; 0.97]		0.93 [0.87; 0.99]		0.93 [0.87; 1.00]		0.93 [0.87; 1.00]		0.93 [0.87; 1.00]	
Q4	2308	124213	0.94 [0.88; 1.01]		0.96 [0.90; 1.03]		0.97 [0.90; 1.04]		0.97 [0.90; 1.04]		0.97 [0.90; 1.04]	

M1: Adjusted for energy (energy without alcohol (kcal/d),

M2: M1+ smoking status (never, former, current), education (without high school diploma, with high school diploma), family history of hypertension (no, yes), and physical activity (Mets/d)

M3: M2+ alcohol (g/d), processed meat (g/d), and fruits and vegetables (g/d)

M4: M2+ alcohol (g/d), processed meat (g/d), fruits and vegetables (g/d), sodium (mg/d), potassium (mg/d), and magnesium (mg/d)

M5: M2+ dietary patterns (western and healthy)

Table 17. Whole-fat and low-fat and dairy consumption and hypertension risk (N= 40 526). E3N Cohort, France 1993 - 2008.

Dairy products (servings)	Cases	Person-years	M1		M2		M3		M4		M5	
			HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Whole-fat												
Q1	2062	111401	Reference	0.02	Reference	0.27	Reference	0.09	Reference	0.14	Reference	0.10
Q2	1671	92380	0.99 [0.93; 1.06]		0.99 [0.93; 1.05]		0.99 [0.93; 1.05]		0.99 [0.93; 1.05]		0.99 [0.93; 1.05]	
Q3	1756	96681	0.99 [0.93; 1.05]		0.97 [0.91; 1.03]		0.97 [0.91; 1.03]		0.97 [0.91; 1.03]		0.97 [0.91; 1.03]	
Q4	1864	96510	1.03 [0.97; 1.10]		1.00 [0.94; 1.07]		1.01 [0.94; 1.07]		1.00 [0.94; 1.07]		1.00 [0.94; 1.07]	
Q5	1987	96338	1.09 [1.02; 1.16]		1.04 [0.98; 1.11]		1.06 [1.00; 1.13]		1.05 [0.99; 1.12]		1.06 [0.99; 1.13]	
Low-fat												
Q1	2001	101223	Reference	0.97	Reference	0.71	Reference	0.76	Reference	0.95	Reference	0.59
Q2	1791	95861	0.97 [0.91; 1.03]		0.96 [0.90; 1.03]		0.96 [0.90; 1.02]		0.96 [0.90; 1.02]		0.96 [0.90; 1.03]	
Q3	1811	99012	0.94 [0.88; 1.00]		0.94 [0.88; 1.00]		0.95 [0.89; 1.01]		0.94 [0.88; 1.00]		0.95 [0.89; 1.01]	
Q4	1859	99027	0.98 [0.92; 1.04]		0.97 [0.91; 1.03]		0.98 [0.92; 1.04]		0.97 [0.91; 1.04]		0.98 [0.92; 1.05]	
Q5	1878	98186	0.99 [0.93; 1.05]		0.98 [0.92; 1.04]		1.00 [0.93; 1.06]		0.99 [0.92; 1.06]		1.00 [0.94; 1.07]	

M1: Adjusted for energy (energy without alcohol (kcal/d),

M2: M1+ smoking status (never, former, current), education (without high school diploma, with high school diploma), family history of hypertension (no, yes), and physical activity (Mets/d)

M3: M2+ alcohol (g/d), processed meat (g/d), and fruits and vegetables (g/d)

M4: M2+ alcohol (g/d), processed meat (g/d), fruits and vegetables (g/d), sodium (mg/d), potassium (mg/d), and magnesium (mg/d)

M5: M2+ dietary patterns (western and healthy)

Table 18. Sensitivity analyses. Dairy consumption and hypertension risk without participants with diabetes, hypercholesterolemia, overweight or obesity (N= 38 454). E3N Cohort, France 1993 - 2008.

Dairy products (servings)	Cases	Person-years	M1		M2		M3		M4		M5	
			HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Total												
Q1	1389	83703	Reference	0.70	Reference	0.55	Reference	0.33	Reference	0.77	Reference	0.19
Q2	1391	84040	1.00 [0.93; 1.08]		1.01 [0.94; 1.09]		1.01 [0.94; 1.09]		1.01 [0.93; 1.08]		1.02 [0.94; 1.10]	
Q3	1403	83135	1.01 [0.94; 1.09]		1.03 [0.95; 1.11]		1.03 [0.96; 1.11]		1.02 [0.95; 1.10]		1.04 [0.96; 1.12]	
Q4	1403	82523	1.03 [0.95; 1.11]		1.03 [0.95; 1.11]		1.04 [0.96; 1.12]		1.02 [0.95; 1.11]		1.05 [0.97; 1.13]	
Q5	1367	81347	1.01 [0.93; 1.09]		1.02 [0.94; 1.10]		1.03 [0.96; 1.12]		1.01 [0.93; 1.10]		1.05 [0.97; 1.14]	
Milk												
Q1	3068	178662	Reference	0.53	Reference	0.65	Reference	0.83	Reference	0.52	Reference	0.92
Q2	1118	72045	0.90 [0.84; 0.96]		0.89 [0.84; 0.96]		0.89 [0.83; 0.96]		0.89 [0.83; 0.96]		0.90 [0.84; 0.96]	
Q3	1384	81911	0.97 [0.91; 1.03]		0.97 [0.91; 1.03]		0.97 [0.91; 1.04]		0.97 [0.91; 1.03]		0.97 [0.91; 1.04]	
Q4	1383	82130	0.97 [0.91; 1.03]		0.97 [0.91; 1.04]		0.98 [0.92; 1.05]		0.97 [0.90; 1.03]		0.99 [0.93; 1.06]	
Yogurt												
Q1	1419	83039	Reference	0.34	Reference	0.34	Reference	0.15	Reference	0.35	Reference	0.15
Q2	1363	81910	1.01 [0.93; 1.09]		1.01 [0.93; 1.09]		1.01 [0.93; 1.09]		1.01 [0.93; 1.08]		1.01 [0.94; 1.09]	
Q3	1628	96671	1.02 [0.95; 1.10]		1.02 [0.95; 1.10]		1.02 [0.95; 1.10]		1.01 [0.94; 1.09]		1.02 [0.95; 1.10]	
Q4	1178	71963	0.97 [0.90; 1.05]		0.97 [0.90; 1.05]		0.99 [0.91; 1.07]		0.98 [0.91; 1.06]		0.99 [0.92; 1.07]	
Q5	1365	81166	1.03 [0.95; 1.11]		1.03 [0.95; 1.11]		1.04 [0.97; 1.13]		1.02 [0.95; 1.11]		1.04 [0.97; 1.13]	
Cottage cheese												
Q1	1868	112818	Reference	0.30	Reference	0.20	Reference	0.46	Reference	0.31	Reference	0.30

Q2	977	58369	1.03 [0.95; 1.11]		1.02 [0.94; 1.10]		1.02 [0.95; 1.10]		1.02 [0.95; 1.11]		1.02 [0.94; 1.10]	
Q3	1413	82409	1.05 [0.98; 1.13]		1.05 [0.98; 1.12]		1.05 [0.98; 1.13]		1.05 [0.98; 1.12]		1.04 [0.97; 1.12]	
Q4	1411	83823	1.02 [0.95; 1.09]		1.03 [0.96; 1.10]		1.03 [0.96; 1.11]		1.03 [0.96; 1.10]		1.02 [0.95; 1.10]	
Q5	1284	77329	0.98 [0.92; 1.06]		0.97 [0.91; 1.05]		0.99 [0.92; 1.06]		0.98 [0.91; 1.06]		0.98 [0.91; 1.05]	
Cheese												
Q1	1317	80899	Reference	0.72	Reference	0.90	Reference	0.72	Reference	0.53	Reference	0.95
Q2	1383	82996	1.03 [0.96; 1.11]		1.03 [0.96; 1.11]		1.03 [0.95; 1.11]		1.03 [0.95; 1.11]		1.03 [0.96; 1.11]	
Q3	1450	83513	1.08 [1.00; 1.16]		1.08 [1.00; 1.17]		1.07 [0.99; 1.16]		1.07 [0.99; 1.15]		1.08 [1.00; 1.16]	
Q4	1462	84015	1.07 [0.99; 1.15]		1.07 [0.99; 1.15]		1.06 [0.98; 1.14]		1.05 [0.97; 1.14]		1.06 [0.99; 1.15]	
Q5	1341	83324	0.99 [0.91; 1.07]		1.00 [0.92; 1.08]		0.99 [0.91; 1.07]		0.98 [0.90; 1.07]		1.00 [0.92; 1.08]	

M1: Adjusted for energy (energy without alcohol (kcal/d)),

M2: M1+ smoking status (never, former, current), education (without high school diploma, with high school diploma), family history of hypertension (no, yes), and physical activity (Mets/d)

M3: M2+ alcohol (g/d), processed meat (g/d) and fruits and vegetables (g/d)

M4: M2+ alcohol (g/d), processed meat (g/d), fruits and vegetables (g/d), sodium (mg/d), potassium (mg/d), and magnesium (mg/d)

M5: M2+ dietary patterns (western and healthy)

Table 19. Sensitivity analyses. Dairy consumption and hypertension risk without the cases during the first 5 years of follow-up (N= 38 398). E3N Cohort, France 1993 - 2008.

Dairy products (servings)	Cases	Person-years	M1		M2		M3		M4		M5	
			HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Total												
Q1	1416	97468	Reference	0.74	Reference	0.50	Reference	0.94	Reference	0.77	Reference	0.64
Q2	1447	98666	1.01 [0.94; 1.09]		1.01 [0.94; 1.09]		1.02 [0.94; 1.09]		1.02 [0.94; 1.09]		1.02 [0.95; 1.10]	
Q3	1489	97864	1.05 [0.97; 1.13]		1.05 [0.98; 1.13]		1.06 [0.99; 1.14]		1.06 [0.98; 1.14]		1.07 [0.99; 1.15]	
Q4	1456	97974	1.03 [0.95; 1.11]		1.01 [0.94; 1.09]		1.03 [0.95; 1.11]		1.02 [0.95; 1.10]		1.04 [0.97; 1.13]	
Q5	1404	97413	0.99 [0.91; 1.07]		0.98 [0.91; 1.06]		1.00 [0.93; 1.08]		0.99 [0.91; 1.08]		1.02 [0.94; 1.11]	
Milk				0.37		0.43		0.56		0.67		0.92
Q1	3091	208678	Reference		Reference		Reference		Reference		Reference	
Q2	1181	84937	0.93 [0.87; 1.00]		0.93 [0.87; 0.99]		0.93 [0.87; 0.99]		0.93 [0.87; 0.99]		0.93 [0.87; 0.99]	
Q3	1516	98058	1.02 [0.95; 1.08]		1.00 [0.94; 1.07]		1.00 [0.94; 1.06]		1.00 [0.94; 1.07]		1.01 [0.95; 1.07]	
Q4	1424	97712	0.96 [0.90; 1.02]		0.96 [0.90; 1.02]		0.97 [0.91; 1.03]		0.97 [0.91; 1.04]		0.99 [0.93; 1.06]	
Yogurt				0.21		0.29		0.06		0.14		0.05
Q1	1505	97655	Reference		Reference		Reference		Reference		Reference	
Q2	1341	95805	0.96 [0.89; 1.04]		0.97 [0.90; 1.04]		0.96 [0.89; 1.04]		0.96 [0.89; 1.04]		0.97 [0.90; 1.05]	
Q3	1684	112923	1.03 [0.96; 1.11]		1.04 [0.97; 1.12]		1.04 [0.96; 1.11]		1.03 [0.96; 1.11]		1.04 [0.97; 1.12]	
Q4	1220	85554	0.95 [0.88; 1.03]		0.95 [0.88; 1.02]		0.97 [0.90; 1.04]		0.96 [0.89; 1.04]		0.98 [0.90; 1.05]	
Q5	1462	97447	1.04 [0.97; 1.12]		1.04 [0.96; 1.12]		1.06 [0.99; 1.14]		1.05 [0.97; 1.13]		1.07 [0.99; 1.15]	
Cottage cheese				0.47		0.09		0.41		0.29		0.26
Q1	1878	130267	Reference		Reference		Reference		Reference		Reference	

Q2	976	67544	1.03 [0.95; 1.11]		1.02 [0.95; 1.11]		1.02 [0.95; 1.11]		1.03 [0.95; 1.11]		1.03 [0.95; 1.11]	
Q3	1428	96007	1.07 [1.00; 1.15]		1.06 [0.98; 1.13]		1.06 [0.99; 1.14]		1.06 [0.99; 1.13]		1.05 [0.98; 1.13]	
Q4	1500	99904	1.04 [0.97; 1.12]		1.03 [0.96; 1.11]		1.04 [0.97; 1.12]		1.04 [0.97; 1.12]		1.03 [0.96; 1.11]	
Q5	1430	95663	0.99 [0.93; 1.06]		0.96 [0.90; 1.03]		0.99 [0.92; 1.06]		0.98 [0.91; 1.05]		0.98 [0.91; 1.05]	
Cheese				0.55		0.61		0.46		0.42		0.62
Q1	1407	97118	Reference		Reference		Reference		Reference		Reference	
Q2	1457	98135	1.04 [0.97; 1.12]		1.05 [0.98; 1.13]		1.04 [0.97; 1.13]		1.05 [0.97; 1.13]		1.05 [0.97; 1.13]	
Q3	1482	97964	1.08 [1.00; 1.16]		1.09 [1.01; 1.17]		1.08 [1.00; 1.16]		1.08 [1.00; 1.16]		1.08 [1.00; 1.16]	
Q4	1490	97867	1.06 [0.99; 1.15]		1.07 [0.99; 1.15]		1.06 [0.98; 1.14]		1.06 [0.98; 1.14]		1.07 [0.99; 1.15]	
Q5	1376	98301	0.99 [0.91; 1.07]		0.99 [0.92; 1.07]		0.98 [0.91; 1.06]		0.98 [0.90; 1.07]		0.99 [0.92; 1.07]	

M1: Adjusted for energy (energy without alcohol (kcal/d)),

M2: M1+ smoking status (never, former, current), education (without high school diploma, with high school diploma), family history of hypertension (no, yes), and physical activity (Mets/d)

M3: M2+ alcohol (g/d), processed meat (g/d), and fruits and vegetables (g/d)

M4: M2+ alcohol (g/d)), processed meat (g/d), fruits and vegetables (g/d), sodium (mg/d), potassium (mg/d), and magnesium (mg/d)

M5: M2+ dietary patterns (western and healthy)

CHAPTER VI: DAIRY PRODUCTS AND HYPERTENSION IN THE MTC STUDY

1. Background

In different countries dairy products are widely consumed because they are considered healthy. They have a complex nutritional content including an important amount of calcium, proteins of high biological value, minerals and vitamins. Nonetheless, the role of dairy products has been questioned due to their content of saturated fat and sodium (particularly in cheese) which were associated previously with cardiovascular disease (233).

Observational prospective studies which evaluated the relation between dairy products and risk of hypertension were not consistent, and limited to American or European populations. Therefore, the Nurses' Health Study (236), found an inverse association between dairy, yogurt, milk and cheese intake and hypertension. In contrast, the Women Health study, reported no association with yogurt and cottage cheese; whereas skimmed-milk, but not whole milk were inversely associated (58). Furthermore, low-fat dairy products were inversely associated with hypertension among Spanish adults (174), the same association was observed in the ARIC study but limited to White but not in African population (171).

In addition of the inconsistency on the results in previous research, no prospective studies have assessed the relation between dairy products and hypertension in Hispanic populations that could be different because of the mixed of European and Amerindian. The aim of this study was to investigate the relation between dairy products intake and risk of hypertension among Mexican adult women.

2. Methods

2.1. Study Population

Among 115 314 participants of the MTC study, women with prevalent hypertension (n = 13 340), history of myocardial infarction and/or stroke, (n = 213), and breast cancer (n = 305) were excluded. Also, women were excluded if they have an implausible energy consumption (> 3500 calorie or < 500), a questionnaire considered to be invalid (response < 70 items on the dietary questionnaire or cereal section missing, n = 17 846), no intake of dairy products (n = 416) and no follow-up (n = 11 205). Thus, the final study population included 71 989 participants.

2.2. Statistical analyses

To minimize the influence of extreme values of dairy consumption, the values of the 95th percentiles of the distribution were assigned to participants with values beyond this range. Dairy product intake was categorized in quartiles using the lowest quartile as the reference. To evaluate the relation between dairy consumption and risk of hypertension and to estimate Hazard ratio (HR) and 95% confidence interval (CI), Cox models with follow-up time scale were used. Time at entry was the response date of the baseline questionnaire (2006 or 2008), exit time was the date of diagnosis of hypertension, death, last follow-up, or the end of the follow-up period (the response date of the last questionnaire, 2008 or 2011), whichever occurred first. The median value for each exposure category was used to estimate linear trend across categories and included as a continuous variable in statistical models.

Risk factors for hypertension that could be associated to total dairy intake or for each type of dairy were adjusted. The first model was adjusted for age (quintiles) and energy intake (tertiles). The main model was adjusted for the main risk factors for hypertension like socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension, physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), hypercholesterolemia, diabetes, indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing) and; dietary variables like fruits and

vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles). Additionally, as a sensitivity analysis, a model adjusted for the main risk factors of hypertension and for dietary patterns was performed (fruits and vegetables, western pattern, and modern Mexican pattern, all in tertiles). All the models were adjusted simultaneously for other dairy.

According to evidence presented in the first chapter of this thesis, risk of hypertension increased with the age (even if this population is younger than the French population) and in individuals with overweight and obesity, this an important factor to emphasize in this Mexican population where the prevalence is high (70%) (158). For this reason, the potential effect modification of the main potential confounders: age (median baseline age, < 43 vs ≥ 43 years) or BMI (< 25, ≥ 25 kg/m^2) was evaluated. Also, individuals with hypertensive parents or siblings could have more risk to present this disease. Thus, an analysis to evaluate an effect modifier of family history of hypertension (yes/no) was conducted as a proxy for genetic susceptibility. In addition, the modification effect of BMI on yogurt consumption was assessed because the evidence showed gut microbiota in people with obesity and normal weight is different (239). Statistical significance of an interaction term between the dairy and the potential effect modifiers was tested. However, these tests could be underpowered for this reason even if the term was not significant the stratification was conducted.

In sensitivity analyses, to limit potential confounding participants with hypercholesterolemia and diabetes were eliminated, since they may have changed their diet during the follow-up. The exclusion of participants with extreme values of dairy consumption (beyond the 95 percentiles of the distribution) were also evaluated in sensitivity of results. Further, some research assumed that BMI may be a mediator in the relation studied. To explore this assumption, the main analyses were conducted without the adjustment of BMI at baseline because it could lead to an attenuation of the association. The treatment for missing data was previously explained in chapter III.

3. Results

Among 71 989 Mexican women the mean age (± SD) was 41.9 (± 7.1) years at baseline. The mean total weekly servings of dairy were 14.7 (± 10.7). The mean of weekly servings for milk was 6.3 (± 6.2), for yogurt was 1.9 (± 2.2) and for cheese was 6.4 (± 4.7). Participants in the highest quartile of total dairy consumption compared with those in the

first quartile, presented a little more family history of hypertension. But they presented less indigenous background, diabetes, hypercholesterolemia, smoking, overweight and obesity. Further they consumed more processed meat, fruits and vegetables (**Table 20**). Total dairy consumption differed across regions, women living in the north of Mexico had the lowest weekly consumption and those who lived in the south the highest.

After an average of 2.3 $\pm$ 1.1 years of follow-up (range 0.2 to 7.7 years), 4 782 incident cases of hypertension were identified (28 cases per 1 000 person-years). The incidence of hypertension in participants in the fourth quartile of total dairy consumption was 31 per 1 000 person-years, whereas it was 27 per 1 000 person-years in those in the first quartile. In multivariable analysis, we found no association between total dairy products and milk consumption and risk of hypertension (**Table 21**). In the age- and energy-adjusted model, when consumers in highest quartiles were compared with those in lowest quartile, a significant association was observed for total dairy (HR 1.11; 95% CI 1.01 - 1.22; p-trend = 0.0002) as well as milk intake (HR 1.12; 95% CI 1.03 - 1.23; p-trend = 0.004). However, after the adjustment for main risk factors for hypertension and dietary factors this association disappeared.

When the relation for yogurt or cheese intake was evaluated individually, no association was observed with risk of hypertension in any of the models, nor a trend through quartiles of dairy products or each type of dairy intake was observed. Additionally, using the same models previously described, the relation between high-fat milk-based products, sugar added dairy, whole-milk, skimmed-milk, fresh cheese and other cheeses and risk of hypertension was analyzed (**Table 22**). Apart for high-fat milk-based products (butter and cream), no association was found with hypertension.

The adjustment for dietary patterns did not change the results in the main or secondary analyses (sensitivity analysis). Exclusion of women who reported diabetes or hypercholesterolemia (**Table 23**) or values beyond of the 95 percentiles of the distribution of dairy intake (**Table 24**) did not result in relevant changes in terms of statistical significance except for high-fat milk-based products which were no longer significative (**Table 25**). Besides, the relation studied was not modified by family history of hypertension (yes/no) or BMI (< 25, ≥ 25 kg/m^2). Non-significant interaction was observed between dairy and the potential modifiers, with the exception of the age. Only for women aged 43 years and older, a significant trend was observed, however any category of dairy consumption was no longer associated with hypertension risk (HR 1.15; 95% CI 0.97 - 1.36; p-trend = 0.01) (**Appendix 10 and 11**). When the BMI was removed

as covariate of the main analyses no changes in the results were observed either (data not shown).

4. Discussion

In this cohort of Mexican women, the intake of total dairy products or types of dairy were not associated with risk of hypertension, even after adjustment for lifestyle and dietary factors. Furthermore, after sensitivity analyses the results did not change. Neither an effect modification of age, family history of hypertension or BMI was observed in the relation studied. The mechanism by which dairy products may be associated with hypertension were not completely elucidated, possibly because of the complexity of milk nutritional content. Previously in this manuscript potential mechanisms between the studied relation were deeply explained. This section was focused on compared and explained the results observed.

Therefore, previous studies were not consistent. The studies in which an association between dairy products and hypertension was observed compared with those who did not, had a larger sample size (varied from 2 245 to 28 886) and the follow-up time varied from 2 to 10 years. They usually found an inverse association with low-fat dairy and hypertension. In the present study we have a larger sample size to conferred us a statistical power to identify associations and our follow-up time is in the range to previous studies. The SUN cohort (174), which is a comparable study to this research in terms of the duration of follow-up time, after 2 years they observed an inverse association between low-fat dairy products and risk of hypertension (n=5 880, cases=180), but not with total or whole-fat dairy. This study was a Mediterranean dynamic cohort of middle-aged Spanish adults including women and men, aged 37 years (range 20 to 90 years) of university graduates. However, in this study low-fat dairy consumers were younger and seemed to have a healthier lifestyle they were more physically active and low-fat consumption was directly associated with fruit and vegetable, potassium and fiber intake; and inversely associated with alcohol and saturated fat consumption.

In addition, the American study ARIC (171), observed that the systolic pressure increased 2.7 mmHg (95% CI -0.3 to - 0.6, p = 0.01) less in participants with higher consumption of skimmed milk compared to those with a low intake, this association was observed only in Caucasian but not in Africans participants. Thus, it could be explained by a genetic susceptibility in this group. The analyses by type of dairy product was only possible with whole-fat milk, no significant association was found, the analyses were not

possible with other type of dairy products due to the small variability in their consumption. There is no information about the relation studied in Hispanic populations, being possible to be different since the mixed of European and Amerindian, as in Mexican population.

Contrary to the findings in this research, the Women Health study (58), including 28 886 women aged 54 years in average, an older population than MTC study found an inverse association between low-fat milk consumption and hypertension risk. This study was conducted in United States, in this country the milk is fortified with vitamin D being the main source of this nutrient for this population. Previously, in the first chapter of this thesis the role of D in hypertension was explained. Thus, the differences of nutritional content of milk may explain the differences in the results.

Consistent with the results in this research, a meta-analysis including 5 cohorts from United States and Netherlands (45 088 participants and 12 959 cases) (242), did not find an association between yogurt consumption and hypertension risk. In contrast, The Nurses´ Health Study showed a significant inverse association. In this study, participants with the highest consumption of yogurt had healthier diets overall, suggesting a combined positive association between yogurt consumption and the diet. Yogurt consumers also consumed less refined carbohydrates, sugar sweetened beverages and processed meat, thus a replacement effect could explain partly the results observed (236). Therefore, in this population is possible that yogurt consumption may be a marker of healthy lifestyle. On the contrary, in the Mexican population it seems that yogurt consumption is not an indicator of healthy lifestyle. According to the ENSANUT National Mexican survey (251), despite yogurt consumers had a higher intake of calcium and protein, they also consumed more saturated fat associated to the dietary pattern of this group, and not to the saturated fat content from the yogurt. Since, among yogurt consumers, the percentage of contribution of saturated fat of yogurt to the total saturated fat consumption was 15.4% (251). Moreover, the contribution of yogurt to the total consumption of free sugars was high 28.3% (251).

In addition, studies with no association had a smaller sample (from 755 to 4 304 participants) but with longer follow-up from 5 to 15 years. A possible reason is that these studies did not have enough statically power to detect an association or a misclassification of the exposure due to a change of the diet during follow-up that may lead to an attenuation of the association. The Rotterdam Study (175) after 2 years of follow-up, observed a significant inverse relation between skimmed dairy products and the risk of hypertension, but not with whole-dairy products. After 6 years, the association

with skimmed dairy products was no longer significant. As suggested previously, this raises the hypothesis that dairy product intake may slow the progression instead of prevent the development of hypertension in certain individuals (175).

In the current study, in agreement with previous reports cheese consumption was not associated with an increase of hypertension risk. Besides the appreciable content of fat and sodium, cheese is a fermented product having several compounds such as calcium, whey protein, vitamin K_2 and specific types of fatty acids which have health benefits (246). Previous studies suggested a neutral effect of cheese consumption on blood lipids (163, 244). A possible explanation is its high content of calcium, which reduced fat absorption in the intestinal track (62). Further, whey protein reduced weight gain, blood pressure, inflammation, oxidative stress markers as well as cardiovascular disease (245) and vitamin K_2 can inhibit vascular calcification (247).

Additionally, dairy consumption according to fat content was evaluated. We analyzed individually the relation between fresh cheese considered a low-fat cheese in Mexican population. Also, we regrouped other types of cheeses with a higher fat content. Both groups of cheeses were not associated with the increase of hypertension risk. Further, whole-milk and skimmed-milk products consumption were not associated either. Previously, The DASH diet (214), a dietary healthy pattern including low-fat dairy, observed a reduction on blood pressure. However, this is a healthy dietary pattern being difficult to evaluate the effect that exerts each component in blood pressure. Thus, the effect of low-fat dairy product may be partly explained due to a combined effect of the pattern and the low-fat dairy consumption. Moreover, in observational studies and in the current study, low-fat dairy consumers frequently are healthier, even if we adjusted for variables like fruits and vegetables and variables as well as health dietary pattern to try to control for healthy lifestyle, we cannot rule out residual confounding (58, 176). In contrast, the National Birth Cohort an increase of risk of hypertension for low-fat dairy consumers was observed (177). A possible explanation is that during certain condition such as hypercholesterolemia, diabetes, overweight or obesity, the consumption of these products is recommended leading to reversal causation.

Besides, high-fat milk-based products initially were associated with hypertension however after removing participants with extreme values of consumption the association disappeared. These products are rich in saturated fat which were previously associated with the increase of LDL cholesterol (63). Nonetheless, in the Nurses' study, no association between hypertension and saturated polyunsaturated or trans-fat

consumption, and hypertension was observed (252). Fat milk content is complex, besides fat saturated, contains nearly 400 fatty acids, many of them only found in this food (159). Some studies suggested that bioactive fatty acids from milk fat were responsible for anti-inflammatory effect and improve of metabolic effects (253, 254).

Besides, no association between added sugar dairy and hypertension risk was found. The evidence demonstrated that high intake of added sugar lead to obesity which is an important risk factor for hypertension (255). This relation was not assessed before, nonetheless previous studies reported a direct association between consumption of added sugar principally from sugar-sweetened beverages and risk of obesity (256-258), type 2 diabetes mellitus (259, 260), dyslipidemias (261) and hypertension (262, 263).

Differences between studies may reflect differences in the distribution of genetic or environmental factors across populations that could influence the effect of dairy products and hypertension. The impact of dairy products and hypertension is unclear and difficult to evaluate because dairy intake may be linked to healthy behaviors leading to residual confounding.

4.1. Strengths and limitations

This study included several strengths, a prospective design, a large sample size, validated measurements and extensive information on lifestyle and dietary factors. Nonetheless, some limitations have to be considered. The diagnosis of hypertension was self-reported, however previous prospective studies in Hispanic population used this measurement, showing to be a valid indicator (264, 265). Further, the diagnosis of hypertension was validated, nonetheless measurement error is possible, since the exposure was assessed before the outcome it seems to be non-differential and may lead to an attenuation of the association.

In addition, dairy products consumption was evaluated once at baseline, thus subject to random error that may result in an underestimation of the true association. However, the dietary questionnaire was validated for Mexican population showing good correlation between the food frequency questionnaire and the 24h recall, the correlation for calcium was 0.60.

The follow-up was short and the date of diagnosis was imputed to calculate the person-years, thus error of measurement is unavoidable. However, the NHS II study reported a

hypertension incident rate of 11.4 cases per 1000 person-years among participants aged 36.0 years (in average), further NHS I study, reported a hypertension incident rate of 38.4 cases per 1000 person-years among older participants aged 55.4 years (266). The hypertension incidence rate in this population was 28 cases per 1000 person-years, according to previous studies it could be an expected rate if we take in consideration the mean age of MTC population 41.9 years. Besides, a short follow-up time may have decreased the power to detect an association, but there were enough cases to detect clinically differences. Moreover, in a previous study (174) with a smaller sample size (n = 5 880) and a similar follow-up detected an association between dairy products and hypertension.

Further, despite the adjustment for the major risk factor of hypertension we cannot ruled out confounding by unmeasured or poorly measured factors. Finally, this study is restricted to Mexican women, which limit the generalizability to different populations.

5. Conclusion

In this large prospective Mexican study, no association was observed between total dairy or types of dairy and risk of hypertension, these findings suggest that dairy products may not play a key role in the risk of hypertension. Thus, individuals can follow the recommendation of 3 daily servings of dairy products to achieved their daily intake of calcium particularly low-fat dairy.

Table 20. Population characteristics according to total dairy products consumption (N=71 989). MTC Cohort, Mexico 2006 - 2011.

Characteristics	Dairy products consumption in quintiles (servings/week)			
	Q1 (N=16 053)	Q2 (N=19 377)	Q3 (N=19 311)	Q4 (N=17 248)
Median intake, servings/week	3.9	9.0	15.0	28.7
Risk factors [1]				
Age, y [2]	41.8 (7.3)	41.7 (7.3)	41.8 (7.1)	42.5 (6.7)
Family history of hypertension	55.5	56.1	57.2	56.9
Indigenous background	12.3	8	6	5.5
Socioeconomic level				
Q1	25.4	23.3	21.7	20.1
Q2	18.1	21.4	26	30.5
Q3	28.2	30.1	31.7	31.7
Q4	28.3	25.2	20.6	17.7
State				
Mexico City	23.6	25.4	24.5	17.4
North	18	16.8	14.3	7
Center	26	28.4	25.8	23.8
South	30.8	27	30.6	41.2
Missing	1.6	2.4	4.8	10.6
Body mass index (kg/m^2)				
Normal	30.1	32.5	34.6	37
Overweight	38.7	38.2	38.6	37.9
Obesity	21.3	20.4	18.5	17.4
Missing	9.9	8.9	8.3	7.7
Diabetes	3.2	2.8	2.6	2.8
Hypercholesterolemia	10.4	9.8	9.1	8.9
Smoking status				
Never	79.6	78.1	76.5	74.6
Former	11	12.5	14	16.6
Current	9.5	9.4	9.5	8.8
Physical activity (mets/d) [2]	29.0 (27.5)	32.6 (29.3)	34.5 (30.3)	32.2 (28.8)
Dietary Factors [2]				
Energy (kcal)	1441(541)	1677 (545)	1904 (574)	2166 (596)
Processed meat (g/d)	0.5 (0.5)	0.6 (0.5)	0.7 (0.6)	0.8 (0.6)
Alcohol (g/d)	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Fruits and vegetables (g/d)	5.3 (4.1)	6.2 (4.2)	7.3 (4.5)	8.2 (4.9)
Whole grains (g/d)	2.3 (1.7)	2.4 (1.7)	2.4 (1.7)	2.4 (1.7)
Sugar-sweetened beverages (g/d)	1.2 (1.3)	1.3 (1.4)	1.5 (1.5)	1.7 (1.6)
Fruit and vegetable pattern [1]				
Q1	31.9	33	32.5	36

Q2	31.7	33.5	34.4	33.5
Q3	36.4	33.5	33.1	30.5
Western pattern [1]				
Q1	39.6	32.8	28.7	33.4
Q2	28.8	33.2	34.9	35.9
Q3	31.6	34	36.4	30.7
Modern Mexican pattern [1]				
Q1	14.2	24.5	38.6	55.2
Q2	27.5	37.3	37.4	29.7
Q3	58.3	38.2	24	15.1

[1] % [2] Mean (SD)

Table 21. Dairy products consumption and hypertension risk (N=71 989). MTC Cohort, Mexico 2006 - 2011.

Dairy products (servings)	Median intake	Cases	Person-years	Age-energy-adjusted		Multivariable	
				HR [95% CI]	p	HR [95% CI]	p
Total							
Q1	3.91	927	34319	Reference	0.0002	Reference	0.32
Q2	8.97	1113	43889	0.93 [0.85; 1.01]		0.93 [0.85; 1.02]	
Q3	15.05	1338	45850	1.05 [0.96; 1.15]		1.03 [0.94; 1.13]	
Q4	28.73	1404	44737	1.11 [1.01; 1.22]		1.01 [0.92; 1.11]	
Milk							
Q1	0.47	953	35664	Reference	0.004	Reference	0.30
Q2	3.00	1188	43034	1.06 [0.97; 1.15]		1.01 [0.93; 1.11]	
Q3	6.23	1263	45377	1.04 [0.96; 1.13]		1.01 [0.93; 1.10]	
Q4	17.50	1378	44719	1.12 [1.03; 1.23]		1.04 [0.95; 1.14]	
Yogurt							
Q1	0	654	21789	Reference	0.12	Reference	0.24
Q2	0.58	1531	57087	0.92 [0.83; 1.01]		0.92 [0.84; 1.01]	
Q3	3.00	1580	58282	0.90 [0.82; 0.99]		0.91 [0.83; 1.01]	
Q4	5.50	1017	31636	1.02 [0.92; 1.14]		1.01 [0.91; 1.13]	
Cheese							
Q1	1.63	954	34999	Reference	0.21	Reference	0.64
Q2	3.81	1212	44147	0.99 [0.91; 1.08]		0.99 [0.91; 1.08]	
Q3	6.70	1241	45085	0.97 [0.89; 1.06]		0.93 [0.85; 1.02]	
Q4	12.50	1375	44564	1.03 [0.94; 1.13]		0.97 [0.88; 1.07]	

Age-energy-adjusted: Age(quintiles) and energy (tertiles)

Multivariable: M1+ socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension (yes, no), physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), treated hypercholesterolemia (yes/no), diabetes (yes/no), indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing), fruits and vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles).

Table 22. Whole-milk, skimmed milk, fresh cheese, other cheeses, high-fat milk-based products and sugar added dairy and hypertension risk (N=71 2006 - 2011.

Dairy products (servings)	Median intake	Cases	Person-years	Age-energy-adjusted		Multivariable	
				HR [95% CI]	p	HR [95% CI]	p
Whole-milk							
Q1	0	1172	42476	Reference	0.95	Reference	0.30
Q2	0.23	1035	32699	1.11 [1.01; 1.21]		1.04 [0.95; 1.14]	
Q3	1.00	1382	50730	1.04 [0.96; 1.12]		1.02 [0.94; 1.11]	
Q4	7.00	1193	42890	1.05 [0.97; 1.15]		1.06 [0.97; 1.16]	
Skimmed-milk							
Q1	0	1220	49682	Reference	<.0001	Reference	0.28
Q2	0.47	850	30169	1.16 [1.06; 1.26]		1.05 [0.96; 1.15]	
Q3	3.00	1399	47373	1.23 [1.13; 1.33]		1.07 [0.99; 1.16]	
Q4	7.58	1313	41571	1.24 [1.14; 1.36]		1.07 [0.97; 1.17]	
Fresh cheese							
Q1	0.23	1201	44290	Reference	<.0001	Reference	0.94
Q2	0.58	713	26498	1.00 [0.91; 1.10]		1.02 [0.93; 1.12]	
Q3	3.00	1721	64333	0.99 [0.92; 1.07]		0.97 [0.90; 1.05]	
Q4	5.50	1147	33674	1.16 [1.07; 1.27]		1.01 [0.92; 1.10]	
Other cheese							
Q1	0.70	984	34002	Reference	0.01	Reference	0.39
Q2	2.16	1348	46403	0.99 [0.91; 1.08]		1.03 [0.95; 1.12]	
Q3	4.40	1183	45110	0.89 [0.82; 0.98]		0.96 [0.88; 1.05]	
Q4	8.58	1267	43280	0.90 [0.82; 0.99]		0.98 [0.89; 1.07]	
High-fat							
Q1	0.23	849	31300	Reference	0.65	Reference	0.03

Q2	0.58	1316	46944	1.02 [0.94; 1.12]		1.02 [0.93; 1.11]	
Q3	1.23	1334	47150	1.01 [0.92; 1.10]		1.02 [0.93; 1.12]	
Q4	4.00	1283	43402	1.02 [0.93; 1.13]		1.09 [0.99; 1.20]	
Added sugar							
Q1	0.23	984	35926	Reference	0.01	Reference	0.08
Q2	0.58	1122	44285	0.98 [0.90; 1.07]		0.98 [0.90; 1.07]	
Q3	1.16	1342	43776	1.19 [1.09; 1.30]		1.11 [1.01; 1.21]	
Q4	3.81	1334	44809	1.13 [1.03; 1.24]		1.09 [0.99; 1.19]	

Age-energy-adjusted: Age(quintiles) and energy (tertiles),

Multivariable: M1+ socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension (yes, no), physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), treated hypercholesterolemia (yes/no), diabetes (yes/no), indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing), fruits and vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles).

Table 23. Sensitivity Analyses. Dairy consumption and hypertension risk without participants with diabetes and hypercholesterolemia (N=63 644). MTC Cohort, Mexico 2006 - 2011.

Dairy products (servings)	Median intake	Cases	Person-years	Age-energy-adjusted		Multivariable	
				HR [95% CI]	p	HR [95% CI]	p
Total							
Q1	3.93	740	30034	Reference	<.0001	Reference	0.14
Q2	8.97	915	38752	0.95 [0.86; 1.04]		0.94 [0.86; 1.04]	
Q3	15.05	1123	40915	1.09 [0.98; 1.20]		1.05 [0.95; 1.16]	
Q4	28.83	1180	39839	1.14 [1.03; 1.27]		1.05 [0.94; 1.17]	
Milk							
Q1	0.47	776	31453	Reference	0.01	Reference	0.25
Q2	3.00	981	37992	1.07 [0.97; 1.18]		1.03 [0.94; 1.13]	
Q3	6.23	1050	40345	1.05 [0.96; 1.16]		1.03 [0.93; 1.13]	
Q4	17.50	1151	39750	1.14 [1.03; 1.25]		1.06 [0.96; 1.17]	
Yogurt							
Q1	0	527	18974	Reference	0.15	Reference	0.32
Q2	0.58	1267	50345	0.93 [0.84; 1.03]		0.93 [0.83; 1.03]	
Q3	3.00	1301	51909	0.90 [0.81; 1.00]		0.90 [0.81; 1.00]	
Q4	5.50	863	28311	1.04 [0.92; 1.17]		1.02 [0.91; 1.15]	
Cheese							
Q1	1.63	776	30573	Reference	0.11	Reference	0.98
Q2	3.81	989	38999	0.98 [0.89; 1.08]		0.98 [0.89; 1.07]	
Q3	6.70	1021	40093	0.96 [0.87; 1.06]		0.91 [0.82; 1.01]	
Q4	12.50	1172	39874	1.04 [0.94; 1.15]		0.98 [0.88; 1.09]	

Age-energy-adjusted: Age(quintiles) and energy (tertiles),

Multivariable: M1+ socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension (yes, no), physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), treated hypercholesterolemia (yes/no), diabetes (yes/no), indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing), fruits and vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles).

Table 24. Sensitivity Analyses. Dairy consumption and hypertension risk without participants extremes values (> 95 percentile) (N=64 695). MTC Cohort, Mexico 2006 - 2011.

Dairy products (servings)	Median intake	Cases	Person-years	Age-energy-adjusted		Multivariable	
				HR [95% CI]	p	HR [95% CI]	p
Total							
Q1	3.91	927	34319	Reference	0.02	Reference	0.83
Q2	8.97	1113	43889	0.94 [0.86; 1.02]		0.94 [0.86; 1.02]	
Q3	15.00	1329	45571	1.07 [0.98; 1.17]		1.04 [0.95; 1.14]	
Q4	25.00	746	25412	1.07 [0.96; 1.18]		0.98 [0.88; 1.09]	
Milk							
Q1	0.47	910	34067	Reference	0.12	Reference	0.81
Q2	3.00	1129	41206	1.05 [0.96; 1.15]		1.01 [0.92; 1.10]	
Q3	6.08	1171	42734	1.03 [0.94; 1.13]		1.00 [0.91; 1.09]	
Q4	17.50	905	31184	1.08 [0.98; 1.19]		1.01 [0.92; 1.12]	
Yogurt							
Q1	0.00	608	20423	Reference	0.16	Reference	0.29
Q2	0.58	1413	53572	0.92 [0.83; 1.01]		0.92 [0.83; 1.01]	
Q3	3.00	1403	53017	0.90 [0.82; 1.00]		0.92 [0.83; 1.01]	
Q4	5.50	691	22179	1.04 [0.93; 1.17]		1.03 [0.91; 1.15]	
Cheese							
Q1	1.58	921	33948	Reference	0.38	Reference	0.52
Q2	3.81	1157	42305	1.00 [0.92; 1.09]		1.00 [0.92; 1.09]	
Q3	6.70	1123	41983	0.97 [0.88; 1.06]		0.93 [0.85; 1.02]	
Q4	11.23	914	30955	1.03 [0.93; 1.14]		0.97 [0.87; 1.08]	

Age-energy-adjusted: Age(quintiles) and energy (tertiles),

Multivariable: M1+ socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension (yes, no), physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), treated hypercholesterolemia (yes/no), diabetes (yes/no), indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing), fruits and vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles).

Table 25. Whole-milk, skimmed milk, fresh cheese, other cheeses, high-fat milk-based products and sugar added dairy and hypertension risk without participants extremes values (> 95 percentile, N=64 695). MTC Cohort, Mexico 2006 - 2011.

Dairy products (servings)	Median intake	Cases	Person-years	Age-energy-adjusted		Multivariable	
				HR [95% CI]	p	HR [95% CI]	p
Whole milk							
Q1	0.00	1066	39076	Reference	0.21	Reference	0.89
Q2	0.23	884	28019	1.13 [1.03; 1.24]		1.06 [0.97; 1.16]	
Q3	1.00	1263	47177	1.04 [0.95; 1.13]		1.02 [0.94; 1.11]	
Q4	7.00	902	34918	1.01 [0.92; 1.11]		1.02 [0.93; 1.13]	
Skimmed- milk							
Q1	0.00	1139	47035	Reference	<.0001	Reference	0.28
Q2	0.47	741	27215	1.13 [1.03; 1.25]		1.03 [0.94; 1.13]	
Q3	3.00	1282	44090	1.21 [1.12; 1.32]		1.06 [0.97; 1.16]	
Q4	7.00	953	30851	1.23 [1.12; 1.36]		1.06 [0.96; 1.17]	
Fresh Cheese							
Q1	0.23	1130	42110	Reference	<.0001	Reference	0.88
Q2	0.58	672	25206	1.01 [0.92; 1.11]		1.03 [0.94; 1.14]	
Q3	3.00	1550	59541	0.99 [0.91; 1.07]		0.97 [0.90; 1.05]	
Q4	5.50	763	22333	1.21 [1.09; 1.33]		1.02 [0.92; 1.13	
Other cheese							
Q1	0.70	898	31582	Reference	0.05	Reference	0.65
Q2	2.16	1226	42983	1.00 [0.91; 1.09]		1.04 [0.95; 1.14]	
Q3	4.40	1073	42278	0.89 [0.81; 0.98]		0.96 [0.88; 1.06]	
Q4	8.00	918	32347	0.93 [0.84; 1.02]		1.00 [0.91; 1.11]	

High-fat							
Q1	0.23	799	29211	Reference	0.63	Reference	0.33
Q2	0.58	1193	43250	1.00 [0.92; 1.10]		1.00 [0.91; 1.09]	
Q3	1.23	1156	42031	0.98 [0.89; 1.08]		0.99 [0.90; 1.09]	
Q4	3.58	967	34698	0.97 [0.88; 1.08]		1.04 [0.94; 1.15]	
Added sugar							
Q1	0.23	932	34232	Reference	0.01	Reference	0.12
Q2	0.58	1040	41448	0.99 [0.90; 1.08]		0.99 [0.90; 1.08]	
Q3	1.16	1112	37529	1.19 [1.08; 1.30]		1.10 [1.00; 1.21]	
Q4	3.81	1031	35982	1.14 [1.03; 1.25]		1.08 [0.98; 1.20]	

Age-energy-adjusted: Age(quintiles) and energy (tertiles),

Multivariable: M1+ socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension (yes, no), physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), treated hypercholesterolemia (yes/no), diabetes (yes/no), indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing), fruits and vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles).

CONCLUSIONS

CHAPTER VII: SUMMARY AND CONCLUSIONS

With this research, the complex relation between two dietary factors and risk of hypertension was able to be better understand and evaluated. The first factor was the dietary total antioxidant capacity in the E3N cohort study and the second factor was dairy products consumption in both studies E3N and MTC cohort study.

Despite the discrepancy of the studies evaluated individually antioxidants intake from observational studies (tended to support a protective effect of individual antioxidants) and clinical trials (reported null (8, 9), or adverse effects (10)) on major cardiovascular events. The findings of this thesis, suggest a beneficial antioxidant effect on hypertension when their cumulative antioxidant power from the diet was evaluated. Therefore, the dietary TAC was associated with a reduced risk of hypertension in a large cohort of French women. These results were stable with time and appeared to be independent of the major risk factors of hypertension. The association remained after exclusion of consumers of antioxidants supplements and in fruit and vegetables consumers below the median population value. The spline regression curve evidenced a steep inverse dose-effect relation between dietary TAC and risk of hypertension, then a leveling off of the association, suggesting a non-linear relation. This could be explained because of the saturation of the body´s capacity to absorb antioxidants from the diet. Undoubtedly, further studies are needed to clarify the underlying biological mechanism.

According to this work, I can conclude a beneficial effect of cumulative effect of antioxidants on risk of hypertension. This protective effect is particular important for individuals with low consumption of fruit and vegetables, since they can be protected against oxidative stress and its consequences, from another source of antioxidants from the diet. However, it is recommended to follow the dietary antioxidants recommendations since according to results observed in the spline regression it seems that the relation with hypertension is non-linear. In addition, as the association was not modified after removed consumers of antioxidant supplements, the possibility is unlikely that these results were only because of their consumption. Besides, hypertension represents a high disease burden in the world, these results may have important public health implications. To confirm these findings, more studies are necessary and a better understand of the biological mechanisms that underlie this inverse significant association.

With regard to dairy products consumption and hypertension. The studies that evaluated this relation previously were conducted mainly in American and European populations showing inconsistent results. According to the current research, in two independent cohorts' studies, no association between total dairy products, milk, yogurt, cottage cheese and cheese consumption with risk of hypertension was found; even after adjustment for the lifestyle and dietary factors. These results appear to be robust as they were unchanged after conducted sensitivity analyses. Furthermore, no effect modification for the main risk factors of hypertension was observed (age, BMI and history of family hypertension). Regarding the secondary analyses, no association either was observed between whole-dairy, low-fat dairy, in both cohorts. Additionally, in the E3N cohort, among cheeses only processed cheese was directly associated with hypertension. In MTC cohort, no association was found with sugar added dairy products. Moreover, at the beginning a direct association between high-fat milk-based products and hypertension was observed. Nonetheless it was no longer significant when participants with extremes values of dairy consumption were removed. These results are less confident since the exposure for this group may be misclassified leading to estimates biased towards the null value.

In conclusion, this thesis provided evidence to support, that dairy product and types of dairy may not have a key role on the development of hypertension. In addition, despite their content of fat and sodium, consumption of cheese may not be considered as deleterious in terms of development of hypertension in adult women. Only processed cheese was involved in the increase of the risk of hypertension, the literature provides some biological plausibility to this association, however more studies are needed to confirm this finding since they were exploratory analyses.

The conflicting results may be due to the methods, the differences of nutritional content of each dairy which can varied across the countries, thus the interaction among their nutrients may be also different. Further, there is lack of international definition of dairy products which could explain the inconsistency between studies for example in some of them considered butter, cream, sugar added dairy and ice cream. However, the nuls results in two independent cohorts, E3N and MTC study, from different populations in terms of distribution of hypertension risk factors, variety of dairy products and a wide range of intake which make the results more consistent.

Food as well dairy products, contains a matrix of important amount of different nutrients. Dairy products globally, is more than the sum of its nutrients leading to different effects on health. Further, the nutritional value of dairy should also consider the bio functionality of the nutrients within these products. From this research, we can continue to follow the recommendation to consume daily dairy products defined as milk, yogurt, cottage cheese, and cheese, accompanied with a balanced diet and healthy life style.

Finally, our diet is based on food, not in individual nutrients, usually consumed together in a meal. Each food has a particular complex structure with different physical and nutritional properties which can influence the digestion of the food as well as the absorption of their nutrients as a result different effects on health.

APPENDICES

Appendix 1. Résumé en français

I. CONTEXTE

L’hypertension est une maladie chronique qui est une cause importante de morbidité, dont l'incidence va augmenter en raison du vieillissement. L’hypertension est considérée comme le principal facteur de risque des maladies cardiovasculaires et comme la première cause de décès dans le monde. Elle a été associée à des complications cardio-vasculaires et rénales telles que les cardiopathies ischémiques, les maladies cérébrovasculaires et les maladies rénales chroniques. Des facteurs de risque modifiables, tels que le tabac, l'IMC, le diabète, l'hypercholestérolémie, l'activité physique et le régime alimentaire, ont été identifiés, mais certains aspects de la contribution du régime alimentaire restent encore flous.

L'un de ces aspects est le rôle des antioxydants, des nutriments capables d'inhiber l'oxydation et de neutraliser les effets négatifs des radicaux libres sur les cellules du corps. Chaque antioxydant a des caractéristiques particulières entraînant des effets différents sur l'organisme, au-delà de leurs interactions. En plus de la source endogène d'antioxydants, la principale source d'antioxydants exogènes est le régime alimentaire. Pour cette raison, ces nutriments ont fait l'objet de plusieurs études au cours des dernières années en raison de leur rôle protecteur éventuel contre plusieurs maladies. Le stress oxydatif a été associé au développement de l'hypertension et des maladies cardiovasculaires. Les preuves provenant d'études observationnelles tendaient à soutenir un effet protecteur des antioxydants alimentaires contre les MCV. Néanmoins, les résultats des essais cliniques sur la supplémentation en antioxydants sont contradictoires, montrant, entre autre, un impact nul, voire délétère. L'évaluation des antioxydants individuels peut ne pas refléter la synergie entre eux, ce qui conduit à une mesure imprécise de l'apport en antioxydants.

Un autre aspect est le rôle des produits laitiers. Ces produits ont une composition nutritionnelle complexe. En plus d’être la source principale de calcium hautement biodisponible, ils contiennent des protéines de haute qualité et contribuent de manière significative à satisfaire les besoins en calcium, magnésium, sélénium, riboflavine et vitamine B12, qui sont essentiels à notre santé. Pour cette raison, les produits laitiers sont largement consommés et recommandés dans différentes populations du monde. Cependant, ces produits n'étant pas homogènes, le contenu nutritionnel peut varier selon les types de produits laitiers. Le lait contient des matières grasses complexes, des protéines de haute valeur biologique, des minéraux et des antioxydants. Les produits fermentés, tels que le yaourt ou le fromage blanc, contiennent des biopeptides dotés d’effets inhibiteurs de conversion de l’angiotensine et du fromage qui, outre sa richesse en calcium, présente une teneur appréciable en graisse et en sodium. Dernièrement, leur consommation a été remise en question en raison de leur teneur en graisses saturées et en sodium, facteurs associés à l’augmentation des maladies

cardiovasculaires. Cependant, l’inconsistance entre les résultats des études pourrait, en partie, être expliquée par les méthodes (méthodes statistiques, mesures de l'alimentation, confusion, etc.), mais aussi par les différences de contenu nutritionnel de chaque type de produit laitier.

II. OBJECTIFS

La présente thèse visait à explorer l'influence des facteurs alimentaires et le risque d'hypertension, en se focalisant principalement à deux expositions, la capacité antioxydante totale et la consommation de produits laitiers dans deux populations.

Par conséquent, le premier objectif spécifique consistait à évaluer la relation entre la capacité antioxydante totale (CAT) diététique et le risque d'hypertension dans la cohorte de femmes française E3N. L'évaluation du CAT alimentaire est une méthode alternative et innovante, qui représente la mesure globale des antioxydants du repas prenant en compte les effets synergiques potentiels entre les antioxydants. À ma connaissance, c'est la première étude analysant cette relation avec un TAC alimentaire.

Le deuxième objectif spécifique était d'évaluer la relation entre la consommation totale de produits laitiers, les types de produits laitiers (lait, yaourt, fromage blanc et fromage) et le risque d'hypertension chez les femmes françaises adultes de l'étude E3N. En outre, dans une analyse secondaire, la relation entre les produits laitiers à faible teneur en matière grasse entière et l'hypertension a également été explorée. En France, seules deux études ont évalué les modifications de la pression artérielle et de la consommation totale de produits laitiers. Aucune association n'a été trouvée. Il n'y a aucune information sur la relation entre chaque type de produit laitier ou différents types de fromages et le risque d'hypertension.

Le troisième objectif spécifique consistait à évaluer la relation entre la consommation totale de produits laitiers et de chaque type de produits laitiers individuellement (lait, yaourt, fromage et produits laitiers sucrés) sur le risque d'hypertension dans la cohorte des femmes mexicaines. Dans une analyse secondaire, la relation entre la consommation de produits laitiers à base de lait entier, de lait écrémé, de produits laitiers gras et de sucre ajouté sur le risque d'hypertension a été également explorée.

Évaluer la relation entre les produits laitiers et l'hypertension dans deux populations différentes présente des avantages non négligeables. 1. Des observations consistantes faites dans des populations présentant une distribution de facteurs de risque d'hypertension différente peuvent augmenter la robustesse des associations. 2. L'exploration des facteurs de risque dans les populations ayant une large distribution de consommation de produits laitiers peut donner des résultats potentiellement difficiles à détecter dans les populations où l'exposition est plus restreinte. En général, l'objectif de la thèse est de contribuer à améliorer la connaissance des facteurs contribuant au développement de l'hypertension.

III. MATÉRIEL ET MÉTHODES

Pour ce travail, j'ai effectué trois analyses secondaires à partir des données de deux cohortes similaires. Deux de ces analyses ont été menées au sein de la cohorte française E3N et la troisième dans la cohorte des enseignantes mexicaines.

1. L'ÉTUDE DE COHORTE E3N

1.1. Présentation de la cohorte

L'étude épidémiologique de la mutuelle générale de l'éducation nationale (E3N) est une cohorte prospective française initiée en 1990 et regroupant 98 995 femmes âgées de 40 à 65 ans assurées par la Mutuelle Générale de l'Education Nationale (MGEN) (178). E3N avait pour objectif d'étudier les principaux facteurs de risque de cancer et de maladies chroniques. E3N est la composante française de l'enquête prospective Européenne sur le cancer et la nutrition (EPIC) (179). La cohorte a reçu l'approbation éthique de la Commission nationale de l'informatique et des libertés (CNIL) et toutes les participantes à l'étude ont signé un consentement éclairé.

1.2. Collecte de données

Des questionnaires ont été envoyés tous les deux à trois ans, permettant ainsi une mise à jour prospectives des données sur l'état de santé et des facteurs de risques de pathologies. Les questionnaires ont permis de collecter des données sur le mode de vie, l'état anthropométrique et l'état de santé. À ce jour, 11 questionnaires ont été envoyés. Le premier a rassemblé des informations sur les caractéristiques sociodémographiques, les antécédents médicaux, la vie reproductive, la consommation de tabac, les caractéristiques anthropométriques, l'activité physique et les antécédents familiaux de cancer (178). Le deuxième questionnaire (Q2, 1992) portait principalement sur les antécédents gynécologiques et les traitements hormonaux. Des mises à jour sur l'état de santé et les traitements médicaux reçus par les participants ont été réalisées à partir de ce questionnaire (Q2 - Q11). Les troisième (Q3, 1993) et huitième (Q8, 2005) questionnaires ont porté sur l'évaluation de la consommation alimentaire. Enfin, le dernier questionnaire (Q11, 2014) a été caractérisé par l'obtention d'informations sur la santé dentaire, la dépression, l'autonomie et les capacités auditives et visuelles.

1.3. Questionnaire alimentaire

En 1993, les données sur l'alimentation ont été recueillies à l'aide d'un questionnaire auto-administrée comportant 208 parties sur l'histoire de l'alimentation. La validité et la reproductibilité du questionnaire alimentaire ont été évaluées (180). La première partie a évalué les fréquences de consommation et les tailles de portion de soixante-six groupes et produits alimentaires. La fréquence a été quantifiée dans onze catégories potentielles : jamais ou moins d'une fois par mois ; 1, 2 ou 3 fois par mois et 1 à 7 fois par semaine. Le questionnaire a été envoyé avec un livret photos pour faciliter l'estimation de la taille des portions (181). Dans une deuxième partie, des questions qualitatives nous ont permis de distinguer les groupes d'aliments considérés en vue de la consommation de 208 aliments ou boissons. Les apports énergétiques et en éléments

nutritifs ont été estimés en multipliant la quantité consommée quotidiennement de chaque aliment par son élément nutritif.

1.4. Exposition

1.4.1. Capacité alimentaire totale en antioxydants

Le CAT alimentaire a déjà été étudié dans deux études antérieures basées sur la cohorte E3N (127, 212). La CAT alimentaire a été estimé à l'aide d'une base de données italienne (122, 267). La méthode TRAP (paramètre antioxydant du piégeage de radicaux totaux) a estimé la CAT des aliments en se basant sur le transfert d'hydrogène pour stabiliser un radical libre (91). Pour chaque article du questionnaire alimentaire, un aliment équivalent dans la base de données du CAT a été choisi. Pour quatre articles (pomme, melon, bière et vinaigre), plus de deux valeurs étaient disponibles et nous avons calculé une moyenne des valeurs disponibles. Lorsque nous n'avons pas trouvé de correspondance directe, nous avons utilisé des valeurs pour un aliment similaire, basées sur la similarité du groupe botanique et des teneurs en vitamines C et E et en polyphénols. Nous n'avons pas pris en compte la capacité antioxydante du café en raison de l'incertitude liée à l'absorption *in vivo* de ses principaux composés antioxydants (127).

1.4.2. Les produits laitiers

Le questionnaire comprenait 23 types de produits laitiers : lait (entier, demi-écrémé, écrémé, concentré ou en poudre) ; yaourt (non sucré et parfumé ou fruité ; classé en entier, écrémé, avec du sucre ou des édulcorants) ; fromage blanc (non sucré et parfumé ou fruité) ; et six types de fromages, y compris le fromage à pâte molle, fondue, bleue, à pâte mi-dure, à pâte dure et de chèvre. En utilisant la définition des produits laitiers du Programme National Français pour la Nutrition et la Santé (PNNS) (268), la consommation de beurre, de crème et de crème glacée n'a pas été incluse, car le beurre et la crème sont considérés comme des produits contenant de l'huile, combinés à d'autres aliments, et la crème glacée est considérée comme un dessert, avec une incertitude quant à la présence réelle de lait dans la crème glacée. Les types de produits laitiers étaient utilisés en portion et la consommation totale de produits laitiers était définie comme la somme des portions de lait, de yaourt, de fromage blanc et d'autres fromages.

1.5. Outcome : Hypertension

Les participantes ont été priées d'indiquer si elles souffraient d'hypertension à l'inclusion (1993) et dans chaque questionnaire de suivi (1994, 1997, 2000, 2002, 2005 et 2008), la date du diagnostic et l'utilisation de traitements antihypertenseurs étaient également renseignés. En 2004, une base de données sur le remboursement des médicaments est devenue disponible pour 97,6% des participantes. Nous avons utilisé la date de diagnostic autodéclarée ou la première date de remboursement du médicament antihypertenseur comme date du diagnostic pour les cas identifiés après 2004.

En outre, en utilisant les informations de la base de données des réclamations du régime d'assurance maladie MGEN, nous avons évalué la validité de l'hypertension

autodéclarée dans la cohorte E3N (105). Nous avons comparé l'auto-évaluation de l'hypertension avec le remboursement du médicament antihypertenseur (n'importe lequel des codes précités). Une valeur prédictive positive de 82% a été observée chez les femmes vivantes en janvier 2004 et s'est poursuivie jusqu'à leur réponse au dernier questionnaire considéré en 2008.

2. ÉTUDE DE LA COHORTE MTC

2.1. Présentation de la cohorte

La cohorte des enseignantes mexicaines (MTC) a été initiée en 2006-2008, 115 314 enseignantes âgées de 25 ans et plus ont répondu à un questionnaire papier renseignant leurs caractéristiques démographiques et reproductives, leur régime alimentaire, leur mode de vie et leurs conditions médicales. Le questionnaire de l'étude a été remis et collecté en collaboration avec les autorités responsables de l'éducation publique de 12 États du Mexique (190). Toutes les femmes ont signé un formulaire de consentement éclairé pour participer à l'étude. Cette étude a été approuvée par le comité d'examen institutionnel de l'Institut national de santé publique du Mexique (INSP). Entre décembre 2011 et février 2014, un questionnaire de suivi a été publié. Soixante-neuf pour cent des participants ont répondu à un questionnaire papier, 2% à un questionnaire en ligne et 11% à une courte interview téléphonique, soit une réponse globale de 82% pour le questionnaire 2011 - 2014 (269).

2.2. Collecte de données

Pour recueillir des données sur les facteurs de risque et les conditions médicales, un questionnaire auto-administré a été envoyé aux participants environ tous les trois ans. Au départ, des données portait sur les mesures anthropométriques, les antécédents en matière de reproduction, l'activité physique, le tabagisme, les antécédents familiaux de maladies chroniques, le dépistage des maladies chroniques, l'utilisation de médicaments et l'état pathologique ont été collectés. En plus, des informations sur le statut socioéconomique, le régime alimentaire, l'utilisation de suppléments, l'activité physique des adolescents et leur exposition solaire ont été obtenues.

Au cours du premier cycle de suivi, les premières informations obtenues ont été mises à jour, évaluant les nouvelles expositions liées à l'alimentation, à l'alcool, à l'adolescence, à la qualité du sommeil et à la dépression (taux de suivi de 83%). Durand le second cycle de suivi, les informations du 1 ère cycle de suivi ont été mises à jour et des informations relatives au stress, aux soins corporels, à l'utilisation de plastiques et au comportement alimentaire ont été ajoutées (190).

2.3. Questionnaire alimentaire

Les informations sur l'alimentation ont été collectées à l'aide d'un questionnaire de fréquence alimentaire semi-quantitatif de 140 questions. Il a été demandé aux participantes de spécifier la fréquence moyenne de consommation au cours de l'année précédente de chaque produit alimentaire dans une unité ou une taille de portion couramment utilisée. Les fréquences de consommation étaient : jamais, une fois par mois ou moins, deux à trois fois par mois, une fois par semaine, deux à quatre fois par semaine, cinq à six fois par semaine, une fois par jour, deux à trois fois par jour, quatre à trois fois par jour, cinq fois par jour et six fois ou plus par jour. Avec la base de données USDA sur la composition des aliments (270) et la base de données utilisée dans l'Enquête nationale sur la santé et la nutrition au Mexique, nous avons calculé les apports en nutriments et en énergie en multipliant le contenu en éléments nutritifs des portions prédéfinies par la fréquence de consommation.

La validité et la reproductibilité du questionnaire ont été évaluées précédemment, dans un sous-échantillon de 134 résidentes de la ville de Mexico (191). Les corrélations de coefficients entre les rappels FFQ et 24 heures pour les apports en énergie, en glucides, en protéines et en lipides étaient respectivement de 0,52, 0,57, 0,32 et 0,63.

3. ANALYSES STATISTIQUES

3.1. Analyses descriptives

Tout d'abord, une analyse exploratoire a été menée afin d'évaluer les distributions des variables et de comprendre leurs comportements. Cela m'a permis d'identifier les modèles d'association entre la variable à expliquer et les variables d'ajustement, ainsi que les modèles entre les variables d'ajustement. Pour les trois études conduites au cours de cette thèse, les caractéristiques des participants ont été décrites à l'aide de statistiques de base telles que la fréquence, la moyenne, l'écart type (SD) et la médiane. A l'inclusion, les caractéristiques des participants ainsi que les facteurs de confusion potentiels ont été décrits en fonction de la variable à expliquer (hypertension) et des principales expositions (capacité antioxydante totale du régime et produits laitiers).

3.2. Mesures d'association

3.2.1. Analyses de survie : Le modèle de risqué proportionnel de Cox

Les éléments théoriques de ces modèles sont présentés dans cette section. L'analyse de survie met l'accent sur l'étude du moment de la survenue d'un événement pour un ou plusieurs groupes. La variable à expliquer est le temps nécessaire pour qu'un événement se produise. Le temps, également appelé temps de survie, peut être exprimé en années, en mois ou en jours, car l'individu commence la procédure de suivi jusqu'à ce que l'événement survienne. Il peut également se référer à l'âge auquel l'individu présente l'événement (198). Dans cette thèse, afin de réaliser l'analyse de survie, le modèle de Cox semi paramétrique a été utilisé. Le modèle de Cox exprime le risque instantané pour un événement donné (hypertension) en fonction du temps et d'un groupe de variables, en tenant compte des données censurées.

3.2.2. Hypothèses des modèles

Le modèle de Cox repose sur deux hypothèses qui ont été vérifiés. La première est la proportionnalité des risques (198) et la seconde, l'hypothèse log-linéaire (198). La première hypothèse a été vérifiée par des méthodes graphiques, sur lesquelles cette hypothèse est remplie, seulement lorsque les fonctions sont parallèles et ne se croisent pas dans le temps. Pour tester la deuxième hypothèse, le risque associé à la variable d'intérêt peut être modélisé, en le catégorisant en centiles (tertiles ou quartiles) en fonction de la distribution de la variable. Lors du traçage des risques en fonction de la médiane de chaque quartile, l'hypothèse est vérifiée si une ligne est obtenue. Si l'hypothèse n'est pas vérifiée, les solutions continues ont été utilisées de manière catégorique.

3.3. Echelle de temps

À l'origine, le modèle de Cox était utilisé pour analyser les données cliniques. Dans ce contexte, l'échelle de temps la plus intuitive était la durée du suivi du traitement et l'âge était considéré comme une variable d'ajustement (199). Cependant, dans les études de cohorte prospectives, les événements sont la survenue de maladies pour lesquelles l'âge peut être un facteur important. Dans la plupart des études de cohorte, l'inclusion dans l'étude ne coïncide pas avec l'apparition de l'exposition aux facteurs de risque. C'est l'une des raisons pour lesquelles il est recommandé, dans ce type d'études, d'utiliser l'âge comme échelle de temps plutôt que le temps de l'étude (199). Une autre raison est que l'âge est un facteur de risque très associé à la maladie à l'étude.

3.4. Spline regression curves

De plus, pour mieux caractériser la forme de l'association, l'analyse sur le TAC alimentaire et l'hypertension a également été réalisée à l'aide d'une régression par spline. Cette méthode est utilisée lorsqu'une variable explicative est continue. Elle fournit un moyen simple de créer, tester et modéliser des relations non linéaires dans des modèles de régression (200). Pour créer des splines, les valeurs du prédicteur (ici la consommation de TAC alimentaire en mmol/jour) doivent être divisées par un nombre de nœuds, pour les premières analyses, quatre nœuds ont été sélectionnés (20e, 40e, 60e et 80e centiles de la distribution).

3.5. Données manquantes

Les données manquantes ont été imputées par la médiane, pour les variables quantitatives, lorsque le pourcentage de données manquantes était inférieur à 5% et pour les variables qualitatives, une imputation par le monde a été faite, c'est-à-dire la catégorie avec la fréquence la plus élevée. Si le pourcentage était supérieur à 5%, une catégorie de données manquantes était créée. Il s'agit d'une procédure pré-établie dans les deux études pour le traitement de ces données.

IV. RÉSULTATS ET DISCUSSION

1. CAPACITÉ ANTIOXYDANTE TOTALE ET HYPERTENSION

1.1. Résultats

La consommation de la CAT alimentaire était inversement associée à l'hypertension dans tous les modèles (**Tableau 9**). Lorsque les quintiles extrêmes ont été comparés, il existait une relation inverse entre le CAT alimentaire et le risque d'hypertension, avec un taux d'hypertension inférieur de 15% dans le quatrième quartile vs premier quartile de la consommation de CAT (HR 0,85 ; IC 95% 0,79 - 0,92 ; p-tendance = 0,0002) dans le modèle multivariée (modèle 3).

La CAT alimentaire a été divisé en CAT café et non café (**Tableau 10**). La CAT non café était associé à une réduction du risque d'hypertension à partir du deuxième quintile et à une relation dose-effet inverse (M3 : $HR_{5vs1quintile}$ 0,85 ; IC 95% 0,79 - 0,92, p-tendance <0,0001). En ce qui concerne la CAT du café, l'association était plus faible, avec une association inverse uniquement avec le cinquième quintile (M3 : $HR_{5vs1quintile}$ 0,86 ; IC 95% 0,75 - 0,97 ; p-tendance 0,03). De plus, les associations entre la CAT alimentaire provenant des principaux contributeurs de CAT et le risque d'hypertension ont été évaluées en utilisant un modèle entièrement partitionné. Seuls les CAT alimentaires provenant du vin, des fruits et légumes et de diverses autres sources restent inversement associés au risque d'hypertension, alors que les CAT provenant du café, du thé ou du chocolat ne le sont pas (**Tableau 11**).

La **Figure 25** présente la forme de l'association entre la CAT alimentaire et le risque d'hypertension. Il existe une forte relation inverse dose-effet entre la CAT alimentaire et le risque d'hypertension jusqu'à une valeur de CAT de 5,0 mmol/jour, puis une stabilisation de l'association. Le risque d'hypertension associé à la consommation de CAT est resté similaire après une analyse de sensibilité.

1.2. Discussion

À notre connaissance, c'est la première étude montrant une association inverse entre la capacité antioxydante totale de l'alimentation et le risque d'hypertension. Des études antérieures ont montré des associations inverses entre la consommation d'aliments riches en antioxydants et le risque d'hypertension. Le régime DASH (Approches diététiques pour enrayer l'hypertension) (215), à base de fruits et légumes, de produits laitiers faibles en matières grasses et de graines entières, a mis en évidence une réduction de la pression artérielle chez les individus sains et hypertendus, ainsi qu'une réduction de risqué de maladie cardiovasculaire. Cependant, les études montrant un effet de la complémentation en antioxydants sur la tension artérielle ne sont pas concordantes (216, 217). Cela suggère que l'équilibre naturel entre les antioxydants alimentaires pourrait être plus efficace pour prévenir l'hypertension que des compléments spécifiques, ce qui pourrait entraîner un excès d'un antioxydant donné et donc un déséquilibre du système antioxydant complexe.

La CAT alimentaire représente une estimation globale des antioxydants contenus dans l'alimentation. Cependant, la capacité de l'alimentation à augmenter la CAT plasmatique est un sujet de débat. Certaines études ont montré la capacité de divers aliments à modifier les biomarqueurs du stress oxydatif (218, 219, 221) et à augmenter la CAT

plasmatique, tandis qu'une autre étude sur une durée semblable chez des fumeurs de sexe masculin s'est avérée augmenter la stabilité du plasma (225). Une autre étude n'a pas permis de modifier les biomarqueurs du stress oxydatif. Globalement, les études d'intervention ont été de courte durée et ne peuvent pas être facilement extrapolées à la consommation réelle à long terme de la CAT.

Dans ces analyses prenant en compte la capacité antioxydante de groupes d'aliments spécifiques, les CAT alimentaires de fruits et légumes, de vin et d'autres aliments divers étaient inversement associés à l'hypertension. Les fruits et les légumes ont toujours été inversement associés à un risque plus faible d'hypertension (228) ou de coronaropathie (216), attribué à leur teneur en antioxydants. Cependant, la consommation élevée de fruits et de légumes est un marqueur bien connu d'un mode de vie sain, de sorte que nous ne pouvons pas exclure que l'association observée puisse être un indicateur indirect de choix de vie sains. Cependant, nous avons également signalé une association inverse avec le plus grand quintile de CAT de café, avec les CAT du vin et avec les CAT de sources plus mineures. Ceci est davantage en faveur d'un effet propre des antioxydants sur le risque d'hypertension.

Il est intéressant de comparer les niveaux de CAT pour le café et ceux d'autres sources. Alors que la CAT pour le café était inversement associée au risque à partir du deuxième quintile, à partir d'un CAT supérieur à 2,95, une association inverse de même ampleur n'a été observée que pour la CAT de café, d'une valeur de 25, soit près de dix fois plus élevée. Ceci est conforme aux questions précédemment rapportées sur la biodisponibilité des différents antioxydants du café, en particulier ceux produits par la réaction de Maillard de taille assez importante (229). Plusieurs études ont déjà signalé que la CAT du café n'était pas lié au risque d'hypertension, probablement en raison d'un équilibre entre les effets antioxydants favorables, les effets vasoconstricteurs défavorables et les associations possibles avec des facteurs de mode de vie négatifs (226). En effet, l'impact du café sur les maladies cardiovasculaires n'est pas clair. Le composé le plus étudié est la caféine; Des études ont montré une augmentation de la résistance vasculaire après une consommation aiguë de café ou de caféine, suggérant un effet de vasoconstriction (126). L'effet à long terme a également été évalué et une méta-analyse d'essais contrôlés randomisés a montré une relation positive entre le nombre de tasses de café et les modifications de la pression systolique (230). Néanmoins, le café est également une source importante d'antioxydants (226). En répartissant la capacité antioxydante du régime entre les composants café et non café de la CAT, nous avons évité l'effet de confusion potentiel d'autres composants du café, car la CAT du café a été analysé individuellement mais ajusté sur les autres composants de la CAT diététique. Nos résultats, avec des associations presque dix fois plus faibles entre la CAT du café et l'hypertension par rapport à d'autres sources de CAT, suggèrent que l'effet antioxydant du café sur l'hypertension serait largement réduit par une biodisponibilité potentiellement plus basse de la CAT du café et des effets cardiovasculaires indésirables de la caféine.

Les conclusions selon lesquelles l'association entre la CAT alimentaire du chocolat ou du thé et l'hypertension artérielle étaient de la même ampleur, mais non statistiquement significatif, suggèrent que dans notre population comptant une forte proportion de non-consommateurs de thé ou de chocolat, les consommations n'étaient pas suffisamment nombreuses pour démontrer toute association. Une étude précédente n'a rapporté aucune association entre la consommation de thé et l'hypertension, mais une association inverse avec la consommation de chocolat ou de cacao (103).

La courbe de régression des splines montrait une forte relation inverse dose-effet entre la CAT alimentaire et le risque d'hypertension jusqu'à une valeur de CAT de 5,0 mmol / jour, puis une stabilisation de l'association ; ces résultats sont conformes aux études précédentes (231). Une explication possible, comme suggéré précédemment, est due à l'excès d'antioxydants ou de vitamines, une saturation de la capacité de l'organisme à absorber cette substance à partir du régime alimentaire (212).

1.3. Conclusion

Ces résultats ont montré qu'un régime CAT élevé était associé à un risque réduit d'hypertension artérielle chez les femmes, suggérant que la promotion d'un régime naturellement riche en antioxydants pourrait aider à prévenir le développement de l'hypertension. Ces résultats doivent être interprétés avec prudence. Il y a encore des questions quant à l'absorption, la distribution et le rôle cellulaire toujours sans réponse. Des études supplémentaires sont nécessaires pour approfondir les associations entre l'apport alimentaire en CAT et les modifications des niveaux de pression sanguine au fil du temps dans d'autres contextes.

2. PRODUITS LAITIERS ET HYPERTENSION DANS LA COHORTE E3N

2.1. Résultats

Lorsque la relation entre la consommation totale de produits laitiers, de lait, de yaourt ou de fromage blanc et de fromage et le risque d'hypertension, a été évaluée, aucune association avec le risque d'hypertension n'a été observée dans les modèles univariés et multivariés (**Tableau 15**). Nous n'avons pas observé de tendance dans les quintiles de produits laitiers totaux ni dans aucun type de produits laitiers.

Les mêmes modèles décrits précédemment ont été appliqués, en considérant chaque type de fromage (**Tableau 16)** et avons observé une association directe significative uniquement avec le fromage fondu (HR 1,11 ; IC 95% 1,05 - 1,18 ; p tendance <0,0001). De plus, l'apport total en produits laitiers faibles en gras a été analysé, mais aucune association n'a été observée (**Tableau 17**). Après exclusion des participants diagnostiqués avec un diabète, une hypercholestérolémie, un surpoids ou une obésité (**Tableau 18**) ou les cas apparus au cours des cinq premières années de suivi (**Tableau 19**), les résultats sont restés similaires. Aucune modification de l'effet de l'âge, des antécédents familiaux d'hypertension ou de l'IMC dans la relation étudiée n'a été observée (**Appendix 7 et 8**).

2.2. Discussion

Les résultats d'études précédentes n'étaient pas concluants concernant la relation entre la consommation de produits laitiers et l'hypertension (58, 172, 175). Dans les populations basées aux États-Unis (172, 175), une relation inverse entre le lait et le lait écrémé et le risque d'hypertension chez des femmes d'âge moyen et plus âgées a été observée. Aux États-Unis, le contenu nutritionnel du lait est différent de celui retrouvé en France. Le lait aux Etats-Unis est enrichi en vitamine D, principale source de cette vitamine dans ce pays. Ceci est particulièrement important car cette vitamine régule l'absorption du calcium par le tractus intestinal et interagit avec l'hormone

parathyroïdienne en maintenant l'homéostasie du calcium (271). La carence en vitamine D pourrait être associée au développement de l'hypertension par une stimulation inadéquate du système rénine-angiotensine (240). Cependant, l'association inverse entre le lait et l'hypertension pourrait être confondue avec les comportements ou les habitudes alimentaires. Dans les études dans lesquelles une association inverse significative avec des produits laitiers à faible teneur en matière grasse a été rapportée (58, 174), les participants ayant une consommation de lait plus élevée étaient plus susceptibles d'avoir un meilleur style de vie que ceux ayant une consommation plus faible.

Dans la présente étude, en accord avec de précédents études (58, 176, 177), les participants ayant une consommation plus élevée de produits laitiers avaient une consommation plus élevée de fruits ou de légumes. Dans notre étude, nous avons ajusté la consommation de fruits et légumes et un régime alimentaire sain, mais aucune association n'a été constatée pour aucun type de produit laitier et aucun risque d'hypertension.

Dans cette étude, l'impact du mode de vie et du régime alimentaire semblait limité en raison de l'ajustement pour ces variables et parce que les femmes consommant davantage de produits laitiers semblaient avoir des habitudes plus saines que les femmes consommant peu de produits laitiers. Auparavant, le régime DASH (214) montrait une association inverse entre les produits laitiers faibles en matières grasses et la pression artérielle. Cependant, cet essai n'était pas conçu pour évaluer l'effet individuel de chacun de leurs composants et la durée de l'intervention était courte. Alonso et al., dans un essai contrôlé randomisé évaluant l'effet spécifique d'un journal intime et faible sur la pression artérielle, n'ont pas trouvé d'association (241).

En outre, des études antérieures, ainsi que celles réalisées dans le cadre de cette étude, ne montraient aucune association avec le fromage blanc (58) ou le yaourt qui sont des produits fermentés (242). Une métanalyse de 5 cohortes des États-Unis et des Pays-Bas, comprenant 45 088 participants et 12 959 cas, n'a pas permis d'établir de lien entre le yaourt et l'hypertension (242). Cependant, l'étude sur la santé des infirmières et infirmiers a montré une association inverse entre le yaourt et l'hypertension. Dans cette population, les participants qui consommaient plus de yaourt (et de produits laitiers), consommaient moins de glucides raffinés, de boissons sucrées et de viande transformée. Ainsi, les résultats observés pourraient être partiellement expliqués par un effet de remplacement (236). Une autre explication possible est la différence de contenu nutritionnel du yaourt selon les pays.

De plus, étant riche en calcium, le fromage pourrait avoir un effet paradoxal en raison de la quantité de sodium et de graisse. Le sodium est le seul facteur alimentaire considéré comme une cause de l'hypertension (234). Conformément aux résultats de notre étude, dans les études Rotterdam (175), CARDIA (172) et The Women's Health Study (58), les participantes consommant beaucoup de fromage n'avaient pas de risque plus élevé d'hypertension. Dans cette recherche, un seul type de fromage, le fromage fondu, était associé positivement au risque d'hypertension présentant un effet dose modeste. Ces fromages sont fabriqués en faisant fondre un ou plusieurs fromages à pâte pressée cuits avec d'autres ingrédients laitiers comme le lait, la crème, le beurre et le sucre. En outre, les fromages fondus sont riches en lipides, en sodium et en sucre et contiennent moins de protéines, de magnésium et de calcium (182), qui constituent des nutriments protecteurs potentiels contre l'hypertension. Le calcium peut se lier aux acides gras de la voie intestinale pour créer des savons insolubles réduisant l'absorption des graisses (62). Le contenu élevé en calcium du fromage peut neutraliser l'effet des graisses sur

les lipides sanguins (163, 244). De plus, une étude controlée et randomisée croisée chez des sujets obèses ou en surpoids (69) a révélé que les graisses saturées sous forme de matrice de fromage, comparées aux sources végétales de graisses saturées, réduisaient l'inflammation post-prandiale, suggérant que tous les aliments riches en graisses saturées n'étaient peut-être pas toutes équivalentes et qu'il y a une possible interaction entre leurs nutriments. En outre, le lactosérum, un lait protéiné, a été associé aux réductions de la prise de poids et de la pression artérielle, de l'inflammation et des marqueurs du stress oxydatif (245). En outre, la vitamine K2, synthétisée uniquement par des bactéries, peut inhiber la calcification vasculaire en jouant un rôle important dans la prévention des MCV et du DT2 (246-248). Néanmoins, ces résultats sur une possible augmentation du risque lié aux fromages fondus doivent être confirmés dans d'autres populations. Ces résultats suggèrent d'explorer, séparément des autres types de produits laitiers, l'impact potentiel du fromage fondu sur les marqueurs cardiovasculaires.

En France, il existe une grande variété de produits laitiers. Par conséquent, le contenu nutritionnel, en particulier en calcium et en graisse, n'est pas le même que dans les autres pays. Dans cette étude, 99% des participants ont consommé du fromage présentant une variabilité importante (au moins 1 portion/jour - plus de 4 portions/jour). Ces résultats sont similaires à ceux de l'étude néerlandaise (176). Cette population est similaire à la population française car elles consomment régulièrement des produits laitiers, ce qui limite les facteurs de confusion.

2.3. Conclusion

Dans cette grande cohorte française prospective, aucune association entre la consommation totale de produits laitiers ou tout type de produits laitiers (lait, yaourt, fromage blanc et fromage) et le risque d'hypertension n'a pas été observée. Ces résultats suggèrent que la consommation de fromage (à l'exception du fromage fondu) pourrait ne pas être considérée comme nuisible en termes de développement de l'hypertension chez les femmes. Ces résultats doivent être confirmés dans des essais contrôlés randomisés.

3. PRODUITS LAITIERS ET HYPERTENSION DANS LA COHORTE MTC

3.1. Résultats

En analyse multivariée, nous n'avons pas trouvé d'association entre les produits laitiers totaux et la consommation de lait et le risque d'hypertension (**Tableau 21**). Dans le modèle ajusté sur l'âge et l'énergie, lorsque les consommateurs des quartiles supérieurs ont été comparés à ceux du quartile inférieur, une association significative a été observée pour les produits laitiers totaux (HR 1,11 ; IC 95% 1,01 - 1,22 ; p-tendance= 0,0002). Ainsi que la consommation de lait (HR 1,12 ; IC 95% 1,03 - 1,23 ; p-tendance= 0,004). Cependant, après ajustement sur les principaux facteurs de risque de l'hypertension, cette association a disparu, mais la même tendance a été observé après ajustement sur les facteurs alimentaires.

Lorsque la relation entre la consommation de yaourt et de fromage a été évaluée individuellement, aucune association n'a été observée avec le risque d'hypertension dans aucun des modèles, sans tendance observée par quartile de produits laitiers ni pour chaque type de produits laitiers. De plus, en utilisant les mêmes modèles décrits précédemment, la relation entre les produits laitiers riches en matières grasses, les produits laitiers additionnés de sucre, le lait entier, le lait écrémé, le fromage blanc et les autres fromages et le risque d'hypertension a été analysée (**Tableau 21**). Hormis les produits laitiers riches en matières grasses (beurre et crème), aucune association avec l'hypertension n'a été constatée.

L'ajustement sur les habitudes alimentaires n'a pas modifié les résultats dans les analyses principales ou secondaires (analyse de sensibilité). L'exclusion des femmes ayant déclaré un diabète ou une hypercholestérolémie (**Tableau 22**) ou des valeurs au-delà des 95 percentiles de la distribution de l'apport laitier (**Tableau 23**) n'a pas entraîné de changements significatifs en termes de significativité statistique, sauf pour les produits laitiers riches en matières grasses qui n'avaient plus d'effet significatif (**Appendix 10 et 11**). Par ailleurs, la relation étudiée n'a pas été modifiée par des antécédents familiaux d'hypertension (oui /non) ni d'IMC (<25, ≥ 25 kg/m^2).

3.2. Discussion

Les études publiées sur ce domaine étaient hétérogènes. Les études dans lesquelles une association entre les produits laitiers et l'hypertension a été observée avaient un échantillon plus important (variant de 2 245 à 28 886) que les études sans relation observée et la durée de suivi variait de 2 à 10 ans. Ils ont généralement trouvé une association inverse entre les produits laitiers faibles en matière grasse et l'hypertension. Dans la présente étude, la taille de notre échantillon nous a conféré une puissance statistique pour détecter des associations et notre temps de suivi est comparable à celui des études précédentes. La cohorte SUN (174), qui est une étude comparable à la présente, recherché en termes de durée de suivi, a observé après deux ans une association inverse entre les produits laitiers faibles en gras et le risque d'hypertension (n = 5 880, cas = 180), mais pas avec les produits laitiers totaux ou entiers. Cette étude était une cohorte dynamique méditerranéenne d'adultes espagnols comprenant des femmes et des hommes, âgés de 37 ans (de 20 à 90 ans) et diplômés d'université. Cependant, dans cette étude, les consommateurs de produits laitiers à faible teneur en matière grasse étaient plus jeunes et

semblaient avoir un mode de vie plus sain, ils étaient plus actifs physiquement et une consommation à faible teneur en matière grasse était directement associée à la consommation de fruits et légumes, de potassium et de fibres ; et inversement associé à la consommation d'alcool et de graisses saturées.

De plus, l'étude américaine ARIC (171) a montré que la pression systolique était plus faible de 2,7 mmHg (IC 95% -0,3 à 0,6, p = 0,01) de moins chez les participants consommant davantage de lait écrémé que chez ceux en consommant peu. L'association n'a été observée que chez les participants de race blanche et non chez les Africains. Ainsi, cela pourrait s'expliquer par une susceptibilité génétique dans ce groupe. Les analyses par type de produit laitier n'étaient possibles qu'avec du lait entier, aucune association significative n'a été constatée. Les analyses n'étaient pas possibles avec d'autres types de produits laitiers en raison de la faible variabilité de leur consommation. Il n'y a aucune information sur la relation étudiée dans les populations hispaniques, une possible différence existe en lien avec le mélange Européen et Amérindien, comme dans la population mexicaine.

Contrairement aux conclusions de cette étude, l'étude Women Health (58), comprenant 28 886 femmes âgées de 54 ans en moyenne, une population plus âgée que l'étude MTC, a mis en évidence une association inverse entre la consommation de lait faible en matière grasse et le risque d'hypertension. Cette étude a été menée aux États-Unis. Dans ce pays, le lait est enrichi en vitamine D, principale source de cet élément nutritif pour cette population. La vitamine D est responsable de l'homéostasie du calcium en régulant l'absorption du calcium par le tractus intestinal. De plus, la vitamine D peut moduler la pression artérielle par la réduction de l'hormone parathyroïdienne ayant un effet direct sur le tissu vasculaire (161). Ainsi, les différences de contenu nutritionnel du lait peuvent expliquer les différences de résultats.

Conformément aux résultats de cette recherche, une méta-analyse comprenant 5 cohortes des États-Unis et des Pays-Bas (45 088 participants et 12 959 cas) (242) n'a pas mis en évidence d'association entre la consommation de yaourt et le risque d'hypertension (RR 0,99 ; 95 % IC 0,96 - 1,01). En revanche, l'étude sur la santé des infirmières a montré une association inverse significative. Dans cette étude, les participants ayant consommé le plus de yaourt avaient une alimentation plus saine, suggérant une association positive combinée entre la consommation de yaourt et le régime. Les consommateurs de yaourt ont également consommé moins de glucides raffinés, des boissons édulcorées au sucre ou de viande transformée. Un effet de remplacement pourrait donc expliquer en partie les résultats observés (236). Par conséquent, dans cette population, il est possible que la consommation de yaourt soit un marqueur d'un mode de vie sain. Au contraire, dans la population mexicaine, il semble que la consommation de yaourt ne soit pas un indicateur d'un mode de vie sain. Selon l'enquête nationale mexicaine ENSANUT (158), bien que les consommateurs de yaourt aient consommé plus de calcium et de protéines, ils ont également consommé plus de graisses saturées, ce qui correspond au régime alimentaire de ce groupe et non à la teneur en graisses saturées du yaourt. Étant donné que, parmi les consommateurs de yaourt, le pourcentage de contribution des graisses saturées de yaourt par rapport à la consommation totale de graisses saturées était de 15,4% (158). De plus, la contribution du yaourt à la consommation totale de sucres libres était élevée de 28,3% (158).

En outre, les études ne montrant pas d'association ont eu un échantillon plus petit (de 755 à 4 304 participants) mais avec un suivi plus long de 5 à 15 ans. Une raison possible est que ces études n'avaient pas suffisamment de puissance statique pour détecter une association ou une classification erronée de l'exposition en raison d'un changement de régime alimentaire au cours du suivi susceptible d'entraîner une atténuation de l'association. L'étude de Rotterdam (175), après deux ans de suivi, a mis en évidence une relation inverse significative entre la consommation de produits laitiers écrémés et le risque d'hypertension, mais pas avec les produits laitiers entiers. Après 6 ans, l'association avec les produits laitiers écrémés n'était plus significative. Comme suggéré précédemment, cela soulève l'hypothèse que la consommation de produits laitiers pourrait freiner l'aggravation plutôt que d'empêcher le développement de l'hypertension chez certains individus (175).

Dans la présente étude, en accord avec les rapports précédents, la consommation de fromage n'était pas associée à une augmentation du risque d'hypertension. Outre le contenu appréciable en matières grasses et en sodium, le fromage est un produit fermenté contenant plusieurs composés tels que le calcium, les protéines du lactosérum, la vitamine K2 et des types spécifiques d'acides gras bénéfiques pour la santé (246). Des études antérieures avaient suggéré un effet neutre de la consommation de fromage sur les lipides sanguins (163, 244). Une explication possible est sa teneur élevée en calcium, qui réduit l'absorption des graisses par la voie intestinale (62). En outre, les protéines du lactosérum réduisent le gain de poids, la pression artérielle, l'inflammation, les marqueurs du stress oxydatif ainsi que les maladies cardiovasculaires (245) et la vitamine K2 peut inhiber la calcification vasculaire (247).

De plus, la consommation de produits laitiers en fonction de la teneur en matière grasse a été évaluée. Nous avons analysé individuellement la relation entre le fromage blanc considéré comme un fromage faible en matière grasse dans la population mexicaine. Nous avons également regroupé d'autres types de fromages plus riches en matières grasses. Les deux groupes de fromages n'étaient pas associés à une augmentation du risque d'hypertension. De plus, la consommation de produits à base de lait entier et de lait écrémé n'était pas associée non plus. Auparavant, le régime DASH (214) avait observé une association non inverse entre les produits laitiers faibles en gras et la pression artérielle. Cependant, il est difficile d'évaluer l'effet de chaque composante d'un régime alimentaire sain sur la pression artérielle. Ainsi, l'effet des produits laitiers à faible teneur en matière grasse peut s'expliquer en partie en raison de l'effet combiné du modèle et de la consommation de produits laitiers à faible teneur en matière grasse. De plus, dans les études observationnelles et dans la présente étude, les consommateurs de produits laitiers faibles en matières grasses sont souvent en meilleure santé, même si nous tenions compte de variables comme les fruits et les légumes, ainsi que de régimes alimentaires équilibrés pour tenter de maintenir un mode de vie sain (confusion résiduelle) (58, 176). En revanche, dans l´étude the National Birth Cohort, une augmentation du risque d'hypertension chez les consommateurs de produits laitiers à faible teneur en matière grasse a été observée (177). Une explication possible est que lors de certaines affections telles que l'hypercholestérolémie, le diabète, le surpoids ou l'obésité, la consommation de ces produits est recommandée, entraînant l'inversion du lien de causalité.

De plus, les produits laitiers riches en matières grasses étaient initialement associés à l'hypertension. Cependant, l'association n'est pas montré parmi les participants ayant des valeurs de consommation extrêmes. Ces produits sont riches en matières grasses saturées, qui étaient auparavant associées à l'augmentation du cholestérol LDL (63). Néanmoins, dans l'étude the Nurses' study (252), aucune association entre l'hypertension et une consommation saturée de graisses poly-insaturées ou trans et l'hypertension n'a été observée. La teneur en lait entier est complexe. Outre les acides gras saturés, elle contient près de 400 acides gras, dont beaucoup ne se trouvent que dans cet aliment (159). Certaines études ont suggéré que les acides gras bioactifs de la matière grasse du lait étaient responsables de l'effet anti-inflammatoire et de l'amélioration des effets métaboliques (253, 254).

En outre, aucune association entre le sucre ajouté dans les produits laitiers et le risque d'hypertension n'a été constatée. Il a été montré qu'une forte consommation de sucre ajouté conduisait à l'obésité, qui est un facteur de risque d'hypertension important (255). Cette relation n'avait pas été évaluée auparavant. Néanmoins, de précédentes études indiquaient une association directe entre la consommation de sucre ajouté provenant principalement de boissons sucrées et le risque d'obésité (256-258), le diabète de type 2 (259, 272), les dyslipidémies (261) et l'hypertension (262, 263).

Les différences entre les études peuvent refléter des différences dans la répartition des facteurs génétiques ou environnementaux entre les populations qui pourraient influer sur les effets des produits laitiers et de l'hypertension. L'impact des produits laitiers et de l'hypertension n'est pas clair et il est difficile à évaluer, car la consommation de produits laitiers peut être liée à des comportements sains menant à une confusion résiduelle.

3.3. Conclusion

Dans cette vaste étude prospective mexicaine, aucune association n'a été observée entre les produits laitiers totaux ou les types de produits laitiers et le risque d'hypertension. Ces résultats suggèrent que les produits laitiers pourraient ne pas jouer un rôle clé dans le risque d'hypertension. Ainsi, les individus peuvent suivre la recommandation de 3 portions quotidiennes de produits laitiers pour atteindre leur apport quotidien en calcium, notamment des produits laitiers faibles en matières grasses.

CHAPTER VII : RESUME ET CONCLUSIONS

Grâce à cette recherche, la relation complexe entre deux facteurs alimentaires et le risque d'hypertension a pu être mieux comprise et évaluée. Le premier facteur était la capacité antioxydante totale de l'alimentation dans l'étude de cohorte E3N et le deuxième était la consommation de produits laitiers dans les deux études : cohorte E3N et MTC.

Malgré les différences entre les études évaluant la consommation individuelle d'antioxydants tirée d'études observationnelles (tendant à soutenir l'effet protecteur des antioxydants individuels) et d'essais cliniques (effets notifiés nuls (8, 9) ou indésirables (10)) sur des événements cardiovasculaires majeurs. Les résultats de cette thèse suggèrent un effet antioxydant bénéfique sur l'hypertension lorsque leur pouvoir antioxydant cumulatif provenant de l'alimentation a été évalué. Par conséquent, le TAC alimentaire était associé à une réduction du risque d'hypertension dans une large cohorte de femmes françaises. Ces résultats étaient stables dans le temps et semblaient être indépendants des principaux facteurs de risque de l'hypertension. L'association est restée la même après l'élimination des consommateurs de compléments en antioxydants et des consommateurs de fruits et légumes inférieurs à la valeur médiane de la population. La courbe de régression des splines a mis en évidence une forte relation inverse dose-effet entre le TAC alimentaire et le risque d'hypertension, puis une stabilisation de l'association, suggérant que l'effet maximum du TAC pourrait être associé à un apport de TAC autour de 5,0. Cela pourrait donc refléter la saturation de la capacité de l'organisme à absorber les antioxydants contenus dans son alimentation.

Selon les résultats de cette thèse, je peux conclure à un effet bénéfique de l'effet cumulatif des antioxydants sur le risque d'hypertension. Cet effet protecteur est particulièrement important pour les personnes consommant peu de fruits et de légumes, car ceux-ci peuvent être protégés du stress oxydatif et de ses conséquences provenant d'une autre source d'antioxydants issue de l'alimentation. Cependant, une forte consommation n'est pas recommandée car aucun effet, au moins sur le risque d'hypertension, n'a été observé, contrairement à la croyance commune selon laquelle un apport élevé en antioxydants est bénéfique. De plus, l'association n'ayant pas été modifiée après l'élimination des consommateurs de complément d'antioxydants, je peux écarter la possibilité que ces résultats résultent uniquement de leur consommation. En outre, l'hypertension représente un fardeau de morbidité élevé dans le monde. Ces résultats pourraient avoir d'importantes répercussions sur la santé publique. Pour confirmer ces résultats, d'autres études sont nécessaires et une meilleure compréhension des mécanismes biologiques à la base de cette association significative inverse serait nécessaire.

En ce qui concerne la consommation de produits laitiers. La plupart des études qui ont évalué la relation étudiée ont été menées principalement dans des pays américains et européens, avec des résultats incohérents. Selon cette étude, aucune association entre la consommation totale de produits laitiers, de lait, de yaourt, de fromage blanc et de fromage et le risque d'hypertension n'a été relevée; même après ajustement sur le style de vie et les facteurs alimentaires. Ces résultats semblent être cohérents et robustes, car ils étaient inchangés après les analyses de sensibilité effectuées. De plus, aucune modification de l'effet du facteur principal de l'hypertension n'a été observée (âge, IMC et antécédents d'hypertension familiale). En ce qui concerne les analyses secondaires, aucune association n'a été observée entre les produits laitiers entiers et les produits laitiers faibles teneur en matières grasses, dans les deux cohortes. De plus, dans la cohorte E3N, parmi les fromages, seul le fromage fondu était directement associé à l'hypertension. Dans la cohorte MTC, aucune association n'a été trouvée avec les produits laitiers

additionnés de sucre. De plus, au début, une association directe entre les produits huileux et l'hypertension a été observée, mais elle a disparu lorsque les participants présentant des valeurs extrêmes de consommation de produits laitiers étaient supprimés des analyses.

En conclusion, cette thèse fournit des preuves quant au fait que les produits laitiers et les types de produits laitiers peuvent ne pas jouer de rôle clé dans le développement de l'hypertension. En outre, aucune association n'a été observée de manière cohérente dans deux populations différentes en termes de distribution des facteurs de risque d'hypertension, de variété de produits laitiers et d'un large éventail d'ingrédients rendant les résultats plus robustes. En outre, malgré leur teneur en matières grasses et en sodium, la consommation de fromages ne peut être considérée comme néfaste en termes de développement d'une hypertension chez la femme adulte. Seuls les fromages fondus étaient impliqués dans l'augmentation du risque d'hypertension. La littérature donne une plausibilité biologique à cette association, mais des études complémentaires sont nécessaires pour confirmer ce résultat.

Les résultats contradictoires peuvent concerner les méthodes, les différences de contenu nutritionnel de chaque produit laitier qui peuvent varier d'un pays à l'autre, ainsi que de l'interaction entre leurs nutriments. En outre, il n'existe pas de définition internationale des produits laitiers qui pourrait expliquer l'incohérence entre les études, par exemple dans certaines d'entre elles portant sur le beurre, la crème, les produits laitiers additionnés de sucre et les glaces.

Les aliments, ainsi que les produits laitiers, contiennent une matrice importante de différents nutriments. Les produits laitiers dans le monde représentent plus que la somme de ses nutriments entraînant différents effets sur la santé. Les valeurs nutritionnelles des produits laitiers devraient être considérées en tenant compte de la bio fonctionnalité des nutriments contenus dans ces produits. À partir de là, nous pouvons continuer à suivre la recommandation de consommer quotidiennement des produits laitiers définis comme du fromage blanc, du yaourt, du lait et du fromage, accompagnés d'une alimentation équilibrée et d'un mode de vie sain.

Enfin, notre régime alimentaire est basé sur la nourriture, et non sur les nutriments individuels, couramment consommés ensemble dans un repas. Chaque aliment a une structure complexe particulière avec des propriétés physiques et nutritionnelles différentes qui peuvent influer sur la digestion de l'aliment ainsi que sur l'absorption de ses nutriments par des effets différents sur la santé.

Appendix 2. Cohort studies evaluating the relation between dairy products intake and hypertension.

Author (year) Study Country	Follow-Up Ages (Min, Max) Women %	n (cases)	Diet Evaluation	Dairy Products Evaluation	HTA Evaluation	Results
Alonso et al (2005) SUN cohort Spain	2 years 37 (20,90) 61%	5880 (180)	FFQ Semi Quantitative (136 items)	15 items Whole and Skimmed In quintiles	Self-Report: Diagnosis Treatment HTA: ≥ 140/90	Inverse association between **skimmed dairy products** and HBP. Q5 vs Q1 HR 0.46; 95% CI 0.26 - 0.84; p = 0.02. There is no significant association between whole-milk and HBP. Q5 vs Q1 HR 1.37; 95% CI 0.77 - 2.72; p = 0.44.
Alonso et al (2009) ARIC Study USA	9 years 53 (45,64) 57 %	8204 (2399)	FFQ (66 items)	6 items Whole and Skimmed Milk 1 ration = 237 ml (8 Oz) In quintiles	Physical exam HTA: ≥ 14/90	Caucasians: Inverse association between **skimmed dairy products** and systolic blood pressure (SBP). When comparing, 3 or + serving/day vs <1 serving/week. PAS increased 2.7 mmHg less (95% CI 0.3 - 6.0; p = 0.01) There is no association of whole-milk and HTN. African Americans: There is no dairy association (whole or skimmed) and HBP.
Wang et al (2008) Women´s Health Study USA	10 years 54 (> 45) 100 %	28 886 (8710)	FFQ Semi Quantitative (131 items)	Whole and Skimmed In quintiles	Self-Report: Diagnosis Treatment HTA: ≥ 140/90	Inverse association between **skimmed dairy products** and HBP. RR 1.00, 0.98, 0.97, 0.95, 0.89; p = 0.001. It is attenuated when adjusted for calcium, but not when adjusted for vitamin D. There is no association with whole dairy products.

Engberink et al (2009) Rotterdam Study Holland	6 years 65 (≥ 55) 57 %	2245 (984)	FFQ Semi Quantitative (170 items)	1. Milk and Milk Products 2. Cheese 3. Skimmed Dairy Products 4. Whole Dairy Products 5.Fermented Dairy Products Total Dairy Products: Each item sums up, except butter and ice cream. In quintiles.	Physical exam HTA: ≥ 140/90 or treatment use	**2 years Analysis** Reverse association of total **milk** and HTA: HR 1.00, 0.82 (0.67, 1.02), 0.67 (0.54, 0.84), 0.76 (0.61, 0.95); p = 0.008**.** **Low-fat dairy:** HR 1.00; 0.75 (0.60, 0.92), 0.77 (0.63, 0.96), and 0.69 (0.56, 0.86); p = 0.003. **Analysis by type of dairy product:** Association between HTA and **low-fat dairy products (p = 0.01), milk and milk products (p = 0.01). There is no dairy association or cheese** (p > 0.6). **6 years Analysis** The **association is attenuated,** total dairy products (p = 0.07) and skimmed dairy products (p = 0.09).
Engberink et al (2009) MORGEN Study Holland	5 years 50 (Information Not Available) 55 %	3454 (713)	FFQ (178 items)	1. Milk and Milk Products 2. Cheese 3. Skimmed Dairy Products 4. Whole Dairy Products 5. Fermented Dairy Products Total Dairy Products: Each item sum up, except butter and ice cream. In quintiles	Physical exam HTA: ≥ 140/90 or with treatment.	Average dairy products consumption 344g / d, less than 110 g/d (< one serving = Q1) to 765 g/d (> 5 servings = Q5). The i**nverse association of skimmed dairy products** and HBP. OR (95% CI) 1.00, 0.78 (0.61, 1.00), 0.81 (0.63, 1.03), 0.82 (0.64, 1.06; p = 0.24)

Héraclides et al (2012) 1946 National Birth Cohort England	10 years 43 (Information Not Available) 53%	1750 (994)	Dietary History Photo Album	1. Total dairy products without cheese 2. Whole Dairy Products 3. Skimmed Dairy Products 4. Fermented Dairy Products	Physical exam HTA: ≥ 140/90 or treatment use	There is no association between HBP and: total dairy products (p = 0.55) total dairy products without cheese (p = 0.50), skimmed dairy products (p = 0.23), whole dairy products (p = 0.069) and fermented dairy products (p = 0.99).
Dauchet et al (2007) SU.VI.MAX France	5 years 50 (20,65) 64%	2341 (606)	Dietary History	Total Dairy Products (Whole + Skimmed) In quartiles	Physical exam HTA: ≥ 140/90	Cross-sectional analysis there is association only in men. In the longitudinal analysis there was no association.
Snijder et al (2008) Hoorn study Holland	6.4 years 59 (50,75) 54%	755 (319)	FFQ semi-Quantitative (92 items)	Total Dairy Products (Whole + Skimmed) Desserts, milk, yogurt	Physical exam HTA: ≥ 140/90	There is no association between dairy products and HTA Q5 vs Q1 OR 0.86; 95% CI 0.52 - 1.42; p> 0.05.
Steffen et al (2005) CARDIA study USA	15 years 25 (18, 30) 57%	4304 (997)	Dietary History	Total Dairy Products (Whole + Skimmed) Milk, yogurt, cheese and desserts	Physical exam HTA: ≥ 130/85 or treatment use	There is no association between total dairy products and HBP (p > 0.05). Inverse association with milk (p = 0.03) and desserts (p = 0.01), but not with cheese (p = 0.57) or yogurt (p = 0.14).

Appendix 3. **Correlation coefficient between continues variables in the first article.**

Correlation Coefficient, N=40 576														
Variables	**FRAP**	**TRAP**	**Age**	**BMI**	**Energy**	**Processed meat**	**Alcohol**	**Fruits and vegetables**	**Physical activity**	**Sodium**	**Potassium**	**Magnesium**	**Omega 3**	**Coffee**
FRAP	1													
TRAP	0.97	1												
	<.0001													
Age	-0.01	0.01	1											
	0.15	0.02												
BMI	0.02	0.01	0.13	1										
	0.00	0.14	<.0001											
Energy	0.41	0.31	-0.11	0.04	1									
	<.0001	<.0001	<.0001	<.0001										
Processed meat	0.13	0.10	-0.13	0.10	0.39	1								
	<.0001	<.0001	<.0001	<.0001	<.0001									
Alcohol	0.49	0.51	0.00	0.03	0.09	0.14	1							
	<.0001	<.0001	0.45	<.0001	<.0001	<.0001								
Fruits and vegetables	0.41	0.34	0.13	0.09	0.29	-0.03	-0.10	1						
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001							
Physical activity	0.06	0.05	0.13	0.01	0.06	-0.01	0.03	0.11	1					
	<.0001	<.0001	<.0001	0.189	<.0001	0.13	<.0001	<.0001						
Sodium	0.27	0.19	-0.03	0.05	0.83	0.46	0.09	0.20	0.05	1				
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001					
Potassium	0.39	0.30	0.02	0.12	0.62	0.19	0.10	0.61	0.09	0.49	1			
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001				
Magnesium	0.24	0.16	-0.09	0.11	0.50	0.22	0.20	0.27	0.05	0.41	0.68	1		

	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001			
Omega 3	0.41	0.28	-0.06	0.13	0.62	0.31	0.19	0.29	0.06	0.51	0.50	0.42	1	
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001		
Coffee	-0.09	-0.12	-0.09	0.08	0.06	0.09	0.09	-0.01	0.00	0.04	0.17	0.80	0.08	1
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.01	0.39	<.0001	<.0001	<.0001	<.0001	

Appendix 4. Sensitivity analysis. Hazard ratios of hypertension according to dietary total antioxidant capacity intake in women with fruits and vegetables consumption lower than the median (N 20 288). E3N Cohort, France 1993 - 2008.

Dietary TAC			M1		M2		M3	
(mmol/day)	Cases	Person-years	HR [95% CI]	p-trend	HR [95% CI]	p-trend	HR [95% CI]	p-trend
Q1 (<2.65)	1251	60633	Reference	0.02	Reference	0.12	Reference	0.01
Q2 (2.65-3.90)	1152	61999	0.90 [0.83; 0.97]		0.91 [0.84; 0.99]		0.90 [0.83; 0.98]	
Q3 (3.91-5.51)	1113	62286	0.86 [0.79; 0.93]		0.88 [0.81; 0.95]		0.85 [0.78; 0.93]	
Q4 (>5.51)	1155	61572	0.90 [0.83; 0.98]		0.93 [0.85; 1.01]		0.87 [0.79; 0.97]	

M1: Age as the time scale + energy excluding alcohol

M2: M1 + (Diabetes, treated hypercholesterolemia, education, family history of hypertension, smoking, physical activity, and body mass index)

M3: M2 + (Na, K, Mg, AGPIw3, alcohol and coffee)

Appendix 5. Additional analyses. Hazard ratios of hypertension according to dietary total antioxidant capacity intake, using FRAP method (N=40526). E3N Cohort, France 1993 - 2008.

Dietary TAC (mmol/day)	Cases	Person-Years	M1		M2		M3	
			HR [95% CI]	p-trend	HR [95% CI]	p-trend	HR [95% CI]	p-trend
				0.002		0.03		0.001
Q1	1935	97869	Reference		Reference		Reference	
Q2	1882	99049	0.94 [0.88; 1.00]		0.95 [0.89; 1.01]		0.94 [0.88; 1.00]	
Q3	1886	99158	0.93 [0.87; 0.99]		0.93 [0.87; 0.99]		0.91 [0.85; 0.98]	
Q4	1811	99111	0.89 [0.83; 0.95]		0.90 [0.85; 0.97]		0.88 [0.82; 0.94]	
Q5	1836	98708	0.90 [0.84; 0.96]		0.93 [0.86; 0.99]		0.87 [0.80; 0.95]	

M1: Age as the time scale + energy excluding alcohol

M2: M1 + (Diabetes, treated hypercholesterolemia, education, family history of hypertension, smoking, physical activity, and body mass index)

M3: M2 + (Na, K, Mg, AGPIw3, alcohol and coffee)

Appendix 6. **Correlation coefficient between continues variables in the second article.**

Correlation Coefficient, N=40 526																	
Variables	**Dairy**	**Milk**	**Yogurt**	**Cottage cheese**	**Cheese**	**Age**	**Physical Activity**	**BMI**	**Energy**	**Western**	**Healthy**	**Alcohol**	**Processed meat**	**Fruits and vegetables**	**Sodium**	**Potassium**	**Magnesium**
Dairy	1																
Milk	0.57	1															
	<.0001																
Yogurt	0.43	0.03	1														
	<.0001	<.0001															
Cottage cheese	0.22	0.04	0.07	1													
	<.0001	<.0001	<.0001														
Cheese	0.65	-0.04	-0.03	-0.03	1												
	<.0001	<.0001	<.0001	<.0001													
Age	-0.02	0.01	-0.02	0.06	-0.04	1											
	0.0002	0.01	<.0001	<.0001	<.0001												
Physical Activity	0.02	0.02	0.001	0.02	0.01	0.13	1										
	<.0001	0.002	0.80	<.0001	0.003	<.0001											
BMI	0.06	0.03	0.04	0.08	0.02	0.13	0.01	1									
	<.0001	<.0001	<.0001	<.0001	0.001	<.0001	0.1886										
Energy	0.42	0.15	0.09	0.08	0.41	-0.11	0.06	0.04	1								
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001									
Western	0.07	-0.05	-0.07	-0.05	0.20	-0.22	0.01	0.07	0.68	1							
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.1538	<.0001	<.0001								

Healthy	0.27	0.15	0.22	0.26	0.05	0.05	0.09	0.17	0.24	-0.08	1						
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001							
Alcohol	-0.04	-0.05	-0.12	-0.07	0.07	-0.004	0.03	0.03	0.09	0.35	0.02	1					
	<.0001	<.0001	<.0001	<.0001	<.0001	0.4524	<.0001	<.0001	<.0001	<.0001	0.0012						
Processed meat	0.10	-0.01	0.03	0.03	0.14	-0.13	-0.01	0.10	0.39	0.59	0.08	0.14	1				
	<.0001	0.0123	<.0001	<.0001	<.0001	<.0001	0.1319	<.0001	<.0001	<.0001	<.0001	<.0001					
Fruits and vegetables	0.17	0.05	0.16	0.18	0.06	0.13	0.11	0.09	0.29	-0.16	0.71	-0.10	-0.03	1			
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001				
Sodium	0.42	0.10	0.03	0.03	0.49	-0.03	0.05	0.05	0.83	0.49	0.21	0.09	0.46	0.20	1		
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001			
Potassium	0.40	0.29	0.23	0.19	0.14	0.02	0.09	0.12	0.62	0.27	0.58	0.10	0.19	0.61	0.49	1	
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001		
Magnesium	0.25	0.07	0.15	0.12	0.18	-0.09	0.05	0.11	0.50	0.39	0.34	0.20	0.22	0.27	0.41	0.68	1
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	

Appendix 7. Stratified analyses. Dairy consumption and hypertension risk stratified by age to median, family history of hypertension and BMI. (N= 40 526). E3N Cohort, France 1993 - 2008.

Dairy product (servings)	M1 HR [95% CI]	p	M2 HR [95% CI]	p	M1 HR [95% CI]	p	M2 HR [95% CI]	p	M1 HR [95% CI]	p	M2 HR [95% CI]	p
	Participants with an age < to the median N=20 260				**Participants without family history of hypertension N=28 901**				**Participants with normal weight N=35 111**			
Total												
Q1	Reference	0.57	Reference	0.48	Reference	0.18	Reference	0.65	Reference	0.64	Reference	0.69
Q2	1.06 [0.96; 1.17]		1.05 [0.96; 1.16]		0.96 [0.88; 1.04]		0.96 [0.88; 1.04]		0.98 [0.91; 1.05]		0.98 [0.92; 1.06]	
Q3	1.05 [0.95; 1.16]		1.06 [0.96; 1.17]		1.06 [0.97; 1.15]		1.05 [0.97; 1.15]		1.02 [0.95; 1.09]		1.02 [0.95; 1.10]	
Q4	1.05 [0.95; 1.16]		1.04 [0.94; 1.15]		1.04 [0.95; 1.13]		1.03 [0.94; 1.12]		1.02 [0.95; 1.10]		1.02 [0.94; 1.10]	
Q5	0.99 [0.89; 1.09]		0.98 [0.88; 1.09]		1.04 [0.95; 1.13]		1.00 [0.91; 1.10]		1.01 [0.93; 1.09]		1.01 [0.93; 1.09]	
	Participants with an age > to the median N=20 266				**Participants with family history of hypertension N=28 901**				**Participants with overweight or obesity N=5 415**			
Total												
Q1	Reference	0.11	Reference	0.50	Reference	0.95	Reference	0.69	Reference	0.39	Reference	0.57
Q2	0.91 [0.83; 0.99]		0.91 [0.83; 0.99]		0.99 [0.90; 1.09]		0.98 [0.88; 1.08]		0.90 [0.77; 1.04]		0.89 [0.77; 1.03]	
Q3	0.99 [0.91; 1.08]		0.98 [0.90; 1.07]		0.97 [0.87; 1.07]		0.96 [0.87; 1.06]		0.97 [0.83; 1.12]		0.97 [0.83; 1.13]	
Q4	1.01 [0.93; 1.10]		0.98 [0.90; 1.08]		1.00 [0.91; 1.11]		0.98 [0.88; 1.08]		0.96 [0.83; 1.11]		0.95 [0.82; 1.10]	
Q5	1.03 [0.94; 1.13]		1.00 [0.91; 1.09]		1.00 [0.90; 1.11]		0.97 [0.87; 1.09]		0.91 [0.78; 1.05]		0.92 [0.78; 1.08]	

M1: Adjusted for energy (energy without alcohol (kcal/d),

M2: M1+ smoking status (never, former, current), education (without high school diploma, with high school diploma), family history of hypertension (no, yes), and physical activity (Mets/d), alcohol (g/d), processed meat (g/d), and fruits and vegetables (g/d), sodium(mg/d), potassium (mg/d), and magnesium (mg/d)

Appendix 8. Stratified analyses. Yogurt consumption and hypertension risk stratified by BMI. (N= 40 526). E3N Cohort, France 1993 - 2008.

Dairy product (servings)	M1		M2	
	HR [95% CI]	p	HR [95% CI]	p
	Normal weight			
	N= 35 111			
Yogurt		0.29		0.30
Q1	Reference		Reference	
Q2	0.99 [0.92; 1.07]		0.99 [0.92; 1.07]	
Q3	1.02 [0.95; 1.09]		1.01 [0.94; 1.08]	
Q4	0.97 [0.90; 1.04]		0.98 [0.90; 1.05]	
Q5	1.03 [0.96; 1.11]		1.03 [0.95; 1.11]	
	Overweight or obesity			
	N= 5 415			
Yogurt		0.89		0.45
Q1	Reference		Reference	
Q2	0.81 [0.69; 0.94]		0.82 [0.70; 0.95]	
Q3	0.92 [0.80; 1.06]		0.93 [0.81; 1.08]	
Q4	0.86 [0.75; 1.00]		0.88 [0.76; 1.03]	
Q5	1.01 [0.88; 1.15]		1.06 [0.92; 1.22]	

M1: Adjusted for energy (energy without alcohol (kcal/d),

M2: M1+ smoking status (never, former, current), education (without high school diploma, with high school diploma), family history of hypertension (no, yes), and physical activity (Mets/d), alcohol (g/d), processed meat (g/d), and fruits and vegetables (g/d), sodium (mg/d), potassium (mg/d), and magnesium (mg/d)

Appendix 9. Correlation coefficient between continues variables in the third article.

Correlation Coefficients, N=71 989																
Variables	**Dairy**	**Milk**	**Yogurt**	**Cheese**	**Age**	**BMI**	**Physical Activity**	**Alcohol**	**Energy**	**Fruits and vegetables**	**Whole grain**	**Processed meats**	**Sweet beverages**	**Fruits & Vegetables Pattern**	**Western Pattern**	**Modern Mexican Pattern**
Dairy	1															
Milk	0.79	1														
	<.0001															
Yogurt	0.52	0.21	1													
	<.0001	<.0001														
Cheese	0.72	0.22	0.26	1												
	<.0001	<.0001	<.0001													
Age	0.05	0.03	0.02	0.04	1											
	<.0001	<.0001	<.0001	<.0001												
BMI	-0.05	-0.03	-0.05	-0.04	0.13	1										
	<.0001	<.0001	<.0001	<.0001	<.0001											
Physical activity	0.01	-0.004	0.03	0.02	-0.04	-0.07	1									
	0.002	0.26	<.0001	<.0001	<.0001	<.0001										
Alcohol	0.03	-0.01	0.03	0.05	0.04	-0.01	0.03	1								
	<.0001	0.0328	<.0001	<.0001	<.0001	0.01	<.0001									
Energy	0.40	0.27	0.23	0.34	-0.01	-0.02	0.13	0.10	1							
	<.0001	<.0001	<.0001	<.0001	0.0001	<.0001	<.0001	<.0001								
Frutis and vegetables	0.22	0.13	0.21	0.16	0.09	-0.03	0.14	0.03	0.60	1						
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001							
Whole grain	0.01	0.02	-0.01	-0.01	-0.04	0.02	0.02	-0.02	0.33	0.07	1					
	0.149	<.0001	0.0002	0.002	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001						
Processed meat	0.12	0.01	0.08	0.18	-0.12	0.03	0.05	0.06	0.34	0.07	0.01	1				
	<.0001	0.0002	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.002					
Sweet bevarages	0.12	0.07	0.08	0.11	-0.03	0.01	0.01	0.03	0.35	0.13	0.05	0.05	1			
	<.0001	<.0001	<.0001	<.0001	<.0001	0.01	0.001	<.0001	<.0001	<.0001	<.0001	<.0001				

Fruits & Vegetables Pattern	-0.04	-0.07	0.06	-0.02	0.11	-0.02	0.10	0.02	-0.04	0.51	-0.09	-0.10	-0.002	1		
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.5636			
Western Pattern	0.01	-0.10	0.01	0.14	-0.06	0.04	0.01	0.18	-0.13	-0.17	-0.41	0.42	-0.10	-0.003	1	
	0.02	<.0001	<.0001	<.0001	<.0001	<.0001	0.0002	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.3969		
Modern Mexican Pattern	-0.35	-0.32	-0.25	-0.17	-0.08	0.11	-0.09	0.03	-0.20	-0.32	0.19	0.03	0.02	-0.004	-0.004	1
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.34	0.34	

Appendix 10. Stratified analyses. Dairy consumption and hypertension risk stratified by age to median, family history of hypertension and BMI (N= 71 989). MTC Cohort, Mexico 2006 - 2011.

Dairy products	Age-energy-adjusted		Multivariable		Age-energy-adjusted		Multivariable		Age-energy-adjusted		Multivariable	
	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
	Age <43 years				Without family history of hypertension				Normal weight			
Total												
Q1	Reference	<.0001	Reference	0.48	Reference	0.07	Reference	0.34	Reference	0.72	Reference	0.21
Q2	0.85 [0.73; 1.00]		0.95 [0.86; 1.06]		0.96 [0.82; 1.13]		0.96 [0.82; 1.13]		0.92 [0.74; 1.15]		0.90 [0.73; 1.12]	
Q3	1.09 [0.93; 1.27]		1.00 [0.90; 1.12]		1.09 [0.92; 1.28]		1.08 [0.92; 1.28]		1.05 [0.84; 1.29]		0.99 [0.80; 1.22]	
Q4	1.23 [1.04; 1.45]		0.95 [0.84; 1.07]		1.11 [0.94; 1.32]		1.06 [0.89; 1.27]		0.99 [0.79; 1.24]		0.86 [0.68; 1.08]	
	Age ≥ 43 years				With family history of hypertension				Overweight or obesity			
Total												
Q1	Reference	0.18	Reference	0.01	Reference	0.001	Reference	0.62	Reference	<.0001	Reference	0.08
Q2	0.96 [0.87; 1.07]		0.88 [0.75; 1.03]		0.92 [0.82; 1.02]		0.92 [0.82; 1.02]		0.94 [0.85; 1.04]		0.94 [0.84; 1.04]	
Q3	1.03 [0.93; 1.15]		1.08 [0.92; 1.26]		1.04 [0.93; 1.16]		1.00 [0.90; 1.12]		1.10 [0.99; 1.22]		1.04 [0.94; 1.16]	
Q4	1.04 [0.92; 1.16]		1.15 [0.97; 1.36]		1.10 [0.99; 1.23]		0.99 [0.88; 1.11]		1.21 [1.09; 1.35]		1.06 [0.94; 1.19]	

Age-energy-adjusted: Age(quintiles) and energy (tertiles),

Multivariable: M1+ socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension (yes, no), physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), treated hypercholesterolemia (yes/no), diabetes (yes/no), indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing), fruits and vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles).

Appendix 11. Stratified analyses. Yogurt consumption and hypertension risk stratified by BMI (N= 71 989). MTC Cohort, Mexico 2006 - 2011.

Dairy products	Age-energy-adjusted		Multivariable	
	HR [95% CI]	p	HR [95% CI]	p
Normal weight				
Yogurt				
Q1	Reference	0.02	Reference	0.30
Q2	0.91 [0.79; 1.06]		0.90 [0.77; 1.05]	
Q3	0.98 [0.84; 1.14]		0.95 [0.82; 1.11]	
Q4	1.11 [0.93; 1.31]		1.00 [0.84; 1.19]	
Overweight or obesity				
Yogurt				
Q1	Reference	0.01	Reference	0.33
Q2	0.96 [0.86; 1.08]		0.95 [0.85; 1.06]	
Q3	0.97 [0.87; 1.09]		0.95 [0.85; 1.07]	
Q4	1.12 [0.98; 1.27]		1.03 [0.91; 1.17]	

Age-energy-adjusted: Age(quintiles) and energy (tertiles),

Multivariable: M1+ socioeconomic status (quartiles), region of residence (north, central, Mexico City and metropolitan area, south, missing), family history of hypertension (yes, no), physical activity (metabolic equivalents/week, tertiles), smoking status (never, past, current), treated hypercholesterolemia (yes/no), diabetes (yes/no), indigenous background (yes/no) and body mass index (normal, overweight, obesity and missing), fruits and vegetables, processed meat, whole grains and sugar-sweetened beverages intake (all in tertiles).

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Titre : Facteurs diététiques et hypertension chez les femmes adultes en France et au Mexique

Mots clés : Hypertension, femmes, alimentation, nutrition, capacité antioxydante totale, produits laitiers, style de vie, cohorte, épidémiologie

Résumé : L'hypertension est un facteur de risque majeur des maladies cardiovasculaires. Il s'agit d'une cause majeure de mortalité dans le monde représentant un enjeu majeur de santé publique. Les facteurs de risque modifiables comme l'alimentation ont été identifiés néanmoins certains aspects du rôle de l'alimentation ne sont pas clair. L'objectif principal de cette thèse est d'évaluer le rôle et l'impact des facteurs alimentaires, en particulier, la capacité antioxydante totale et la consommation de produits laitiers et le risque d'hypertension en utilisant des données de la cohorte E3N et la cohorte mexicaine MTC. La capacité antioxydante totale (CAT) a été inversement associé au risque d'hypertension une alimentation variée et équilibrée. dans la cohorte E3N, après ajustement sur les principaux facteurs de risque. La courbe de regression en spline a montré une forte relation dose effet inverse entre la CAT alimentaire et le risque d'hypertension pour ensuite se stabiliser, suggérant un effet maximal de la CAT. De plus, les résultats ne suggèrent pas d'association entre la consommation totale ou chaque type de produit laitier consommé et de risque d'hypertension. Seulement la consommation de fromage fondu était directement associée à l'hypertension. Donc la prévention de l'hypertension devra aider à réduire l'impact des facteurs de risque modifiables comme l'alimentation en promouvant

Tittle: Dietary factors and hypertension in adult women in France and Mexico

Keywords: Hypertension, women, diet, nutrition, dietary total antioxidant capacity, dairy products, lifestyle, cohort, epidemiology

Abstract: Hypertension is the major risk factor for cardiovascular disease, the principal cause of mortality in the world, representing a significant health burden. Modifiable risk factors, such as the diet, have been identified for hypertension; nonetheless some aspects of the role of the diet remain unclear. The main objectives of this thesis were to evaluate the role and impact of dietary factors, particularly, the dietary total antioxidant capacity, and the consumption of dairy products and the risk of hypertension using data from both the French E3N and Mexican MTC cohort studies. Dietary total antioxidant capacity (TAC) was inversely associated with risk of hypertension in the E3N cohort, after adjustment for the main risk factors. The spline regression curve demonstrated a steep inverse dose-effect relationship between dietary TAC and risk of hypertension, then leveled off, suggesting a maximal effect of TAC. In addition, the results suggest no association between total dairy intake or each type of dairy product consumed and hypertension risk in both the E3N and MTC cohort studies. Only processed cheese consumption was directly associated with hypertension. Therefore, hypertension prevention should aim to reduce the impact of modifiable risk factors, such as the diet, by promoting varied and balanced diets.

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