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THESE

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Nutritional factors in asthma

(Facteurs nutritionnels dans l'asthme)

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RESUME

L'objectif principal de la thèse était de comprendre le rôle complexe des facteurs nutritionnels dans l'asthme, avec une première partie portant sur l'alimentation et une seconde sur l'obésité.

Alimentation – L'objectif était de comparer les typologies alimentaires obtenues par une analyse en composantes principales (ACP) à celles identifiées par une analyse factorielle confirmatoire (AFC) grâce aux données de l'étude E3N (étude épidémiologique auprès des femmes de la MGEN, 30589 femmes). En utilisant les ACP et les AFC, 3 typologies alimentaires ont été identifiées. Selon la méthode, des corrélations différentes étaient observées entre les typologies alimentaires et les groupes d'aliments, conduisant à des associations différentes avec les caractéristiques socio-économiques et l'incidence de l'asthme chez l'adulte.

Obésité – Le premier objectif était de comprendre les rôles conjoints et indépendants, dépendants du temps, de l'activité physique et l'obésité sur l'asthme en utilisant des modèles marginaux structuraux chez 15352 femmes d'E3N. L'obésité était liée de façon causale à l'asthme actuel avec symptômes, indépendamment de l'activité physique. Le second objectif était de considérer le rôle modificateur du surpoids dans l'association entre l'exposition domestique aux sprays de nettoyage et l'asthme chez 304 femmes d'E3N. Parmi les femmes sans traitement anti-inflammatoire, le rôle délétère de l'utilisation de sprays sur l'asthme était plus fort chez les femmes en surpoids.

L'AFC devrait être utilisée pour l'identification des typologies alimentaires en épidémiologie nutritionnelle. L'obésité pourrait causer de l'asthme indépendamment de l'activité physique, et pourrait augmenter l'effet délétère d'autres facteurs environnementaux de l'asthme.

Mots-clés : Epidémiologie, Indice de masse corporelle, Alimentation, Typologies alimentaires, Asthme, Méthodologie

ABSTRACT

The general aim of the thesis was to assess the complex role of nutritional factors in asthma, with a first part focused on diet, and a second part focused on obesity.

Diet – The objective was to compare dietary patterns based on principal component analysis (PCA) to patterns based on confirmatory factor analysis (CFA). The analysis was performed among 30,589 women from the E3N study (epidemiological cohort study among women of the Mutuelle Générale de l'Education Nationale). Whether PCA or CFA was used, 3 patterns were derived. For each pattern, we reported different correlations between food groups and dietary patterns when using PCA or CFA, leading to different associations between dietary patterns with socio-economic characteristics and adult-onset asthma.

Obesity – The first objective was to assess the joint and independent, time-dependent, roles of physical activity and obesity on asthma using marginal structural models. Among 15,352 women from E3N, analyses showed that obesity was related causally to current asthma with symptoms independently of physical activity, whereas no association was reported for physical activity. The second objective was to assess the modifying role of overweight in the association between domestic exposure to cleaning sprays and current asthma. Among 304 women from E3N, analysis showed that among women without anti-inflammatory therapy, the effect of spray use on asthma was higher in overweight women.

CFA should be considered for the assessment of dietary patterns in nutritional epidemiology. Obesity may lead to asthma independently of physical activity, and may increase the deleterious effect of other environmental factors of asthma.

Keywords : Epidemiology, Body mass index, Diet, Dietary patterns, Asthma, Methodology

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PUBLICATIONS AND COMMUNICATIONS

PUBLICATIONS

1. Bédard A, Garcia-Aymerich J, Sanchez M, Le Moual N, Clavel-Chapelon F, Boutron-Ruault MC, Maccario J, Varraso R. A comparison of principal component analysis and confirmatory factor analysis to study the longitudinal effect of dietary patterns on adult-onset asthma in the E3N study. *J Nutr* (*revision*).
2. Bédard A, Varraso R, Dumas O, Sanchez M, Clavel-Chapelon F, Zock JP, Kauffmann F, Le Moual N. Household use of cleaning sprays and asthma activity in elderly women from the French E3N cohort *Respir Med* 2014; 108:171-180.
3. Bédard A, Dumas O, Kauffmann F, Garcia-Aymerich J, Siroux V, Varraso R. Potential confounders in the asthma–diet association: how causal approach could help? *Allergy* 2012; 67:1461–1463.

COMMUNICATIONS

1. Bédard A, Garcia-Aymerich J, Sanchez M, Le Moual N, Clavel-Chapelon F, Boutron-Ruault MC, Maccario J, Varraso R. A comparison of principal component analysis and confirmatory factor analysis to study the longitudinal effect of dietary patterns on adult-onset asthma in the E3N study. *Lungstorming Meeting*, Fontenay-Tresigny, June 2014 (invited communication).
2. Bédard A, Varraso R, Dumas O, Sanchez M, Clavel-Chapelon F, Zock JP, Kauffmann F, Le Moual N. Household use of cleaning sprays and asthma activity in elderly women from the French E3N cohort. *2nd French-German school of Pneumology Meeting*, Tours, September 2013 (poster).
3. Bédard A, Varraso R, Dumas O, Sanchez M, Clavel-Chapelon F, Zock JP, Kauffmann F, Le Moual N. Household use of cleaning sprays and asthma activity in elderly women from the French E3N cohort. *European Respiratory Society Meeting*, Barcelona, September 2013. *Eur Respir J* 2013;42:Suppl.57,745s (poster discussion).
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COMMUNICATION AS CO-AUTHOR

1. Le Moual N, Bédard A, Dumas O, Varraso R, Kauffmann F, Zock JP. Relevance of exposure to cleaning agents beyond cleaning professionals: Private homes and healthcare workers. *Epidemiology in Occupational Health Meeting*, Utrecht, June 2013 *Occup Environ Med* 2013;70(suppl 1):A26 (poster).

ABBREVIATIONS

ADII: Adapted Dietary Inflammatory Index

AHEI: Alternate Healthy Eating Index

AHEI-P: Alternate Healthy Eating Index adapted to pregnancy

AHR: Airway Hyperresponsiveness

ATS: American Thoracic Society

aMED: alternate Mediterranean diet

BIA: Bioelectrical Impedance Analysis

BMI: Body Mass Index

BMRC: British Medical Research Council

CDC: Centers for Disease Control and Prevention

CFA: Confirmatory Factor Analysis

COPD: Chronic Obstructive Pulmonary Disease

DALYs: Disability-Adjusted Life Years

DASH: Dietary Approaches to Stop Hypertension

DDS: Diet Diversity Score

DEXA: Dual-Energy X-ray Absorptiometry

DGI: Dietary Guidelines Index

DHA: Docosahexaenoic Acid

DII: Dietary Inflammatory Index

DQI: Diet Quality Index

DQI-R: Diet Quality Index Revised

DR: Diet Record

DVS: Dietary Variety Score

E3N: Epidemiological prospective cohort study among women of the MGEN

EGEA: Epidemiological study on the Genetics and Environment of Asthma

ECRHS: European Community Respiratory Health Survey

EPA: Eicosapentaenoic Acid

EPIC: European Prospective Investigation on Cancer

FBQI: Food-Based Quality Index

FeNO: Fractional exhaled Nitric Oxide

FFQ: Food-Frequency Questionnaire

FGP: Food Guide Pyramid

FP7-Escape : European Study of Cohorts for Air Pollution Effects

FPI: Food Pyramid Index

FRAP: Ferric Reducing Antioxidant Power

FVS: Food Variety Score

GINA: Global INitative for Asthma

GWAS: Genome-Wide Association Study

HDI: Healthy Diet Indicator

HEI: Healthy Eating Index

HFI: Healthy Food Index

HRT: Hormone Replacement Therapy

hs-CRP: high-sensitivity C-Reactive Protein

ICS: Inhaled Corticosteroids

IgE: Immunoglobulin E

Kcal/day: kilocalories per day

KIDMED Index: Mediterranean Diet Quality Index in children and adolescents

LABA: Long-Acting β2-Agonists

LCA : Latent Classes Analysis

MDQI: Mediterranean Diet Quality Index

Med Score: Mediterranean diet Score

Med Score Pregnancy: Mediterranean diet Score during Pregnancy

METs: Metabolic Equivalents

MGEN: Mutuelle Générale de l'Education Nationale

NAR/MAR: Nutrient Adequacy Ratio

NHANES: National Health and Nutrition Examination Survey

NHS: Nurses' Health Study

NRFS: Not Recommended Foods Score

ORAC: Oxygen Radical Absorbance Capacity

PCA: Principal Component Analysis

PLS: Partial Least-Squares Regression

PNNS-GS: Programme National Nutrition Santé-Guideline Score

PUFAs: Polyunsaturated Fatty Acids

RCTs: Randomized Controlled Trials

RFS: Recommended Food Score

RHINE: Respiratory Health in Northern Europe

RRR: Reduced Rank Regression

SABA: Short-Acting β2-Agonists

SES: Socio-Economic Status

SU.VI.MAX : SUpplémentation en VItamines et Minéraux AntioXydants

TAC: Total Antioxidant Capacity

TEAC: Trolox Equivalent Antioxidant Capacity

T_H2: T-Helper type 2 lymphocytes

TRAP: Total Radical-Trapping Antioxidant Parameter

UK: United Kingdom

US: United States

USDA: US Department of Agriculture

WHO: World Health Organization

TABLE OF CONTENTS

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, affecting around 300 million individuals around the world (1). Asthma is a complex disease, with strong clinical heterogeneity and phenotypic variability over time. This heterogeneity can be observed at different levels: clinical, biological or etiological (2). The prevalence of asthma has nearly doubled over the last decades, more particularly in Westernized countries, and aside from genetic determinants, it has been hypothesized that these increases are a consequence of changing environmental and/or lifestyle factors (3). Contrary to cardiovascular diseases or cancer, the study of the role of nutritional factors in chronic respiratory diseases, particularly in asthma, is relatively new in the international literature. The modification of dietary habits (less fruits/vegetables, more ready to eat meals), the obesity epidemic, and the decrease in physical activity, have been suggested to play a role in the increase of asthma prevalence worldwide (4).

In nutritional epidemiology, studies on specific foods or nutrients have traditionally been conducted. However, several conceptual and methodological limitations have been raised and studying dietary patterns has recently been proposed to study the effects of overall diet, rather than the effects of specific foods or nutrients (5), leading to important methodological developments (6,7). Studies on diet and asthma showed conflicting results according to the age of asthma-onset and the method used to estimate diet (4,8–11).

Obesity on the other hand, is a well known risk factor for asthma in adults, especially in women, but mechanisms that underlie this relationship are still unclear (12). Recent studies showed that obesity was associated with more severe asthma, worse asthma control (13) and reduced response to asthma medications (14), leading to the conclusion that asthma in the obese may represent a unique phenotype (15). It is also possible that obesity is an epiphenomenon of more complex interrelations with other nutritional, environmental, behavioral or social factors, that should be addressed as well (3,4). The interrelationships between the three nutritional factors (i.e., obesity, diet and physical activity) are complex and poorly studied. Besides these interrelationships, it is also possible that the association between asthma and obesity may be mediated by social or environmental factors.

The general aim of the thesis is to assess the complex role of nutritional factors in asthma, with a first part focused on dietary habits, and a second part focused on obesity.

The first chapter presents firstly, general aspects regarding the epidemiology of asthma, secondly, a review of the literature regarding the different tools to assess dietary habits and their association with asthma over the life span, thirdly a review of the literature regarding the different tools to estimate body composition and the role of obesity in asthma, and finally, a review of the literature regarding interrelations that may occur within nutritional factors, and between nutritional and environmental factors, in relation to asthma outcomes.

The specific objectives of this thesis are then presented (second chapter).

The third chapter presents the population among which our analyses were conducted, the data that were available to conduct them and the methods that were used.

The fourth chapter presents the results that were obtained, on one hand, regarding dietary habits, and on the other hand, regarding obesity. Regarding dietary habits, two aspects were addressed: the identification of dietary patterns and its methodological issues, and their association with new adult-onset asthma. Regarding obesity, two aspects were addressed: obesity was first considered as a risk factor of asthma, along with physical activity, and then the role of obesity on asthma was considered in interaction with an environmental factor of asthma.

The last chapter presents a summary of the main results and their implications regarding public health and methodological aspects related to the assessment of dietary patterns, the main limitations of the performed analyses, and finally the perspectives from the thesis.

STATE OF THE ART

Contrary to cardiovascular diseases or cancer, the study of the role of nutritional factors in chronic respiratory diseases, particularly in asthma, is relatively new in the international literature. The modification of dietary habits (less fruits/vegetables, more ready to eat meals), the obesity epidemic, and the decrease in physical activity, have been suggested to play a role in the increase of asthma worldwide (4). The following chapter presents first, general aspects regarding the epidemiology of asthma. Secondly, the association between diet and asthma is presented, first by reminding the different tools to measure and estimate diet, and then, by presenting an exhaustive literature review regarding the association between diet and asthma over the life span. Thirdly, the association between obesity and asthma is presented, also by reminding the different tools to estimate body composition, and then, by reviewing the recent literature regarding obesity and asthma. Finally, as nutritional factors (i.e., diet, physical activity and obesity) may interact with each other, but also with several environmental factors, recent hypotheses have been raised regarding these different interrelationships in relation to asthma outcomes. They are presented and discussed, first regarding interrelations that may occur within nutritional factors, and then between nutritional and environmental factors, leading to the issues of confounding or mediation.

1. Asthma

In the next section, general aspects of the epidemiology of asthma are presented, first regarding clinical features, then regarding the phenotypic heterogeneity and variability over time of the disease, and finally regarding epidemiological aspects.

1.1. Clinical features

Asthma is a chronic inflammatory disease of the airways, clinically characterized by recurring symptoms, such as wheezing, shortness of breath, chest tightness and cough, by a variable airflow obstruction that is reversible, with or without the use of treatment, and by airway hyperresponsiveness to allergen, pharmacologic or physiological stimuli. These characteristics are associated with airway inflammation, causing variable expiratory airflow, i.e., difficulty breathing air out of the lungs due to bronchoconstriction (airway narrowing), airway wall thickening, and increased mucus (16).

The concepts of asthma severity, which reflects the intrinsic severity of the disease, and asthma control, which reflects the activity of the disease over a short period of time, are important in evaluating patients and their response to treatment, as well as for public health, registries and research (1). The control of asthma incorporates the current clinical control, or extent of impairment (assessed with day and night symptoms, use of reliever therapies, activity limitations, and lung function) and the occurrence of asthma exacerbations (17). Clinical guidelines have proposed to assess asthma severity with the intensity of treatment required to achieve good control, which, to be applicable in epidemiological studies, requires information on both long-term use of asthma medication and repeated phenotypic characterization. Uncontrolled asthma, defined according to the recommendations of the Global INitiative for Asthma (GINA), affects one third of subjects with asthma in Europe, with significant geographical variability (20% to 67% depending on the country, about one third in France) (18).

The goal of asthma management is to achieve and maintain optimal asthma control (reductions of symptoms, prevention of attacks or bronchial obstruction, quality-of-life improvement), by reducing airway inflammation and preventing fixed airways obstruction. Optimal asthma control takes months or even years to achieve in some patients. Fine-tuning of medications, identification of triggers, the use of a written action plan and facilitation of

self-management education are all crucial to achieve asthma control. In addition to the control of environmental factors, asthma management rests on regular intake of medications, even in the absence of symptoms, which do not cure the disease. Reliever medications (i.e., short-acting β2-agonists (SABA) associated or not with anticholinergic drugs and oral corticosteroids) are used to reverse bronchoconstriction occurring during asthma attacks and exacerbations. Maintenance therapies are based on inhaled corticosteroids, which are the cornerstone of the therapeutic management, associated or not with long-acting β2-agonists (LABA) or other medications according to the control of the disease (16). Asthma management remains a hot topic internationally. The use and the place of LABA remains controversial because of a possible excess of severe attacks and mortality in some sub-populations of subjects with asthma (19,20). Furthermore, the presence of treatment-resistant asthma, also called "refractory asthma" (generally to corticosteroids), commonly seen in subjects with severe disease (2), has led to the development of therapeutic alternatives over the last decades, such as leukotriene modifiers or biotherapies (i.e., omalizumab, mepolizumab).

1.2. Phenotypic heterogeneity and variability over time

Asthma is a complex disease, with strong clinical heterogeneity and phenotypic variability over time. Its clinical expression varies over time, on different time scales: one day, one month, according to seasons (in relation to allergens, air pollution…), but also on several years; asthmatic patients may experience periods of remission, sometimes followed by a relapse of symptoms (21). Asthma can occur at any age, but usually occurs during childhood. Asthma incidence during childhood is greater in boys than in girls whereas after puberty, asthma incidence is greater in women than in men, and remains higher throughout the reproductive years (22). Asthma in the elderly is characterized by more frequent irreversible airway obstruction and accelerated lung function decline, due to airway remodeling (causing airway wall thickening), and sometimes co-existing chronic obstructive pulmonary disease (COPD) (23). Co-existence of asthma, chronic bronchitis, emphysema and COPD in different combinations is common among patients (24). A study conducted in the United States (US) and the United Kingdom (UK) showed that concomitant diagnosis of asthma, chronic bronchitis, or emphysema accounted for half of the obstructive lung diseases in adults over 50 years-old (25). Another study conducted in New Zealand showed that asthma accounted for 55% of COPD cases in adults over 50 years-old (26).

Asthma definition is evolving; although asthma has been considered as a single disease for years, recent studies have increasingly focused on its heterogeneity, promoting the concept that asthma involves multiple phenotypes or consistent groupings of characteristics. This heterogeneity can be observed at different levels: clinical (e.g. severity of the disease, evolution of the disease), as well as biological (e.g. allergic/non-allergic, eosinophilic/non-eosinophilic inflammation), or etiological (2). For a long time, asthma was widely believed to be an allergic, eosinophilic and T_H2-(T-helper type 2 lymphocytes) mediated disease. However, epidemiological studies of the last decades have suggested that asthma is attributable to atopy in less than half of the cases (27). A recent large study among children investigated the comorbidity of eczema, rhinitis, and asthma in immunoglobulin E (IgE) - sensitised and non-IgE-sensitised children, and showed that children with comorbidities and without IgE-sensitisation at the age of 4 had higher relative risks of comorbidity at the age of 8 than did children who were sensitised to IgE (28). Age of onset is also important in phenotyping asthma; adult-onset asthma differs from childhood-onset asthma on different aspects: it is often non-atopic, more severe, and has worse prognosis and poorer response to standard asthma treatment (29).

Besides the clinical approach based either on expert guidelines or on a limited number of asthma features, epidemiological research performed over the past one to two decades has sought to understand better the heterogeneous clinical nature of asthma using non-biased analyses (30). Novel phenotypes have been identified using such comprehensive statistical-based approaches able to simultaneously integrate multiple disease features, including age at onset, atopy, severity of airways obstruction and requirement for medication (31). Examples of these phenotypes include early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations (32–37). Cluster analysis refers to a multivariate mathematical method for the quantification of similarity between the individuals on the basis of specified variables, and the grouping of individuals into clusters based on that similarity. Although the process of choosing variables introduces some bias during the statistical process, asthma phenotypes identified using such models are generally more similar than different across studies, revealing that age at disease onset was a key differentiating factor (31).

1.3. Epidemiological aspects

Prevalence

Asthma is a global health problem affecting around 300 million individuals around the world. It is estimated that around 250,000 people die prematurely each year as a result of asthma (1). Asthma has been classified as the 28th (out of 291 diseases) cause of disability-adjusted life years (DALYs) worldwide (38). The prevalence of asthma has nearly doubled over the last decades, more particularly in Westernized countries. A large study, implemented in 2002-2003 by the World Health Organization (WHO), was conducted among 178,215 adults from 70 countries, and estimated the prevalence of physician-diagnosed asthma at 4.3% worldwide, ranging from 0.2% (in China) to 21.0% (in Australia) (39). However, while the prevalence of asthma is still increasing in some countries, it has been suggested that the increase in the asthma epidemic is coming to an end in some countries with a high prevalence of the disease (40,41). In France, in 2006, more than 10% of the general population had ever had asthma and the prevalence of current asthma, defined by the presence of asthma symptoms or the use of asthma medication in the past 12 months, reached almost 7% (42). The societal and economic cost of asthma is increasing and the total cost of asthma is substantial, with approximately €17.7 billion per year in Europe (43), and €1.5 billion per year in France (44).

Etiological aspects

Over the past four decades, the prevalence of asthma has markedly increased in Westernized countries, and aside from genetic determinants, it has been hypothesized that these increases are a consequence of changing environmental and/or lifestyle factors. Asthma is thus considered to be due to a complicated interplay of genetic, environmental, lifestyle and social factors (3). However, in spite of much research effort, the causation of asthma remains largely unknown.

Genetic factors – Asthma has an important genetic component. As at 2011, scientific literature indicated that 173 genes have been associated with asthma or clinical conditions related to asthma, and the number continues to increase (45). However, many genetic factors act primarily through complex mechanisms that involve interactions with other genes and environmental factors and/or epigenetic mechanisms, and such genetic factors may be missed if they are examined individually. Therefore, research is now focusing on the development of gene–gene (GxG) and gene–environment (GxE) interaction studies, including epigenetic alterations (46). Moreover, these studies have shown that genetic factors may differ according

to age of asthma onset. This also stresses the importance of phenotyping asthma appropriately.

Environmental factors - In the indoor environment, exposure to allergens such as dust mites, pets (especially cats and dogs), cockroaches, mice and fungi are important risk factors for the development and exacerbations of allergic asthma (47). Contact with livestock in the farming environment during childhood, causing optimal immunological maturation, is an important factor in preventing allergies and asthma (48). Studies in adolescents and adults have shown that the effect of a farming environment in childhood persists as a protective effect into adult life (49). According to the hygiene hypothesis, the decrease in early contacts with infectious agents, in particular through contacts with livestock, could explain the increase in prevalence of asthma and allergies (48).

The role of exposure to air pollution on asthma is biologically relevant as air pollution causes inflammation. The acute effects of ambient air pollution on asthma are well established, leading to more severe morbidity (exacerbations, emergency visits, increased medication intake and other acute manifestations occurring in asthma) (47). There is growing evidence for a role of chronic exposure to air pollution on asthma incidence in children (50). The role of air pollution in adult-onset asthma (i.e. asthma incidence) has been investigated only in a few studies (50), and should not be extrapolated from studies in children because childhood-onset and adult-onset asthma are two distinct asthma phenotypes, with different clinical, biological and genetic characteristics. However, a recent large longitudinal study has shown a positive association between air pollution and asthma onset in adults (51).

In adulthood, asthma is now the first occupational respiratory disease and more than 400 agents have been specifically identified as disease-related (52). The risk of adult-onset asthma attributable to occupational exposures has been estimated at approximately 15% (53). Evidence is increasing regarding the role of exposure to cleaning products to explain part of the increase in asthma prevalence observed in most developed countries (16,54,55). Deleterious effects of occupational exposure to cleaning products have been reported for asthma (56–58), asthma incidence (59) and asthma severity (60), in particular in cleaners (56,57) and healthcare professionals (58,59). The use of cleaning products in spray form has increased in past decades (61). The harmful effect of products in spray form used by spray painters (62), machine workers (63), or in agriculture (64) at work, have been observed in several diseases. Bello *et al.*, studying detailed tasks among cleaners, classified the use of cleaning sprays as high risk for inhalation exposure (65,66). Although it has been studied very

little, there is increasing evidence of the deleterious role of the use of cleaning products in spray form at work in asthma activity and incidence (54,58,59).

Besides occupational exposures, domestic exposures to cleaning products appear as an emergent risk factor. The risk of asthma attributable to domestic exposures to cleaning products could represent as much as 15% in adults (67). The deleterious role of weekly use of cleaning products in spray form during household cleaning tasks was suggested for asthma in the European Community Respiratory Health Study (ECRHS) (67) and in the French Epidemiological study on the Genetics and Environment of Asthma (EGEA) (68). A weekly use of at least two household sprays was associated with asthma incidence (67) and poorly controlled asthma (68). Therefore, domestic exposure to cleaning sprays may represent an important problem for public health, especially in women. The use of products in spray form facilitate respiratory exposure (better than those in non-spray form) (65). Allergens and irritants are deposited in large airways by turbulent flow, causing chronic inflammatory changes (69). The size of particles determines how quickly the particle settles, to what extent it follows the movements of the air and the probability of being deposited in a given part of the human respiratory system (70). In an experimental scenario simulating human exposure to aerosol, a potential harmful exposure to a household bathroom cleaner/sanitizer spray, after evaporation, with nanoparticles, has been suggested (71). Understanding the role of the size of particles from cleaning sprays, which may differ according to the type of sprays (aerosol, atomizer), need further studies, including information on dose–response relationships.

Lifestyle factors - The role of exposure to tobacco smoke on asthma is biologically relevant as tobacco smoke, which contains several chemicals, causes oxidative stress, i.e. imbalance between pro-oxidant and antioxidant defenses in favor of oxidants, leading to inflammation (47). Maternal smoking during pregnancy and exposure to tobacco smoke in the home deteriorate child's lung function and increase his or her life-long risk of asthma (72). In contrast, the effects of both passive and active smoking on asthma in adults are more unclear. Although some recent studies have reported associations between active smoking and adult-onset asthma, the role of tobacco exposure in asthma development in adults is still debated. On the other hand, many studies have showed deleterious effects of tobacco exposure on asthma control, showing that smoking asthma patients have more symptoms and exacerbations than nonsmoker asthma patients, and that smoking increases the risk of hospitalization as well as the occurrence of asthma-related deaths (72). Though cigarette smoking has been shown to increase asthma severity and accelerate decline in lung function, a large proportion of subjects with asthma start and continue to smoke (73).

Nutritional factors - Contrary to cardiovascular diseases or cancer, the knowledge about the role of nutritional factors in chronic respiratory diseases is relatively new in the international literature. The modification of dietary habits (less fruits/vegetables, more ready to eat meals), the obesity epidemic, and the decrease in physical activity, have been suggested to play a role in the increase of asthma worldwide (4). The effect of physical activity on asthma is controversial, with the possibility of reverse causation being an issue (i.e. asthma may limit the practice of physical activity) (74). It is also argued whether physical activity relates more to the evolution than the development of asthma (75–77). Sedentary behavior is not simply the inverse of physical activity. Even in physically active people, increased sedentary time, and more particularly television-viewing, is associated with increased metabolic risk (78). The frequency of sighs is reduced during television viewing and one could speculate that an absence of these deep breaths, and their modulatory effect on bronchoconstriction, could lead to the development of asthma symptoms (78). The hypotheses regarding the role of diet and obesity in asthma are presented in details in the next sections.

Social factors - Even though socio-economic status (SES) is linked to air pollution, occupation, nutrition and lifestyle factors, the role of socio-economic factors in asthma has been scarcely discussed in reviews on the environment (3). Measuring SES is difficult in epidemiology, and a source of methodological complexity comes from the fact that these variables can be taken into account either at individual level or at area level. At the individual level, lower SES was reported to be associated to more severe/symptomatic asthma or poorly controlled asthma, and poor adherence to inhaled corticosteroids was reported to be associated with lower income and lower educational level (47). Very few studies have evaluated SES through area-level index to study association with asthma, and brought conflicting results (79).

2. Diet

This section presents, first a summary of the tools that are available in nutritional epidemiology to collect data on diet, secondly the different statistical methods that have been developed to assess dietary habits, and finally a review of the literature on the associations between diet and asthma.

2.1. Tools to collect data on diet in nutritional epidemiology

The three most common methods used to collect data on diet are: the 24-hour dietary recall (24-hour recall), the diet record (DR) and the food-frequency questionnaire (FFQ). The 24-hour recall method is an in-depth interview conducted by a trained dietary interviewer. Subjects are asked to report all foods and beverages consumed in the past 24 hours, recalled from memory, which can be a source of error, especially for the quantification of portion sizes. The DR method includes a detailed listing of all food consumed on one or more days. Food intakes are recorded by the participant at the time the foods are eaten, to minimize reliance on memory. This method requires participants to be trained in methods keeping complete and accurate food record. In a FFQ, subjects report how frequently certain food and beverage items were consumed over a specific period of time (typically one year). Most FFQ versions ask questions on portion size of every food item, as well as general questions about common cooking practices (e.g. type of fat typically added while cooking). Nutrient intakes are then calculated by multiplying the reported frequency of each food by the amount of nutrient in a serving of that food, which are assessed using food composition tables (80,81).

The 24-hour recall and DR methods are based on foods and amounts actually consumed by an individual on one or more specific days, as opposed to the FFQ method, which allow to report usual intake over longer periods of time. Although the 24-hour recall and DR methods allow greater specificity and accuracy, they are short-term methods and thus, require an extensive effort to collect and process multiple days of food records or recalls in order to take into account seasonal or day-to-day variability. These methods are expensive, inappropriate for assessment of past diet, and imply important participant burden and thus, are hard to apply in epidemiological studies (82). On the other hand, the FFQ method allows minimizing error of day-to-day consumption but introduce errors of estimation and averaging over long time intervals. Reproducibility and validity of FFQs have largely been studied and overall, showing good reproducibility and validity (83).

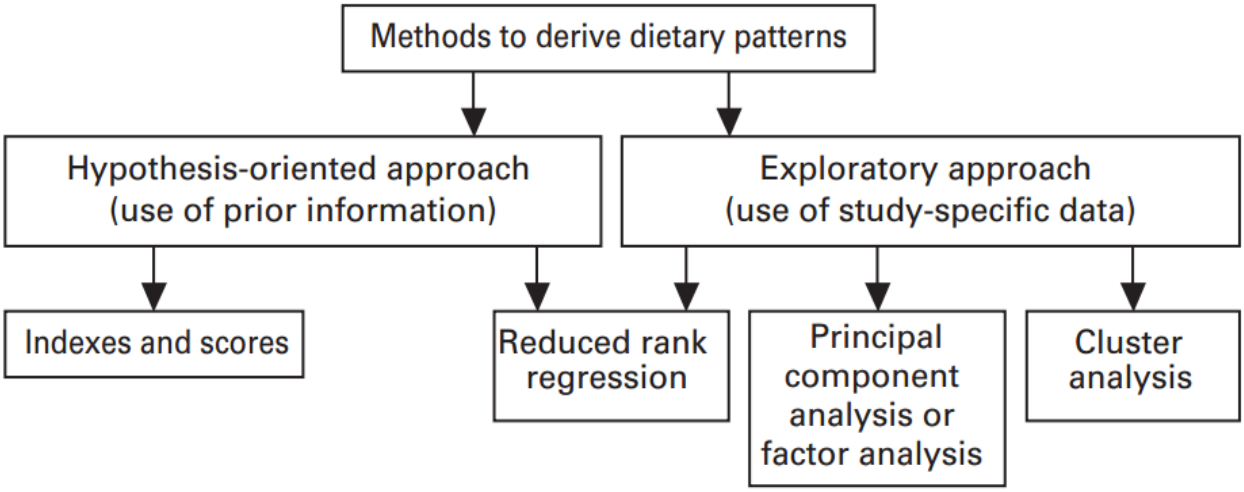
2.2. Assessment of dietary patterns in nutritional epidemiology

In nutritional epidemiology, studies on specific foods or nutrients have traditionally been conducted. However, several conceptual and methodological limitations have recently been raised (5). First, diet is a complex exposure variable: people do not consume isolated foods or nutrients, but rather meals consisting of a complex combination of foods, which themselves contain nutrients, which can interact with each other. Moreover, the high correlation between consumed foods and nutrients makes it difficult to disentangle their separate effects. Another problem, when investigating the simultaneous effects of different foods, is that statistically significant associations can more easily occur by chance, thus raising the need to take into account multiple testing. Lastly, estimation of nutrient intakes requires food composition databases, which need to be adapted to the cultural and social context of the study population. Moreover, cultural habits impact the diet composition and the way foods are consumed together, and thus, should be taken into account when assessing dietary habits in observational studies. For all these reasons, studying dietary patterns has been proposed to study the effects of overall diet, rather than the effects of specific foods or nutrients. Studying dietary patterns is particularly relevant when investigating the role of diet on diseases such as asthma, for which no specific food or nutrient has clearly been identified (4). Two general approaches have been used to define dietary patterns in observational studies. The first approach, called *a priori*, is based on prevailing hypotheses and guidance about the role of nutrients in disease prevention, whereas the second approach, called *a posteriori* is data driven. Other more recent methods that lie between those two approaches (i.e. using both available dietary data of the study and prior knowledge), have also been proposed (see Figure 1).

Whereas studying specific foods or nutrients is more relevant in terms of etiological aspects (as it enables to study the mechanisms of how food may affect asthma), studying dietary patterns is more relevant in terms of public health implications. In particular, *a priori* scores, which are based on international nutritional recommendations, enable to assess the impact of these recommendations on population's health.

The next section presents the three approaches that can be used to derive dietary patterns: the *a priori* approach, the *a posteriori* approach and the methods "in between".

Figure 1. Approaches to define dietary patterns in observational studies (reproduced from Schulze *et al. Br J Nutr* 2006 (84))



2.2.1. The *a priori* approach

The *a priori* approach allows the calculation of a score that describes an ideal diet with a disease-specific focus, based on previous knowledge about the role of nutrients in disease prevention. Several *a priori* dietary indexes have been proposed either a) based on recommended foods and nutrients, or b) based on biological properties.

2.2.1.1. Dietary patterns based on healthy foods and nutrients

The most used dietary scores are presented below. As they are based on the intake of "healthy foods/nutrients" or on the avoidance of "unhealthy foods/nutrients", they evolve over time to account for new knowledge in nutritional epidemiology.

The Mediterranean diet score

The most frequently used is the Mediterranean diet score, which was originally developed by Trichopoulou *et al*. in the Greek population in 1995 (85), in order to evaluate the hypothesis that the traditional Mediterranean diet has beneficial effects on health and survival (85,86). The Mediterranean diet score was based on 8 components characteristics: high monounsaturated:saturated fat ratio, moderate ethanol consumption, high consumption of legumes, high consumption of cereals (including bread and potatoes), high consumption of fruits and nuts, high consumption of vegetables, low consumption of meat and meat products, and low consumption of milk and dairy products. A value of one or zero point was assigned to each component, using the gender–specific median of study subjects as cut-off value. Thus, the score ranged from 0 to 8 (see Table 1). The score was modified several times in order to take into account new knowledge in nutritional epidemiology. It was modified first by including high consumption of fish as a component (87), and then by excluding the dairy products component, by taking into account only whole-grain cereals in the cereals component and only red and processed meats in the meat/meat products component, and by considering high consumption of nuts as a component, leading to an alternate Mediterranean diet (aMED) index that ranged from 0 to 9 (88). The Mediterranean diet score was also modified by removing the alcohol component and by presuming dairy products to be a protective component, in order to be adapted to pregnant women (89); and a KIDMED Index (Mediterranean Diet Quality Index in children and adolescents) was derived to be applied among children (90) (see Table 1).

One limitation to the Mediterranean diet score comes from the fact that this score has been developed in Mediterranean countries and thus may not be adapted to non-Mediterranean countries, which do not consume the same foods. Even if the scoring is based on population-specific median values, non-Mediterranean people with a high Mediterranean score may have a lower consumption of Mediterranean foods than Mediterranean people with a low Mediterranean score.

Table 1. Components of the Mediterranean diet score, alternate Mediterranean diet score, Mediterranean diet score during pregnancy and KIDMED score, and scoring criteria

Component	**Med Score*** **(+1 point)** (85)	**aMED index*** **(+1 point)** (88)	**Med Score Pregnancy*** **(+1 point)** (89)	**KIDMED Index**† (90)
Vegetables (servings/day)	≥ median	≥ median	≥ median	+1: regularly once a day +1: more than once a day
Legumes (servings/day)	≥ median	≥ median	≥ median	+1: pulses more than once a week
Fruits and nuts (servings/day)	≥ median	-	≥ median	-
Fruits (servings/day)	-	≥ median	-	+1: fruit or fruit juice every day +1: second fruit every day
Nuts (servings/day)	-	≥ median	-	+1: regularly (≥ 2-3 times/week)
Cereals (servings/day)	≥ median	-	≥ median	+1: cereals or grains for breakfast
Whole grains (servings/day)	-	≥ median	-	-
Meat/meat products (servings/day)	≤ median	-	≤ median	-
Red/processed meats (servings/day)	-	≤ median	-	-
Fish (servings/day)	-	≥ median	≥ median	+1: regularly (≥ 2-3 times/week)
Monounsaturated to saturated fat ratio (servings/day)	≥ median	≥ median	-	-
Ethanol (g/day)	Men: 10-50 g/day Women: 5-25 g/day	5–15 g/day	-	-
Milk and dairy products (servings/day)	≤ median	-	≥ median	+1: one dairy product for breakfast +1: 2 yoghurts and/or some cheese daily
Pasta or rice (servings/day)	-	-	-	+1: almost every day (≥ 5 times/week)
Baked goods and pastries	-	-	-	-1: commercially baked goods or pastries for breakfast
Sweets and candy	-	-	-	-1: several times per day
Fast-food consumption	-	-	-	-1: more than once a week
Skipping breakfast	-	-	-	-1
Olive oil at home	-	-	-	+1

Med Score: Mediterranean diet score, aMED index: alternate Mediterranean diet index, Med Score Pregnancy: Mediterranean diet score during pregnancy; KIDMED Index: Mediterranean diet quality index in children and adolescents

* 1 point if criterion met; 0 point otherwise

† 0 point if criterion not met

The Healthy Eating Index

The Healthy Eating Index (HEI) was proposed in 1995 by the US Department of Agriculture (USDA) to provide dietary guidelines in order to decrease the prevalence of major chronic diseases (91). It was based on the consumption of 10 components: grains, vegetables, fruits, milk, meat, overall fat, saturated fat, cholesterol, sodium and the amount of variety in diet. Each component ranged from 0 (worst) to 10 (best), according to recommended intakes. All the component scores were summed in order to obtain a total score that ranged from 0 to 100, with a higher score representing a healthier diet. However, the HEI was only associated with a modest reduction in risk of major chronic diseases, and was criticized for not distinguishing between whole grains and highly refined starches, between red meat and fish, or between all types of fat (92,93). Following the publication of the dietary guidelines that are issued every 5 years by the US Department of Agriculture, the HEI has been updated twice: first in 2005 and second in 2010. The HEI-2005 (94) and HEI-2010 (95) were based on 12 components that were energy-adjusted on a density basis (per 1,000 kilocalories per day) in order to characterize diet quality while controlling for diet quantity and address the problem of consumption of energy-dense and nutrient poor foods.

The Alternate Healthy Eating Index

To overcome the issues of the HEI, an Alternate Healthy Eating Index (AHEI) was proposed in 2002 (96), based on 9 components: vegetables, fruits, nuts and soy, the ratio of white (seafood and poultry) to red meat, cereal fiber, *trans* fatty acid, the ratio of polyunsaturated fatty acids (PUFAs) to saturated fatty acids, long-term multivitamin use, and alcohol consumption. Each component ranged from 0 (worst) to 10 (best), according to criteria for minimum and maximum scores that are presented in Table 2. Intermediate intakes were scored proportionately between 0 and 10 and all the component scores were summed in order to obtain a total score. It was further updated in 2010, in order to take into account more recent dietary guidelines, which for example, advise against a high consumption of soda and other sugar-sweetened beverages (97). Thus, the AHEI-2010 was based on 11 component characteristics: high consumption of vegetables, high consumption of fruits, high consumption of whole grains, low consumption of sugar-sweetened beverages and fruit juice, high consumption of nuts and legumes, low consumption of red and processed meats, low consumption of *trans* fatty acid, high consumption of long-chain (n-3) fatty acids : EPA

(eicosapentaenoic acid) and DHA (docosahexaenoic acid), high consumption of PUFAs (intakes of EPA and DHA not included), low consumption of sodium, and moderate consumption of alcohol. All the component scores were summed in order to obtain a total score that ranged from 0 to 110 (see Table 2). The AHEI also has been adapted to pregnancy (AHEI-P), by removing the alcohol, long-term multivitamin use, and nuts and soy components, and by including three new components that reflect intake of nutrients particularly important during pregnancy: folate, iron, and calcium (98) (see Table 2).

When the association between the AHEI-2010 and the HEI-2005 and risk of major chronic diseases were assessed, the AHEI-2010 was found to be more strongly associated with a lower risk of chronic disease than the HEI-2005, and more particularly coronary heart disease and diabetes (97).

Table 2. Components of the AHEI, AHEI-2010 and AHEI-P and scoring criteria

Component	**AHEI** (96)		**AHEI-2010** (97)		**AHEI-P** (98)	
	Minimum score (0)	**Maximum score (10)**	**Minimum score (0)**	**Maximum score (10)**	**Minimum score (0)**	**Maximum score (10)**
Vegetables (servings/day)	0	≥ 5	0	≥ 5	0	≥ 5
Fruit (servings/day)	0	≥ 4	0	≥ 4	0	≥ 4
Cereal fiber (g/day)	0	≥ 15	-	-	0	≥ 25
Whole grains (g/day)						
Men	-	-	0	90	-	-
Women			0	75		
Sugar-sweetened beverages and fruit juice (servings/day)	-	-	≥ 1	0	-	-
Nuts and soy (servings/day)	0	≥ 1	-	-	-	-
Nuts and legumes (servings/day)	-	-	0	≥ 1	-	-
Ratio of white to red meat	0	≥ 4	-	-	0	≥ 4
Red and processed meat (servings/day)	-	-	≥ 1.5	0	-	-
***trans* fat** (% of energy)	≥ 4	≤ 0.5	≥ 4	≤ 0.5	≥ 4	≤ 0.5
Ratio of polyunsaturated to saturated fat	≤ 0.1	≥ 1	-	-	≤ 0.1	≥ 1
Long-chain (n-3) fats (EPA+DHA) (mg/day)	-	-	0	250	-	-
PUFA* (% of energy)	-	-	≤ 2	≥ 10	-	-
Duration of multivitamin use	< 5 years†	≥ 5 years†	-	-	-	-
Sodium (mg/day)	-	-	Highest decile	Lowest decile	-	-
Alcohol (servings/day)						
Men	0 or > 3.5	1.5 – 2.5	≥ 3.5	0.5 – 2.0	-	-
Women	0 or > 2.5	0.5 – 1.5	≥ 2.5	0.5 – 1.5		
Calcium (mg/day)	-	-	-	-	0	≥ 1,200
Folate (µg/day)	-	-	-	-	0	≥ 600
Iron (mg/day)	-	-	-	-	0	≥ 27
Total score	**2.5**	**87.5**	**0**	**110**	**0**	**90**

*PUFA: Polyunsaturated fatty acids

†Minimum score: 2.5; Maximum score: 7.5

The Programme National Nutrition Santé-Guideline Score

In France, the Programme National Nutrition Santé-Guideline Score (PNNS-GS) has been proposed to reflect adherence to French nutritional recommendations (99). It included 13 components: 8 referred to food-serving recommendations (fruit and vegetables; bread, cereal, potatoes, and legumes; milk and dairy products; meat, poultry, seafood, and eggs; and nonalcoholic beverages and alcohol intake), 4 referred to moderation in consumption (added fats, added fat ratio, added sugars from sweetened foods, and salt) and one referring to physical activity recommendations on a daily basis. Scoring and cut-off values were decided using information provided by the National Program on Nutrition and Health, themselves based on epidemiologic and clinical evidence (see Table 3). Points were deducted for overconsumption of salt and sweets and when energy intake exceeded the needed energy level by more than 5%. The PNNS-GS has been found to be inversely associated with obesity risk and weight gain, especially in men, in the French SU.VI.MAX (SUpplémentation en VItamines et Minéraux AntioXydants) study (100).

Other indexes

Other indexes have been proposed as well, such as the Diet Quality Index Revised (DQI-R) (101) or the Recommended Food Score (RFS) (102), which were based on the same dietary guidelines as the HEI (i.e. dietary guidelines issued by the USDA). Compared to the HEI, the DQI-R did not include meat or milk intakes, but included iron and calcium intakes (101), whereas the RFS only focused on the weekly use of fruits, vegetables, whole grains, lean meats or meat alternates, and low-fat dairy products. Many other scores that we will not further discuss, have been proposed as well, such as the Diet Quality Index (DQI), the Healthy Diet Indicator (HDI), the Mediterranean Diet Quality Index (MDQI), the Food-Based Quality Index (FBQI), the Healthy Food Index (HFI), the Food Pyramid Index (FPI), the Nutrient Adequacy Ratio (NAR/MAR), the Dietary Variety Score (DVS), the Food Variety Score (FVS), the Diet Diversity Score (DDS), the Dietary Guidelines Index (DGI), the Not Recommended Foods Score (NRFS), the Food Guide Pyramid (FGP) patterns, the Dietary Approaches to Stop Hypertension (DASH) diet (103,104), and more recently, the Nordic Food Index (105).

Table 3. Components of the PNNS-GS and scoring criteria

Nutrient	Recommendation	Scoring criteria	Score
Fruits and vegetables	At least 5/d	[0-3.5[	0
		[3.5-5[	0.5
		[5-7.5[	1
		≥7.5	2
Bread, cereals, potatoes, and legumes	At each meal according to appetite	[0-1[	0
		[1-3[	0.5
		[3-6[	1
		≥6	0.5
Whole-grain food	Choose whole grains and whole-grain breads more often	[0-1/3[	0
		[1/3-2/3[	0.5
		≥2/3	1
Milk and dairy products (eg, yogurt, cheese)	3/day (≥55 years-old: 3 to 4/day)	[0-1[	0
		[1-2.5[	0.5
		[2.5-3.5] (≥55 years-old: [2.5-4.5])	1
		>3.5 (≥55 years-old: >4.5)	0.5
Meat and poultry, seafood, and eggs	1 to 2/day	0	0
		]0-1[	0.5
		[1-2]	1
		>2	0
Seafood	At least twice/week	<2 servings/wk	0
		≥2 servings/wk	1
Added fats	Limit consumption	Lipids from added fats >16% total energy intake/day	0
		Lipids from added fats ≤16% total energy intake/day	1
Vegetable added fats	Favor fats of vegetable origin	No use of vegetable oil or ratio vegetable oil/total added fats ≤0.5	0
		No use of added fats or ratio vegetable oil/total added fats >0.5	1
Sweetened foods	Limit consumption	Added sugars from sweetened foods ≥15% EI/d	−0.5
		Added sugars from sweetened foods 10%-15% EI/d	0
		Added sugars from sweetened foods <10% EI/d	1
Beverages			
Water and soda	Drink water as desired Limit sweetened beverages: no more than one glass/d	<1 L water and >250 mL soda/d	0
		≥1 L water and >250 mL soda/d	0.50
		<1 L water and ≤250 mL soda/d	0.75
		≥1 L water and ≤250 mL soda/d	1
Alcohol	Women advised to drink ≥2 glasses of wine/day and ≥3 glasses/day for men	Ethanol >20 g/d for women and >30 g for men	0
		Ethanol ≤20 g/d for women and ≤30 g for men	0.8
		Abstainers and irregular consumers (< once a week)	1
Salt	Limit consumption	>12 g/d	−0.5
		]10-12] g/d	0
		]8-10] g/d	0.5
		]6-8] g/d	1
		≤6 g/d	1.5
Physical activity	At least the equivalent of 30 min of brisk walking/day	[0-30[min/day	0
		[30-60[min/day	1
		≥60 min/day	1.5

2.2.1.2. Based on biological properties

Besides dietary scores based on the intake of "healthy foods/nutrients", other scores have been proposed to assess the biological properties of diet. Therefore, scores have been developed to estimate a diet rich in antioxidants, or a diet with anti-inflammatory properties. Two of these scores are presented below.

The Dietary Total Antioxidant Capacity

Studies that investigated the effects of antioxidants on health outcomes have generally analyzed the effect of one single antioxidant independently of others. The dietary total antioxidant capacity (TAC) may be a suitable approach to measure their joint effects (106). TAC is a concept describing an antioxidant's capacity for reducing oxidants while taking into account the synergism between compounds (107). TAC considers the cumulative action of all the antioxidants present in the matrix (plasma, saliva, food extracts, tissues, etc.), giving an insight into the assessment of the non-enzymatic antioxidant network. TAC can be applied to both foods and biological systems, and is defined as the moles of radicals neutralized per liter (or gram) of tested sample. The use of TAC has been proposed in epidemiological studies as a tool to assess the total antioxidant capacity of diet (107). Dietary TAC can be assessed using food frequency questionnaires or food records by summarizing known TAC values of different food items. TAC food databases have been constructed by using four specific assays to quantify TAC in foods: the ferric reducing antioxidant power (FRAP) (108,109), the Trolox equivalent antioxidant capacity (TEAC) (106,110), the total radical-trapping antioxidant parameter (TRAP) (106,110), and the oxygen radical absorbance capacity (ORAC) (111). An overall dietary TAC score can then be assessed by multiplying the TAC value of each food/beverage by their reported intake and then, by summing these values. The most important contributors to TAC are fruits (especially berries), vegetables, nuts, legumes, cereals, coffee, tea, chocolate, red wine, fruit juice, spices and herbs (106,108–111). However, caution is needed when assessing TAC values given that each antioxidant assay has a different mechanism, redox potential, reaction media, etc. Thus, it has been recommended to use at least two different methods (preferably with different mechanisms) to assess TAC values (112). Moreover, given that TAC is an *in vitro* parameter, it may not necessarily reflect antioxidant level *in vivo* (112). Nevertheless, the estimation of dietary TAC from FFQs has been showed to be valid and reproducible in northern (113) and southern European countries (114).

The Dietary Inflammatory Index

The Dietary Inflammatory Index (DII) has been developed by Cavicchia *et al.* (115) to provide an overall score for the inflammatory potential of individuals' diets. The DII is based on the results of an extensive literature search incorporating cell culture, animal, and epidemiologic studies on the effect of specific foods and constituents on specific inflammatory markers, published through 2007. A score was assigned to each food and constituent dependent on the number of articles found, the study type and design of each article, and the findings of articles (i.e. a positive score was assigned for anti-inflammatory effects and a negative score was assigned for pro-inflammatory effects). An overall DII score was then assessed by multiplying the DII score of each food/ constituent by their reported intake and then, by summing these values. Thus, the DII categorized individuals' diets on a continuum from maximally anti-inflammatory (highest score) to maximally pro-inflammatory (lowest score). The DII included 32 nutrients, but also commonly consumed components of the diet including flavonoids, spices, and tea (see Table 4). The DII was also validated against the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) (115).

An adapted dietary inflammatory index (ADII) has recently been developed (116), excluding several components to avoid an overestimation of inflammatory effects of ethanol, fat, and energy. Thus, beer, wine, liquor and total fat were excluded. Energy was excluded because the inflammatory effect of energy was considered to be equivalent to the sum of the inflammatory effects of all energy-providing macronutrients. Finally, some flavonoids and spices which were not available, were excluded. On the other hand, the ADII included *trans* fatty acids. All dietary components intakes were adjusted for energy intake by using the residual method to reduce the between-person variation in dietary intake (117), and thus allowing use of the ADII as a measure of diet quality. To equilibrate the intake of all nutrients to the same unit and avoid the variation in the ADII being driven by a few dietary components with a large range in intake, each component intake was standardized. Unlike the DII, the ADII categorized individuals' diets on a continuum from maximally pro-inflammatory (highest score) to maximally anti-inflammatory (lowest score). The ADII was found to be more strongly associated with markers of inflammation than the DII (116).

Meanwhile, the DII has been updated, by including peer-reviewed journal articles published from 2007 to 2010 in the literature search, and refining the scoring algorithm to relate individuals' food intakes to a reasonable set of global norms (standardized intakes), using a world composite database based on food consumption data sets from eleven countries (118). In comparison with the former DII, the new DII further included several components

such as *trans* fatty acids, pepper, thyme/oregano, rosemary, onion and eugenol. The new scoring categorized individuals' diets on a continuum from maximally pro-inflammatory (highest score) to maximally anti-inflammatory (lowest score).

Table 4. Foods and constituents included in the Dietary Inflammatory Index (115)

Constituent	Adjusted score	Measure
Energy	−0.0549	kJ/d
Energy*	−0.23	kcal/d
Garlic	0.27	g/d
Ginger	0.18	g/d
Saffron	0.18	g/d
Turmeric	0.774	g/d
Tea	0.552	g/d
Caffeine	0.035	g/d
Wine	0.48	g/d
Beer	0.2	g/d
Liquor	0.1	g/d
Alcohol	0.534	g/d
Carbohydrate	−0.346	g/d
Fiber	0.52	g/d
Fat	−0.323	g/d
(n-3) Fatty acids	0.384	g/d x 10
(n-6) Fatty acids	−0.016	g/d x 10
MUFA	−0.05	g/d
Saturated fat	−0.25	g/d
Protein	0.05	g/d
Cholesterol	−0.21	mg/d
Vitamin A	0.58	μg/d ÷100
Thiamin	0.05	mg/d
Riboflavin	0.16	mg/d
Niacin	0.26	mg/d
Vitamin B-6	0.286	mg/d
Folic Acid	0.214	μg/d
Vitamin B-12	−0.09	μg/d
Vitamin C	0.367	mg/d
Vitamin D	0.342	μg/d
Vitamin E	0.401	mg/d
***β*-carotene**	0.725	μg/d ÷ 100
Magnesium	0.905	mg/d
Zinc	0.316	mg/d
Iron	0.029	mg/d
Selenium	0.021	mg/d
Quercetin	0.49	mg/d
Luteolin	0.43	mg/d
Genistein	0.68	mg/d
Daidzein	0.17	mg/d
Cyanidin	0.13	mg/d
Epicatechin	0.12	mg/d

* The score was computed based on metric units (i.e., kcal/d).

2.2.2. The *a posteriori* approach

The *a posteriori* approach is data driven, with dietary patterns statistically derived independently of their relevance to any disease. This approach allows consideration of how foods and nutrients are consumed in combinations. Among several exploratory methods, cluster analysis and principal component analysis (PCA) are the most frequently used methods to derive *a posteriori* dietary patterns (119).

2.2.2.1. Cluster analysis

Cluster analysis is a subject oriented method, where individuals with similar dietary habits are grouped together into mutually exclusive classes. Cluster analysis is based on distance measures between observations of individuals. The objective of cluster analysis is to minimize intra-cluster variance, while maximizing inter-cluster variance. Initial cluster seeds are followed by repeated comparisons between the means of initial clusters and subsequent updates of cluster groupings and means. Subjects are moved between clusters and new means are computed until the distances between the observations within clusters are small enough compared with the distances between cluster means (84).

2.2.2.2 Principal component analysis (PCA)

The method

PCA is an “exploratory method”, oriented to variables with the aim of reducing the number of explanatory variables (i.e., food items). PCA aggregates food items or food groups on the basis of the degree to which they are correlated with one another. The goal is to identify linear composites of food items or food groups that account for the largest amount of variation in diet between individuals. A score is thus calculated for each dietary pattern, representing a linear combination of the observed variables. The patterns identified are usually rotated by an orthogonal transformation to achieve simple structure with greater interpretability (84).

Limitations

In a recent simulation study, Bakolis *et al.* questioned the widespread use of PCA in nutritional epidemiology, explaining that, since the aim of PCA is to summarize the overall dietary intake variation in the population, regardless of disease variation, it is not an appropriate statistical approach to identify associations between diet and a health outcome (7). One frequent criticism regarding the use of PCA is the low proportion of variance that is usually explained. Other limitations have been raised, related to the fact that the use of PCA implies making many arbitrary decisions that may largely influence findings when studying dietary patterns in associations with a health outcome. Indeed, applying PCA implies a decision on which food items to combine into food groups, the number of factors to extract, the method of rotation, or the labeling of the derived factors (5,120).

The labeling of the factors is an important issue that deserves further consideration. Labeling factors is arbitrary and is based on an investigator's interpretation, which can be misleading. Food patterns with different labels can be very similar: "Prudent-like" patterns are also labeled "Healthy" or "Mediterranean" for instance. Conversely, patterns that have the same labels are not always similar (119). Whereas there is a consistency across worldwide studies to identify a "Prudent" and a "Western" pattern, these patterns were originally identified in U.S. populations and thus, reflect more specifically an American dietary behavior. In a UK study for instance, the pattern labeled "Prudent" had very low contributions for fruits and was distinguished, among others, from a pattern labeled "Vegetable and fruit" (121). The "Drinker" pattern, on the other hand, was mostly identified in European and South American populations (122,123).

Furthermore, dietary behaviors are specific to the cultural and social context of each country. A meta-analysis on dietary patterns and asthma, performed in five centres from three European countries, found conflicting results because of cultural heterogeneity between countries (124). When identifying dietary patterns, foods are grouped according to cultural dietary habits. Several patterns labeled "Traditional" and characterized by high consumptions of both "Prudent"-like foods (vegetables) and "Western"-like foods (processed meat, red meat, rice), have been identified in European (121) and Asian studies (125). A study describing the dietary patterns of ten European countries found differences in terms of dietary behaviors, as well as socio-demographic determinants, between North and South European countries (126). Dietary habits depend on social aspects as well: the same foods are not consumed according to the socioeconomic level. Therefore, caution is needed when labeling the dietary patterns, especially for the interpretation of the associations found with a health

outcome, which may vary between countries (cultural context) and between people (social context).

2.2.3. Methods in between

Recently, other methods that lie between the *a priori* and *a posteriori* approaches have been proposed, either defining dietary patterns as a latent variable or not.

2.2.3.1 Alternative methods to PCA without latent variables

Other exploratory methods have been proposed as alternatives to PCA to derive dietary patterns, such as reduced rank regression (RRR) and partial least-squares regression (PLS) (127,128). Like PCA, RRR and PLS identify dietary patterns by determining linear combinations of the predictors (i.e., food items). RRR allows a choice of disease-specific response variables, such as biomarkers or key nutrients, thus allowing knowledge about hypothesized biological pathways to be taken into account. Whereas the goal of PCA is to explain as much predictor variation as possible, the goal of RRR is to explain as much response variation as possible. The PLS method is a compromise between PCA and RRR, and balances the two goals of explaining variability in selected biomarkers or key nutrients, as well as explaining variability in food items. The treelet transform (TT) method, which combines the quantitative pattern extraction capabilities of PCA with the interpretational advantages of cluster analysis, has also been proposed (129). TT works in the same manner as PCA, with the difference that each factor only involves naturally grouped subsets of the original variables (i.e., food items).

2.2.3.2 Alternative methods to PCA with latent variables

Structural equation modeling (SEM) has been widely used in social and psychiatric areas to specify latent variables associated with psychological measurements (observed variables) (130). According to the type of observed and latent variables (qualitative or quantitative), different statistical methods have been proposed: latent classes (observed and latent variables both qualitative), latent profiles (observed quantitative variable and latent qualitative variable), latent traits (observed qualitative variable and latent quantitative variable), and confirmatory factor analysis (CFA, observed and latent variables both

qualitative). Even if structural equation modeling is intuitively appealing, because it is based on theory and also reduces some of the subjectivity involved in the exploratory procedures, very few studies have used CFA in nutritional epidemiology.

In 2002, an international workshop on dietary patterns proposed the alternative use of SEM, which allows specification and testing of a latent variable model where latent variables are dietary patterns and measures are food group intakes, assessed via their variance-covariance matrix (131). SEM allows to take into account previous knowledge and hypothesize the number of factors to retain, whether or not these factors are correlated, and which food groups load onto and reflect which factors. In contrast to exploratory methods, SEM allows specification of a model in which some loadings are equal to zero.

Usually, SEM models are used as a secondary step to examine the robustness and goodness-of-fit of the factor structures identified through a first step using exploratory methods (usually PCA) (132–135) or *a priori* hypotheses from the literature (136,137). In a Danish study (134), two dietary patterns were derived using PCA in a sub-sample of the population. In order to assess the reproducibility of these dietary patterns, CFA was applied in another sub-sample, but only using the food groups that obtained high loadings (i.e. $\geq$0.40) when PCA was derived. Loadings obtained using CFA were found to be very similar to those obtained using PCA (134). In a Swedish study (135), PCA was first conducted, defining six dietary patterns. CFA was then conducted to confirm patterns that had $\geq$4 items with factor loadings $\geq |0.20|$; thus, 4 of 6 patterns were confirmed. The authors also concluded that the benefit from CFA over exploratory factor analysis in dietary studies was not yet clear (135). The terminology of CFA (i.e., confirmatory) is misleading because CFA has mainly been used as a secondary step to "confirm" dietary patterns derived using PCA or derived using *a priori* hypotheses from the literature.

To our knowledge, six studies have used latent classes analysis (LCA) to derive dietary patterns, without performing exploratory methods first (i.e., as a one-step approach) (138–143). Up to now, only one study used CFA as a one-step approach, in the same context as PCA, i.e., by specifying that latent variables might depend on all the available food groups, thus defining a model in which a parameter is estimated for each food group, for each pattern. This study showed that patterns derived using CFA were more statistically meaningful in terms of relevance and more stable in terms of statistical properties than dietary patterns derived using PCA (6).

2.3. The association between diet and asthma

The role of diet has been recently proposed in asthma. First, the different hypotheses and mechanisms proposed are reviewed, and then, a detailed review of the literature regarding the association between diet and asthma is presented.

2.3.1. Hypotheses and mechanisms

In this section, the different hypothesis and mechanisms to explain the role of diet in asthma are reviewed. First, the hypothesis of oxidative stress through dietary antioxidant intake is presented, then the hypothesis of inflammation through dietary PUFAs intake. More recently proposed hypotheses are then presented, first regarding vitamin D intake, and then regarding epigenetic mechanisms, through methyl donor nutrients.

Dietary antioxidant intake

Normally, the lung exists in an oxygen-rich environment balanced between the toxicity of oxidants (generated through normal cellular function or exposure to pro-oxidants) and the protective activities of several intracellular and extracellular antioxidant defense systems. A tight control of redox balance is critically important for the maintenance of normal pulmonary cellular function (144). Disequilibrium, either through an increase in oxidant stress or a compromise of antioxidant resources, can initiate a series of pathophysiologic events in the lung that culminates in cellular death and pulmonary dysfunction (145). A shift of the oxidant/antioxidant balance in favor of oxidants has been termed "oxidative stress". Researchers have hypothesized that a diet low in antioxidants such as beta-carotene and vitamins C and E may reduce natural defenses and increase susceptibility to oxidant attack and airway inflammation (146).

On the other hand, it has been suggested that an “antioxidative stress” (i.e. an excess of antioxidants) might increase susceptibility to allergic disease and asthma as well. In case of oxidative stress, T_H1-type immune response dominates, whereas in case of antioxidative stress, the T_H1-type immune response is down regulated and T_H2-type immune response dominates, thereby promoting the T_H2-type cells and IgE production. This mechanism extends the ‘‘hygiene hypothesis’’ which favours the view that a lack of exposure to infections, endotoxins and dirt in childhood, which are triggers for T_H1-type immune

response, would result in a persistence of T_H2-type immune response (147). Some researchers have thus suggested that the recent increase in the prevalence of asthma in westernized countries could be a consequence of increased availability of processed and antioxidant enriched foods, causing antioxidant stress. However, this hypothesis is primarily based on *in vitro* immunological observations and on the fact that the UK National Diet and Nutrition Survey observed an increase in the intake of some antioxidant-rich foods, such as fruit juice, over the last decades in the United Kingdom (148).

The alternate hypothesis, which has been more commonly proposed, is that changes in dietary habits, methods of cultivation, increased transportation and storage and processing of foods led to declining antioxidant intake, causing oxidative stress and contributing to asthma development. This hypothesis is supported by several studies that observed that the intake of vitamin E and selenium has decreased over the last decades in the United Kingdom (148). A case-control study showed a decrease in activities of SOD, catalase, glutathione peroxidase (GPx), and serum TAC levels in plasma in asthma patients (149). Serum TAC levels were inversely associated with asthma severity and positively correlated with FEV_1 in asthmatic patients. Another study among asthma patients showed a positive association between serum TAC levels in plasma and lung function (150).

Dietary polyunsaturated fatty acid intakes

The emerging role of chronic inflammation in the major chronic diseases of westernized countries, including cardiovascular disease, type 2 diabetes mellitus, Alzheimer's disease and many types of cancer, has stimulated research into the influence of nutrition and dietary patterns on inflammatory indexes (151). Asthma is a chronic inflammatory disease and thus, inflammation has also been suggested as a possible underlying mechanism to explain the possible effects of diet on asthma (152). It has been hypothesized that the increased intake of n-6 PUFAs (present in spread oils and oils sourced from vegetables) and the decreased intake of n-3 PUFAs (present in oily fish such as salmon and mackerel) in Westernized countries have strongly contributed to the rise in asthma prevalence. Linoleic acid (a polyunsaturated n-6 fatty acid) is in the production pathway of several prostanoids and leukotrienes active in bronchoconstriction and neutrophil chemotaxis (153). By contrast, n-3 PUFAs compete with arachidonic acid (a polyunsaturated n-6 fatty acid) to form less active metabolites, and may thereby reduce airway inflammation and bronchoconstriction (153).

The Mediterranean diet, which includes most of these components, may therefore best fulfill requirements for an anti-inflammatory diet (151). A cross-sectional study conducted in 2005 compared several *a priori* dietary scores in relation to several markers of inflammation, and found that the AHEI and aMed scores were associated with significantly lower concentrations of most biomarkers, whereas the RFS, HEI and DQI-R were not significantly associated with most of the biomarkers (88). The DII, which includes more anti-inflammatory foods than the Mediterranean diet, and has been proposed more recently, may be a more relevant measure of an "anti-inflammatory diet" (115).

Vitamin D

Vitamin D intake represents a combination of dietary intake of vitamin D (eg, fortified milk) and vitamin D synthesized in the skin upon exposure to UVB radiation from sunlight. This unique situation has perhaps hindered research on the relation of overall vitamin D intake to risk of chronic disease. There are several emerging mechanisms by which vitamin D may affect asthma, including 1) vitamin D effects on airway smooth muscle modulation of gene expression and chemokine secretion, leading to decreased alveolar smooth muscle proliferation and decreased airway inflammation, two effects that might prevent airway obstruction; 2) vitamin D–mediated reversal of steroid resistance; and 3) improved handling of respiratory infections, leading to decreased asthma exacerbation (154).

Epigenetic mechanisms

Other mechanisms have also been proposed more recently, such as DNA methylation, which is a type of epigenetic regulation and represents a mechanism underlying some gene–environment interactions on complex diseases such as asthma (155). More particularly, it has been proposed that changes in DNA methylation can affect the pathogenesis of asthma by increasing or decreasing the expression of disease-susceptibility genes. Folate, choline, betaine and vitamins B12, B6 and B2 are nutrients acting as methyl donors (156,157).

Whereas very few studies have been conducted on this topic, the role of the microbiome in health is currently gaining wider recognition. The intestinal microbiome has been shown to be actively involved in the production and metabolism of these B vitamins and other methyl donors nutrients and thus, future studies on diet and asthma will need to account for the effects of the microbiome (157).

2.3.2. State of the art on diet and asthma

Asthma is a heterogeneous disease over time, with phenotypic variability according to age of onset (2). Dietary habits evolve throughout life and may thus influence health in different ways and by different mechanisms, according to the window of exposure. During pregnancy, maternal diet is very important for the offspring and has been related to the child's cognitive development (158), as well as many diseases later in life, such as obesity (159). Whereas maternal diet during pregnancy may have long-term effects on the offspring development and health, dietary habits during childhood and through adult-life, may also have shorter-term effects. Thus, windows of exposure may have an impact on the effects of diet on asthma.

In the next section, the literature on the associations between dietary habits and asthma is reviewed according to windows of exposure (maternal diet during pregnancy, diet during childhood and diet during adulthood), first with diet estimated through foods and nutrients, and then with diet estimated through dietary patterns.

2.3.2.1. Studies on specific foods or nutrients

Results are presented in Table 5, according to the different windows of exposure previously described, and according to the type of study (cross-sectional, longitudinal, or interventional studies).

Maternal diet during pregnancy

Regarding maternal diet during pregnancy, a small number of cohort studies have highlighted associations between childhood asthma and reduced maternal intake of vitamin E, zinc, fruits and vegetables, and PUFAs during pregnancy (4,160,161). Several intervention studies have investigated the potential for maternal omega-3 PUFA supplementation to prevent childhood asthma and overall, findings are inconclusive (161). Inconclusive findings were reported for maternal intake of selenium, and no association was reported for maternal intake of vitamins C and A (4,160,161). Regarding maternal intake of vitamin D, inconclusive findings were reported. In fact, two studies, conducted in Spain (162) and New Zealand (163), reported significant inverse associations between maternal intake of vitamin D and risk of respiratory infections in offspring's early childhood, but not with wheezing or asthma in offspring's childhood. The role of maternal intake of folate (through dietary intake or supplementation) has been investigated in several birth cohort studies. Overall, these studies

do not support the hypothesis of moderate or strong effects of folate on asthma. Regarding the role of other methyl donor nutrients, only one birth cohort study has assessed the role of maternal intake of vitamins B12, B6 and B2 during pregnancy, reporting no significant association (156,157).

Diet during childhood

Regarding the childhood period, the highest level of evidence comes from the beneficial intake of fruits and vegetables during childhood (4,160,161). Overall, the evidence for associations between asthma and specific nutrients is weak, but nonetheless suggestive in relation to vitamins A and E, zinc, vitamin D and PUFAs; no association was reported for vitamin C or selenium (4,160,161). However, there is a need for longitudinal studies and well-conducted RCTs to confirm these findings. One RCT has recently been published, assessing the effects of fruits, vegetables, fish oil and probiotics supplementation in asthmatic children, and reported beneficial effects of the supplementation on the use of short-acting inhaled bronchodilators and inhaled corticosteroids, and on pulmonary function (164). Regarding vitamin D, one RCT has been published using data from the Northern Finland Birth Cohort 1966 and reported that large-dose vitamin D supplementation in infancy was associated with an increased risk of atopy, allergic rhinitis, and asthma later in adulthood (165). The role of intake of folate (through dietary intake or supplementation) has been investigated in several observational studies among children. Overall, these studies do not support the hypothesis of moderate or strong effects of folate on asthma. Regarding the role of other methyl donor nutrients, only one RCT has assessed the role of vitamin B6 in asthmatic children, showing significant improvements in use of bronchodilators and cortisone (156,157).

Diet during adulthood

Among adults, observational studies (mostly cross-sectional), have reported associations between asthma and vitamin A, selenium, and fruits and vegetables, and inconclusive findings regarding intake of vitamin C, vitamin E and PUFAs. Overall, the body of observational evidence is inherently weak because of the biases and limitations of the cross-sectional and case–control studies that predominate. However, one recent longitudinal study with 20 years of follow-up, reported significant inverse associations between dietary

PUFAs intake and asthma incidence (166). Regarding vitamin D intake, few studies have been conducted in relation to asthma in adults. A cross-sectional study conducted in the 2005–2006 National Health and Nutrition Examination Survey (NHANES) reported a strong protective effect of vitamin D against wheeze and asthma exacerbations (167), whereas one longitudinal study did not report any association between serum levels of vitamin D and asthma incidence (168). Several RCTs have been conducted, but they do not support the use of vitamin C, vitamin E, selenium or PUFAs supplements to complement conventional therapy for asthma (4,161). The role of intake of folate (through dietary intake or supplementation) has been investigated in several observational studies among adults, reporting conflicting results. Regarding the role of other methyl donor nutrients, no improvement in lung function was reported in a RCT assessing the effects of choline supplementation in asthmatic adults, whereas beneficial effects on asthma severity were suggested in a RCT assessing the role of vitamin B6 supplementation in asthmatic adults. Regarding the role of vitamin B12, one cross-sectional study reported no association with asthma in adults (156,157).

Taken together, these findings underscore the importance of conducting prospective studies and clinical trials to understand better the role of antioxidants, n-3 PUFAs, vitamin D and methyl donor nutrients on asthma and wheeze in children and adults.

Table 5. Main findings regarding the associations between foods and nutrients with asthma or wheeze (adapted from Varraso *et al*. *Curr Allergy Asthma Rep* 2012 (4))

	Maternal diet during pregnancy		**Diet in childhood**			**Diet in adulthood**		
	Longitudinal	Intervention	Cross-sectional or case–control	Longitudinal	Intervention	Cross-sectional or case–control	Longitudinal	Intervention
Antioxidants								
Vitamin C	x	?	x	?	?	+	x	x
Vitamin E	+	?	+	?	?	+/–	+	x
Vitamin A	x	?	+	?	?	+	?	?
Selenium	+/–	?	x	?	?	+	?	x
Zinc	+	?	+	?	?	?	?	?
Fruits and Vegetables	+	?	++	?	?	++	++	?
PUFAs	+	+/–	+	?	x	+	+/-	+/–
Vitamin D	+/–	?	?	+	-	+	x	?
Methyl donor nutrients								
Folate	x	?	+/–	x	?	+/–	?	?
Choline	?	?	?	?	?	?	?	x
B12	x	?	?	?	?	x	?	?
B2	x	?	?	?	?	?	?	?
B6	x	?	?	?	+	?	?	+

?: no study, x: no association, +/–: inconclusive findings, +: suggestive beneficial effect, ++: conclusive beneficial effect, -: suggestive deleterious effect

2.3.2.2. Studies on *a priori* scores and *a posteriori* dietary patterns

Studies on foods and asthma showed conflicting results according to the age of asthma-onset (window of exposure) (4).

Maternal dietary patterns during pregnancy

The seven longitudinal studies conducted on associations between maternal diet during pregnancy and asthma in the offspring (4 studies using *a priori* methods and 3 studies using *a posteriori* methods) are summarized in Table 6 (89,169–173).

The four studies using *a priori* methods investigated the effects of a Mediterranean diet, using either a Mediterranean score or the aMed index adapted for pregnancy (89,169–171). Only one of these studies, which was conducted in Spain, reported a significant inverse association between the Mediterranean diet score during pregnancy and persistent wheeze (89). The study conducted in the United States have also assessed the AHEI-P, without reporting associations, either with recurrent wheeze, or with ever asthma (170).

Three studies used *a posteriori* methods to assess associations between maternal dietary patterns during pregnancy and asthma; all used PCA to derive dietary patterns. In the UK study, five dietary patterns were derived (i.e. 1) Health conscious, 2) Traditional, 3) Processed, 4) Vegetarian, 5) Confectionery). An inverse association between a "Vegetarian" pattern and later-onset asthma was reported (172). In the study conducted in the United States, two dietary patterns were derived (i.e. 1) Prudent, 2) Western), but no association was reported between any of the dietary patterns and recurrent wheeze, nor ever asthma (170). In the Japanese study, three dietary patterns were derived (i.e. 1) Healthy pattern, 2) Western pattern, 3) Japanese pattern). Unexpectedly, a significant inverse association was reported between the "Western" pattern and current wheeze. The authors explained it by the fact that the "Western" pattern was positively correlated with intake of α-linolenic acid, vitamin E, and β-carotene, and thus, may not be representative of an "unhealthy diet" (173).

Overall, the evidence is weak, but these studies favor no association between dietary pattern during pregnancy and asthma/wheeze in the offspring.

Table 6. Longitudinal studies on maternal dietary patterns during pregnancy and asthma in offspring

Reference	Population	Respiratory phenotype	Assessment of dietary patterns	Results	Comments
***A priori* score**					
Chatzi L *et al. Thorax* 2008 (89)	Menorca (Spain) 460 mother-infant pairs (6.5 years of follow-up)	- Persistent wheeze at age 6.5 (≥once/year) - Atopic wheeze (current wheeze and atopy) at age 6.5 - Atopy at age 6.5 (positive skin-prick test response)	Mediterranean diet score adapted to pregnant women	- Significant inverse associations between maternal diet during pregnancy and persistent wheeze (OR for high score (≥4): 0.22 [0.08 -0.58]), atopic wheeze (OR: 0.30 [0.10-0.90]) and atopy (OR: 0.55 [0.31-0.97])	
De Batlle J *et al. Allergy* 2008 (169)	Mexico 1,476 children (6-7 years-old)	- Asthma ever (doctor diagnosis of asthma, asthmatic bronchitis or reacting airways disease) - Wheezing ever - Current wheezing (last 12 months) (self-administered questionnaire)	Score similar to the original Mediterranean diet score (85), with the exclusion of ethanol, inclusion of fish, and of junk food and fat consumption instead of monounsaturated:saturated fat ratio (recalled diet)	No significant associations between mother's diet score during pregnancy and asthma outcomes at age of 6-7	- No adjustment for energy intake
Lange NE *et al. J Allergy Clin Immunol* 2010 (170)	United States (Project Viva) 1,376 mother-infant pairs (3 years of follow-up)	- Recurrent wheeze (≥once before the age of 2 and ≥once in the 3rd year) - Ever asthma at age of 3 (doctor diagnosis) (self-administered questionnaire)	1) aMED index (88) adapted for pregnancy (exclusion of ethanol, inclusion of dairy products as beneficial, and unsaturated instead of monounsaturated fats in the fat ratio), 2) AHEI-P (98)	No association between any of the two scores and recurrent wheeze, nor with ever asthma	- No adjustment for energy intake - No association with eczema, lower respiratory tract infections or atopy
Chatzi L *et al. Br J Nutr* 2013 (171)	Greece and Spain; meta-analysis 1771 mother–infant pairs from the Spanish INMA study and 745	- Ever wheezing in the first year of life (INMA), in the first 9 months of life (RHEA)	Score similar to the Mediterranean diet score during pregnancy (89), with the inclusion of the monounsaturated to saturated	No association between the Mediterranean score and wheeze (RR for score ≥6: 0·97 [0.77-1.24], p for heterogeneity = 0.44)	No association between the Mediterranean score and physician-diagnosed atopic eczema

	pairs from the Greek RHEA study		fat ratio		
***A posteriori* score**					
Shaheen SO *et al. Thorax* 2009 (172)	UK (ALSPAC study) 14,062 mother-infant pairs (7.5 years of follow-up)	- At age of 3.5: 1) current wheezing (last 12 months), 2) early wheezing phenotypes (non-, transient infant, later onset and persistent wheezers) - At age of 7.5: 1) current wheezing, 2) current doctor-diagnosed asthma (self-reported)	Dietary patterns derived using PCA: 1) Health conscious, 2) Traditional (vegetables, red meat, poultry) 3) Processed 4) Vegetarian 5) Confectionery (chocolate, sweets, biscuits, cakes, puddings)	- Borderline significant inverse association between the "Vegetarian" pattern and later onset wheeze at age of 3.5 (OR for 1 standard deviation increase: 0.92 [0.85-1.00], p for trend = 0.06) - No association between the other dietary patterns and asthma outcomes	No association between dietary patterns and eczema, atopy, lung function or bronchial responsiveness
Lange NE *et al. J Allergy Clin Immunol* 2010 (170)	United States (Project Viva) 1,376 mother-infant pairs (3 years of follow-up)	- Recurrent wheeze (≥once before the age of 2 and ≥once in the 3rd year) - Ever asthma at age of 3 (doctor diagnosis) (self-administered questionnaire)	Dietary patterns derived using PCA: 1) Prudent, 2) Western	No association between any of the two dietary patterns and recurrent wheeze, nor with ever asthma	- No adjustment for energy intake - No association with eczema, lower respiratory tract infections or atopy
Miyake Y *et al. Pediatr Allergy Immunol* 2011(173)	Japan (OMCHS Study) 763 mother–child pairs (16–24 months of follow-up)	- Current wheezing (last 12 months) at age 16–24 months	Dietary patterns derived using PCA: 1) Healthy pattern, 2) Western pattern, 3) Japanese pattern (rice, miso soup, sea products, and fish)	- Significant inverse association between the "Western" pattern and current wheeze (OR for highest quartile: 0.59 [0.35–0.98]) - No associations between current wheeze and the "Healthy" or the "Japanese" pattern	- "Western" pattern positively correlated with intake of α-linolenic acid, vitamin E, and β-carotene - No association for eczema

ALSPAC: Avon Longitudinal Study of Parents and Children; OMCHS: Osaka Maternal and Child Health Study; INMA: INfancia y Medio Ambiente

Dietary patterns during childhood

The 13 studies conducted on associations between dietary patterns and asthma during childhood (10 studies using *a priori* methods, 2 studies using *a posteriori* methods and one study using RRR) are summarized in Table 7 (89,169,174–184).

Most studies using *a priori* methods investigated the effects of a Mediterranean diet, using either a Mediterranean score (adapted for children) (169,174–178) or the KIDMED score (89,175,179); all studies were cross-sectional. Three of these studies did not report associations between the Mediterranean score and asthma outcomes (89,175,178), but two of them were conducted in small populations (89,175), suggesting that a lack of power may explain the lack of association. On the other hand, five studies reported significant inverse associations for the Mediterranean scores in association with different asthma/wheezing outcomes (169,174,176,177,179). One of these studies, which was a meta-analysis conducted in the International Study on Allergies and Asthma in Childhood (ISAAC Phase Two), including 50,004 children from 20 countries, reported significant inverse associations for the Mediterranean score with current wheezing and ever asthma (177). A meta-analysis of most of these studies was conducted in 2013 and concluded that its findings are in favor of an association with asthma, wheeze and asthma severity (180).

One case-control study derived the dietary TAC among Spanish children, showing significant inverse associations with current asthma, more particularly in those with nonsmoker parents (181). Smoking is an important confounder when studying the dietary TAC because on one hand, smoking has oxidant effects on health, and on the other hand, smoking is positively associated with coffee, which highly contributes to TAC. These results support the hypothesis of the antioxidant/pro-oxidant role of diet on asthma and are consistent with findings from an Italian study that reported similar results for respiratory health (FEV_1 and FVC), particularly in premenopausal/never smoker women (132).

Two studies used *a posteriori* methods to assess associations between dietary patterns and asthma during childhood: one Dutch longitudinal study conducted on young children (182) and one Brazilian cross-sectional study (183). Both studies used PCA and reported a significant positive association with their “Western” patterns, in relation to occurrence of frequent wheezing (182) and current wheezing (183). One cross-sectional Taiwanese study used RRR to derive a “Energy dense, nutrient poor” food pattern, and reported significant positive associations, in particular with current asthma and current severe asthma (184).

Overall, regardless of the method used to assess diet, findings are in favor of an association between dietary habits and asthma/wheeze during childhood. However, these studies being mostly cross-sectional, and prone to reverse causation, there is an urgent need for longitudinal studies to help understand better the role of diet in the etiology of asthma in children.

Table 7. Studies on dietary patterns during childhood and asthma

Reference	Population/design	Respiratory phenotype	Assessment of dietary patterns	Results	Comments
***A priori* score**					
Garcia-Marcos L *et al*. *Thorax* 2007 (174)	Spain 20,106 children (6-7 years-old); cross-sectional study	Current asthma (wheezing in the last 12 months) divided in two categories: - Current severe asthma (CSA): ≥4 wheezing attacks, sleep disturbed ≥1 night/week, or episode of speech limitation in the last 12 months - Current occasional asthma (COA): current asthma not clinically significant	Mediterranean score constructed as follows: - for fruit, fish, vegetables, legumes, cereals, pasta, rice, and potatoes: 0 if never/occasionally; 1 if once-twice a week; 2 if ≥3 times a week. - for meat, milk, and fast food: 0 if ≥3 times a week; 1 if once-twice a week; 2 if never/occasionally	- Significant inverse association between the Mediterranean score and CSA in girls (OR for 1 unit increase: 0.90 [0.82-0.98]) but not in boys (OR: 0.98 [0.91-1.06]) - No association between the Mediterranean score and COA	- No adjustment for energy intake - No association between the Mediterranean score and rhinoconjunctivitis
Chatzi L *et al. Thorax* 2007 (175)	Crete (Greece) 690 children (7-18 years-old) ; cross-sectional study	- Wheezing ever - Wheezing ever with atopy - Current wheezing - Nocturnal cough (last 12 months)	Score based on the KIDMED score (90): similar for the fruits, vegetables, fish, cereals, dairy products and nuts items + inclusion of brown bread daily (+1), weekly consumption of red meat > white meat (-1) and margarine weekly (-1)	- Non significant inverse associations with asthma outcomes (for wheezing ever, OR for highest tertile: 0.67 [0.34-1.32], p for trend = 0.23) - Borderline significant inverse association with current nocturnal cough (OR for highest tertile: 0.49 [0.23-0.96], p for trend = 0.10)	- No adjustment for energy intake - Significant inverse association with allergic rhinitis ever - Similar results obtained when an alternative Med Score (adaptated to children) was used instead of the KIDMED score
Chatzi L *et al. Thorax* 2008 (89)	Menorca (Spain) 460 mother-infant pairs; cross-sectional study	- Persistent wheeze at age 6.5 (≥once/year) - Atopic wheeze (current wheeze and atopy) at age 6.5 - Atopy at age 6.5 (positive skin-prick test response)	Child's diet at age 6.5: based on the KIDMED score (90), except for two items that were not available (skipping breakfast, baked goods and pastries)	Non significant inverse associations between child's diet at age 6.5 and wheeze/atopy	

De Batlle J *et al. Allergy* 2008 (169)	Mexico 1,476 children (6-7 years-old) ; cross-sectional study	- Asthma ever (doctor diagnosis of asthma, asthmatic bronchitis or reacting airways disease) - Wheezing ever - Current wheezing (last 12 months) (self-administered questionnaire)	Score similar to the original Mediterranean diet score (85), with the exclusion of ethanol, inclusion of fish, and of junk food and fat consumption instead of monounsaturated:saturated fat ratio	- For the child's Med score: significant inverse associations with asthma ever (OR for highest tertile: 0.61 [0.36–1.02], p for trend = 0.03) and wheezing ever (OR for highest tertile: 0.52 [0.35–0.78], p for trend = 0.001) but no association with current wheezing	- No adjustment for energy intake - Significant inverse association between the child's Med score and rhinitis ever, current sneezing and current itchy-watery eyes
Castro-Rodriguez JA *et al. J Pediatr* 2008 (176)	Spain 1,757 children (3-4 years-old) ; cross-sectional study	Current wheezing (last 12 months)	Mediterranean score similar as the one used by Garcia-Marcos *et al.* (174)	Significant inverse association between the Mediterranean score and current wheezing (OR for highest quartile: 0.54 [0.33-0.88])	- No adjustment for energy intake - Association was independent of obesity and physical activity
Nagel G *et al. Thorax* 2010 (177)	20 countries; meta-analysis (ISAAC Phase Two) 50,004 children (8-12 years-old) ; cross-sectional study	- Current wheezing (last 12 months) - Ever asthma (self-reported)	Mediterranean score as follows: - for vegetables, fruit, fruit juice and fish: 0 if <once a week; 1 if ≥once a week; 2 if ≥ once a day - for meat, burgers and fizzy drinks: 0 if ≥ once a day; 1 if ≥once a week; 2 if <once a week	Significant inverse association for the Mediterranean score with current wheezing (OR for 1 unit increase: 0.97 [0.94-0.99], p for trend=0.03, I^2=6%), and ever asthma (OR for 1 unit increase: 0.95 [0.92-0.99], p for trend=0.03, I^2=27%)	- No adjustment for energy intake - No association for the Mediterranean score with skin prick testing positivity or with bronchial hyper-responsiveness
Gonzalez Barcala FJ *et al. Pediatr Allergy Immunol* 2010 (178)	Spain 7,454 children (6-7 years-old) and 7,391 teenagers (13-14 years-old) ; cross-sectional study	- Current asthma (wheezing in the last 12 months) - Current severe asthma (≥4 wheezing attacks, sleep disturbed ≥1 night/week, or episode of speech limitation in the last 12 months) - Exercise-induced asthma (last 12 months)	Mediterranean score similar as the one used by Garcia-Marcos *et al.* (174)	- Overall, no association between the Mediterranean diet score and the three asthma outcomes - In a subanalysis among girls aged 6–7 years old: significant positive association between the 2nd quartile of the Mediterranean diet score and current severe asthma (OR: 2.26 [1.21–4.22])	- No adjustment for energy intake
Arvaniti F *et al. Pediatr Allergy Immunol* 2011 (179)	Greece (PANACEA study)	- Asthma symptoms (ever wheezing, exercise-induced	*KIDMED index* (90)	- Significant inverse association between the KIDMED score and asthma symptoms (OR for 1 unit	

	700 children (10-12 years-old) ; cross-sectional study	wheezing, nocturnal cough, ever diagnosed asthma) (self-administered questionnaire)		increase: 0.86 [0.75-0.98])	
Garcia-Marcos L *et al. Pediatr Allergy Immunol* 2013 (180)	Meta-analysis on 7 published studies (89,169,174–177,179) and one congress abstract on Mediterranean diet score and asthma in children; cross-sectional study	- Current wheeze (in the last 12 months) - Current severe asthma (≥4 wheezing attacks, sleep disturbed ≥1 night/week, or episode of speech limitation in the last 12 months) - Asthma ever (doctor diagnosis)	Because the method of estimation of the Mediterranean diet score was not uniform, all the scores were categorized into tertiles	- For current wheeze: significant inverse association with the Mediterranean score (OR for highest tertile: 0.85 [0.75–0.98]), driven by Mediterranean centers (OR: 0.79 [0.66–0.94] versus 0.91 [0.78–1.05] for non-Mediterranean centers) - For current severe wheeze: significant inverse association for Mediterranean centers (OR: 0.66 [0.48–0.90]) but no association for non-Mediterranean centers (OR: 0.99 [0.79–1.25]) - For asthma ever: significant inverse association with the Mediterranean score (OR: 0.86 [0.78–0.95]), with the difference between regions being negligible (p=0.98)	
Rodríguez-Rodríguez E *et al. Eur J Pediatr* 2014 (181)	Spain 78 children (9-12 years-old); 26 cases, 52 controls; case-control study	- Current asthma: physician diagnosis + treatment in the last 12 months (self-administered questionnaire)	Dietary TAC: 483 foods measured by FRAP (mmol Fe(II)/100 g), 140 by TRAP (mmol Trolox equivalents/100 g), and 158 by TEAC (mmol Trolox equivalents/100 g)	- Significant inverse associations between current asthma and dietary TAC assessed using FRAP (OR for score ≥ median: 0.27 [0.10–0.75], and TEAC (OR: 0.36 [0.14–0.96]) and non significant association with TAC assessed using TRAP (p-value=0.11) - Stronger associations among children with non smoker parents (with FRAP, OR: 0.23 [0.07–0.71]; with TEAC, OR: 0.35 [0.13–0.97]; and with TRAP, OR: 0.43 [0.15–1.23])	- Associations only adjusted for energy intake
***A posteriori* score**					
Tromp II *et al. Eur Respir J* 2012 (182)	The Netherlands (Generation R Study)	- Frequency of wheezing (never, 1-3 times, ≥4 times) at the age of 2, 3	Dietary patterns derived using PCA at age of 14 months:	- For the “Health conscious” pattern: no association with wheezing or shortness of breath	Significant positive association between the “Western” pattern and

	2,173 children; longitudinal study (age at baseline:14 months, followed-up until the age of 4)	and 4 - Frequency of shortness of breath (never, 1-3 times, ≥4 times) at the age of 2, 3 and 4	1) Health conscious, 2) Western	- For the "Western" pattern: significant positive association with frequent wheezing (≥4) at age of 3 (RR for highest tertile: 1.47 [1.04-2.07]) and non significant positive association with frequent shortness of breath (≥4) at age of 4 (RR for highest tertile: 1.36 [0.95-1.96])	frequent respiratory tract infections (≥4) at age of 4
De Cássia Ribeiro Rita S *et al. Pediatr Allergy Immunol Pulmonol* 2013 (183)	Brazil 1,187 children (6-12 years-old) ; cross-sectional study	- Wheezing (last 12 months)	Dietary patterns derived using PCA: 1) Western, 2) Prudent	- Significant positive association between the "Western" pattern and current wheezing (OR for score > 75 percentile: 1.77 [1.10-2.84]) - Non significant inverse association between the "Prudent" pattern and current wheezing (OR for score > 75 percentile: 0.82 [0.52-1.28])	
Alternative methods (in between)					
Lee SC *et al. Asia Pac J Clin Nutr* 2012 (184)	Taiwan (Nutrition and Health Survey of Taiwan Elementary School Children) 2,082 children (7-12 years-old) ; cross-sectional study	- Current asthma (wheezing attacks in the last 12 months) - Current severe asthma (≥4 attacks in the last 12 months) - Nocturnal cough (last 12 months) - Exercise-induced wheeze (last 12 months) - Ever asthma	Dietary pattern derived using RRR with asthma symptom score (0-8) as dependent variable: "Energy dense, nutrient poor " food pattern	- Significant positive association with current asthma (OR for highest quartile: 2.42 [1.19-4.93], p for trend = 0.01), current severe asthma (OR for highest quartile: 4.45 [1.59-12.5], p for trend = 0.003), and nocturnal cough (OR for highest quartile: 1.82 [1.07-3.11], p for trend=0.05) - No association with exercise-induced wheeze or ever asthma	

ISAAC: International Study on Allergies and Asthma in Childhood; PANACEA study: Physical Activity, Nutrition and Allergies in Children Examined in Athens study

Dietary patterns during adulthood

The 13 studies conducted on associations between dietary patterns and asthma during adulthood (3 studies using *a priori* methods and 10 studies using *a posteriori* methods) are summarized in Table 8 (8–11,121,124,125,185–190).

Two studies using *a priori* methods, investigated the effects of a Mediterranean diet: one cross-sectional study, using the aMed index, among Portuguese asthmatic adults (185) and one interventional study encouraging adults with symptomatic asthma in New-Zealand to adopt a Mediterranean diet (186). Whereas a significant inverse association were reported with uncontrolled asthma in the cross-sectional study (185), no significant changes on asthma control or quality of life were reported in the interventional study (186).

One case-control study derived the DII (highest score meaning high pro-inflammatory diet) among Australian adults, showing significant positive associations with asthma (187), suggesting the inflammatory/anti-inflammatory role of diet on asthma.

Most studies conducted in adults used *a posteriori* methods (10 out of 13); all of them used PCA to derive dietary patterns (8–11,121,124,125,188–190). In all the 5 cross-sectional studies and the case-control study, significant or borderline significant associations with asthma/wheeze were reported for at least one dietary pattern (121,124,125,188–190). Two studies reported an increased risk of asthma or wheeze with a "Western-like" diet: one cross-sectional Japanese study reported a significant positive association between a "Fast food and quick sugar" pattern and current wheeze (188), whereas one cross-sectional Australian study reported a significant positive association between a "Meats /cheese" pattern and ever asthma (190). A meta-analysis with a cross-sectional design, on dietary patterns and asthma, performed in five centres from three European countries, reported conflicting results. The authors explained it by the cultural heterogeneity between countries (124). Because of cultural differences leading to very heterogeneous dietary patterns, these studies were not easily comparable. Overall, there was no real consistency between these findings.

Only four longitudinal studies were conducted on dietary patterns and new adult-onset asthma: one study of Chinese Singaporeans that identified a "Meat–dim sum" and a "Vegetable–fruit–soy" pattern (8), two US studies that identified a "Prudent" and a "Western" pattern (9,10), and one French study that identified a "Prudent", a "Western" and a "Nuts and wine" pattern (11). None of these studies reported a significant association between dietary

patterns and new adult-onset asthma but the French study reported a significant positive association between the “Western” pattern and asthma severity, and a significant inverse association between the “Nuts and wine” pattern and asthma severity (11).

Overall, the results are conflicting. In cross-sectional studies, dietary patterns were associated with asthma, but these findings were not confirmed in longitudinal surveys. Regarding asthma severity and control, few studies were conducted among asthmatics, reporting associations between dietary patterns, with frequent asthma attacks and asthma control. Further studies are needed to understand better whether or not diet induces, or modulates, asthma in adults.

Table 8. Studies on dietary patterns during adulthood and asthma

Reference	Population	Respiratory phenotype	Assessment of dietary patterns	Results	Comments
***A priori* score**					
Barros *et al*. *Allergy* 2008 (185)	Portugal 174 asthmatic adults (over 16 years-old) ; cross-sectional study	- Asthma control : based on lung function, exhaled nitric oxide, asthma control questionnaire (ACQ) score - Asthma quality of life : Asthma life quality (ALQ) test	Score based on the aMed index developed by Fung et al (6) except for the ethanol item (men: 5-25 g/day, women: 5-15 g/day)	- For asthma control: significant inverse association between the aMed score and uncontrolled asthma (OR for highest tertile: 0.22 [0.05-0.85], p for trend = 0.03) - For asthma quality of life: no association	
Sexton P *et al. J Asthma* 2013 (186)	New Zealand; interventional study: 38 adults with symptomatic asthma allocated to: high-intervention (encouraged to adopt Mediterranean diet and received intensive initial advice and 41h sessions with dietitian); low-intervention (less intensive advice and 2h with a dietitian), and control groups	Follow-up visits at 12 weeks after randomization: - Asthma control : asthma control questionnaire (ACQ) - Asthma quality of life : Asthma life quality questionnaire (AQLQ)	Mediterranean score constructed as follows: - for non-refined cereals, fruits, vegetables, legumes, olive oil, fish and potatoes: 0 to 5 for never, rare, frequent, very frequent, weekly and daily consumption - for red meat and products, poultry and full fat dairy products: scores on a reverse scale were assigned	- Increased Mediterranean score in the high-intervention group ($p < 0.001$) - Non significant improvements in several AQLQ subdomains in the two intervention groups. - No changes in asthma control	- Non significant improvements in lung function in the two intervention groups. - No changes in inflammatory markers in the two intervention groups
Wood LG *et al. Clin Exp Allergy* 2014 (187)	Australia 160 adults (over 18 years-old); case-control study: 99 cases,	Cases defined by doctor's diagnosis of asthma, respiratory symptoms in the last 12 months, airway hyper-responsiveness to	Score based on the updated DII (118), using 25 of the 45 possible food parameters, including carbohydrates, proteins,	Significant positive association between the DII and asthma (OR for 1 unit increase: 1.70 [1.03-2.14])	- Significant inverse association between the DII and FEV1 - No adjustment for energy intake

	61controls	hypertonic saline and no exacerbation, respiratory tract infection or oral corticosteroids in the past 4 weeks	zinc, magnesium, vitamin B1, vitamin A, thiamin		
***A posteriori* score**					
Butler LM *et al. Am J Respir Crit Care Med* 2006 (8)	Chinese in Singapore (Singapore Chinese Health Study) 52,325 (45-74 years-old), longitudinal study: 2-11 years of follow-up (1993-2004)	- Incident asthma: based on self-reported age of onset - Incident asthma confirmed during validation home visit	Dietary patterns using PCA: 1) Meat-dim sum 2) Vegetable-soy-fruit	No association between the "Meat-dim sum" and "Vegetable-soy-fruit" patterns and incident asthma/confirmed incident asthma	- Associations adjusted for nonstarch polysaccharide intake (dietary fiber) - Significant positive association between the "Meat-dim sum" pattern and new onset of persistent cough with phlegm
Varraso R *et al. Thorax* 2007 (10)	United States (HPFS study) 42,917 men (40-75 years-old at baseline), longitudinal study: 12 years of follow-up (1986-1998)	Adult-onset asthma: doctor diagnosis + use of asthma medication within the last 12 months (self-administered questionnaires)	Dietary patterns using PCA: 1) Prudent 2) Western	No association between the "Prudent" and "Western" patterns and adult-onset asthma	- Significant inverse association between the "Prudent" pattern and newly diagnosed COPD - Significant positive association between the "Western" pattern and newly diagnosed COPD
Varraso R *et al. Am J Clin Nutr* 2007 (9)	United States (Nurses' Health Study) 72,043 women (38-63 years-old at baseline), longitudinal study: 16 years of follow-up (1984-2000)	Adult-onset asthma: doctor diagnosis + use of asthma medication within the last 12 months (self-administered questionnaires)	Dietary patterns using PCA: 1) Prudent 2) Western	- Borderline significant positive association between the "Prudent" pattern and adult-onset asthma (RR for highest quintile:1.23 [0.99-1.53], p for trend = 0.07) - No association between the "Western" pattern and adult-onset asthma	- Significant inverse association between the "Prudent" pattern and newly diagnosed COPD - Significant positive association between the "Western" pattern and newly diagnosed COPD
Takaoka M *et al. Respir Med* 2008	Japan 153 female	- Current asthma : current use of asthma medication or	Dietary patterns using PCA:	- For current asthma: no association - For current wheeze: significant	No adjustment for energy intake

(188)	students (mean age: 21); cross-sectional study	asthma attack in the last 12 months - Current wheeze - Asthma symptom score (0-8)	1) Fruits, vegetables, 2) Fast food and quick sugar, 3) Meat, fish, sea food, 4) Milk and yoghourt, 5) Butter and rapeseed oil	positive associations with the "Fast food and quick sugar" pattern (p for trend = 0.01) and with the "Butter and rapeseed oil" pattern (p for trend = 0.003) - For asthma symptom score: borderline significant positive association with the "Fast food and quick sugar" pattern (p for trend = 0.06)	
Varraso R *et al. Eur Respir J* 2009 (11)	France (E3N Study, French part of EPIC) 54,672 women (42-71 years-old at baseline), longitudinal study: 10 years of follow-up (1993-2003)	- Ever asthma (physician-diagnosis) - Current asthma (last 12 months) - Adult-onset asthma: physician diagnosis + coherent reported age of asthma onset - Frequent asthma attacks (≥1/week) among asthmatic females (self-administered questionnaires)	Dietary patterns using PCA: 1) Prudent 2) Western 3) Nuts and wine	- For ever asthma, current asthma or adult-onset asthma: no association - For frequent asthma attacks among asthmatics: significant inverse association with the "Nuts and wine" pattern in asthmatic females (OR for highest tertile: 0.65 [0.31-0.96]), and positive association with the "Western" pattern in asthmatic females without supplements use (OR for highest tertile: 1.79 [1.11-3.73])	
Bakolis I *et al. Allergy* 2010 (121)	United Kingdom 1,453 adults (16-50 years-old); case-control study: 599 cases, 854 controls	- Cases defined by asthma attack, waking with shortness of breath in the last 12 months or current use of asthma medication - Asthma severity: frequency of waking at night because with asthma symptoms, asthma quality of life score	Dietary patterns using PCA: 1) Prudent, 2) Vegetable and fruit, 3) Western, 4) Vegetarian (dairy products, white pasta and legumes), 5) Traditional (vegetables, red meat and offal)	- For asthma: borderline significant positive association with the "Vegetarian" pattern (OR for highest quintile: 1.43 [0.93–2.20], p for trend = 0.08) and borderline significant inverse association with the "Traditional" pattern (OR for highest quintile: 0.68 [0.45–1.03], p for trend = 0.07) - For asthma severity: no association	- Significant positive association between the "Prudent" pattern and chronic bronchitis
McKeever TM *et al. Am J Clin Nutr* 2010 (189)	The Netherlands (MORGEN-EPIC study) 12,648 adults (20-59 years-old) ;	- Wheeze (last 12 months) Asthma (physician-diagnosed) (self-administered questionnaire)	Dietary patterns using PCA: 1) Cosmopolitan (meat and potatoes), 2) Traditional	- For wheeze: significant positive association with the "Cosmopolitan" pattern (OR for highest quintile: 1.3 [1.0–1.5], p for trend <0.0001) - For asthma: significant positive	- Significant positive association between the "Traditional" pattern and COPD prevalence - Significant inverse

	cross-sectional study		(vegetables, fish, and chicken), 3) Refined food	association with the "Cosmopolitan" pattern (OR for highest quintile: 1.4 [1.0–1.9], p for trend = 0.05)	association between the "Traditional" pattern and FEV1
Hooper R *et al. Br J Nutr* 2010 (124)	Three countries (five centres) in the ECRHS–II (Germany, UK, Norway); meta-analysis 1,174 adults (29-55 years-old); cross-sectional study	- Current asthma: asthma attack, waking with shortness of breath in the last 12 months or current use of asthma medication - Asthma symptom score (0-5) - Bronchial responsiveness	Dietary patterns using PCA: 1) Meat and potato, 2) Fish, fruits, and vegetables	- Overall, no association between respiratory phenotypes and dietary patterns - For asthma symptom score and the "Meat and potato" pattern: significant inverse association for the German centres (ratio of mean number of symptoms per quintile: 0.81[0.68–0.97]) and positive associations in UK centres (1.34 [1.09–1.67], and Norway centre (1.24 [1.00–1.55])	
Shi Z *et al. PLoS One* 2012 (125)	China (Jiangsu Nutrition Study) 1,486 adults (over 20 years-old) ; cross-sectional study	Ever asthma (physician-diagnosis) (face to face interviews by health workers)	Dietary patterns using PCA: 1) "Macho" (animal foods, alcohol), 2) Traditional (rice, fresh vegetables), 3) Sweet tooth, 4) Vegetable rich	- Significant positive association between the "Traditional" pattern and ever asthma (OR for 1 standard deviation increase: 2.25 [1.45-3.51]) - No association between the "Macho", "Sweet tooth" and "Vegetable rich" patterns, and ever asthma	
Rosenkranz R *et al. Nutr J* 2012 (190)	Australia (45 and up Study) 156,035 adults (over 45 years-old); cross-sectional study	Ever asthma (physician diagnosis) (self-administered questionnaire)	Dietary patterns using PCA For men: 1) Meats /cheese, 2) Fruits/vegetables, 3) Poultry/seafood, 4) Grains/alcohol For women: 1) Meats, 2) Fruits/vegetables, 3) Poultry/seafood, 4) Cereal/alcohol 5) Cheese/brown bread	- In men: significant positive association with the "Meats /cheese" pattern (OR for highest quintile: 1.18 [1.08–1.28]) - In women: significant positive association with the "Poultry/seafood" pattern (OR for highest quintile: 1.06 [1.00–1.14]) and significant inverse association with the "Cheese/brown bread" pattern (OR for highest quintile: 0.88 [0.82–0.94])	- No adjustment for total energy intake (not assessed) - Significant positive association between the "Fruits/vegetables" pattern and asthma/hayfever in women

ECRHS: European Community Respiratory Health Survey; HPFS: Health Professionals Follow-up Study; E3N: Epidemiological prospective cohort study among women of the MGEN - *Mutuelle Générale de l'Education Nationale*; EPIC: European Prospective Investigation on Cancer

3. Obesity

This section presents firstly a summary of the measures available in nutritional epidemiology to assess obesity, and then a review of the literature on the association between obesity and asthma.

3.1. Assessment of obesity in epidemiology

Body mass index (BMI), as proposed in 1869 by Quetelet, is obtained by dividing the weight (in kilograms) by the squared height (in meters). It is widely used in epidemiological studies because weight and height are easy to collect and can be assessed quite accurately, even by self-report. Validity of these self-reports have been addressed in several studies, showing that despite small tendencies to overestimate height and underestimate weight, especially in women, the correlation between self-reported and direct measures has been found to be relatively high (191,192). However, BMI reflects absolute mass, and thus, the use of BMI in epidemiological studies does not allow body fat distribution to be taken into account.

The World Health Organization (WHO) has proposed BMI thresholds to define overweight and obesity. A "healthy" weight is thus defined as a BMI between 18.5 to 24.9 kg/m². Underweight is defined as a BMI lower than 18.5 kg/m², whereas overweight is defined as a BMI greater than 25.0 kg/m², and obesity, as a BMI greater than 30.0 kg/m² (193). In epidemiological studies, a "healthy" weight is often defined as a BMI between 20.0 to 24.9 kg/m². A large pooled analysis of 19 prospective studies, including 1.46 million adults, was conducted to assess the relation between BMI and mortality, and showed that the lowest all-cause mortality was generally observed in the BMI range of 20.0 to 24.9 kg/m² (194). Because of the normal changes in weight and height that occur during growth, BMI levels among children must be expressed relative to their age and sex peers (195). Therefore, it has been proposed to categorize BMI into age and sex-specific percentiles, based on the Centers for Disease Control and Prevention (CDC) BMI growth charts (196). According to the CDC standards, a "healthy" weight is defined as a BMI between the age and sex-specific 5^{th} and 85^{th} percentiles. Underweight is defined as a BMI lower than the age and sex-specific 5^{th} percentile, whereas overweight is defined as a BMI greater than the age and sex-specific 85^{th} percentile, and obesity, as a BMI greater than the age and sex specific 95^{th} percentile (196).

The human body can be considered as two major compartments: adipose tissue (storage fat) and lean tissue. Therefore, body mass can be divided in two relative mass components: lean mass and fat mass. Lean body mass is very heterogeneous as it includes bone, muscle, extracellular water, nervous tissue, various organs and all cells other than adipocytes (that are a component of adipose tissue) (197). If for instance, we compare two persons with the same BMI but with different repartitions between lean and fat mass, it is likely that higher fat mass/lean mass ratio will have more adverse metabolic effects. Therefore, studying body compartments, when assessing the effects of obesity on a health outcome, is relevant in epidemiological studies.

Several anthropometric measures have been proposed to estimate adiposity. In general, adiposity has been expressed as percent body fat (i.e. fat mass/ total body mass x 100%). Densitometry has been considered to be the gold standard for measuring adiposity. Densitometry is based on the principle that fat tissue is lighter than fat-free tissue. The ratio of weights measured in air and under water, thus, provides an estimate of percent body fat (198). This method is hard to apply in epidemiological studies. In the mid-1980s, dual-energy x-ray absorptiometry (DEXA) has also been proposed. This method can distinguish fat mass, fat-free mass and bone mineral mass, by the differential absorption of the high and low energy x-rays by these tissues (199). Another more recent method is bioelectrical impedance analysis (BIA), which is based on the principle that the lean body mass, which consists largely of ions in a water solution, conducts electricity far better than does fat tissue (203). Thus, the fat mass and percent body fat can be easily calculated. This method, which is simple and rapid, and thus more easily applicable to epidemiological studies than densitometry or DEXA, showed good reproducibility. However, when the relative validity of BIA versus BMI in assessing adiposity has been studied the NHANES III population, it was found that BMI was more highly correlated with obesity-related risk factors for cardiovascular disease, than most BIA measurements (204).

The calculation of waist-to-hip circumference ratio is an alternative easier way to measure adiposity in epidemiological studies. However, the interpretation of waist-to-hip circumference ratio is complicated because it is the ratio of two complex variables. Although waist circumference is a fairly unambiguous measure of abdominal fat, hip circumference reflects both muscle and fat, as well as bony structure (200). Studying each of these variables alone is also relevant, especially since waist circumference is involved in the definition of metabolic syndrome (abdominal obesity defined as waist circumference > 102 cm in adult men and > 88 cm in adult women) (205). Skinfold measurements are also widely used to

measure adiposity in epidemiological studies. The advantage of this method is that it provides a direct measure of body fat. Its major limitations are that not all fat is accessible to the calipers (such as intra-abdominal and intra-muscular fat), and that the distribution of subcutaneous fat can vary considerably over the body, creating difficulties in interpretation when measurements at one or only a few sites are used to represent overall body fat composition (200). Another method, based on self-report, has been proposed by Sørensen *et al*. to evaluate adiposity at different stages of life (206). It consists of estimating its body silhouette using pictograms, varying from a very thin silhouette to a very large silhouette (see Appendix 1). A study comparing directly measured BMI at age 20 to recalled silhouettes at age 20 reported 55 years later, and showed a high correlation between the two assessments, especially among women (207).

In conclusion, many anthropometric measures have been proposed to assess obesity or adiposity. Not the same mechanisms are evaluated according to the measure used and each method has advantages and limitations. Nevertheless, BMI is the most widely used method in epidemiological studies. Spiegelman *et al*. found remarkably high correlations between BMI and absolute fat mass assessed using densitometry. BMI was also found to be correlated to a lesser extent to percent body fat (208). Similar results were obtained in a more recent study in a large population using DEXA to measure adiposity (209).

3.2. The association between obesity and asthma

This section presents a review of the literature on the association between obesity and asthma. First, the main findings of the last 15 years regarding the nature of the association are presented. Then, the recent literature regarding the existence of an obese-asthma phenotype is presented. Finally, the different mechanisms that have been proposed to explain the association between obesity and asthma are presented.

3.2.1. The obesity-asthma association in the last 15 years

The prevalence of obesity has nearly doubled since 1980 (210), concomitantly with the increase of asthma prevalence. These parallel trends in developed countries suggested a relation between obesity and asthma. At first, studies aimed to assess the nature of the

association and it was not clear whether obesity caused asthma or asthma caused obesity, through physical activity limitation (211). In 1999, Camargo *et al*. were the first to show that obesity preceded asthma in the Nurses' Health Study (NHS) study (212). Since then, many longitudinal studies confirmed that obesity precedes asthma (213) and now, obesity is a well known risk factor for asthma.

Regarding windows of exposure, while several studies suggested that a high BMI during childhood may predict risk of developing asthma in adulthood (214), other suggested that overweight early in life may not have a long lasting effect on childhood asthma, if the child develops normal weight later on (198,215,216). Other studies concluded that it was more the evolution of weight (baseline BMI along with weight gain/weight loss over follow-up period) that matters and that weight gain prior to adulthood might increase the risk of asthma later in life (217). These findings highlight the importance of longitudinal studies spanning from childhood to adulthood in investigating the obesity-asthma association (214).

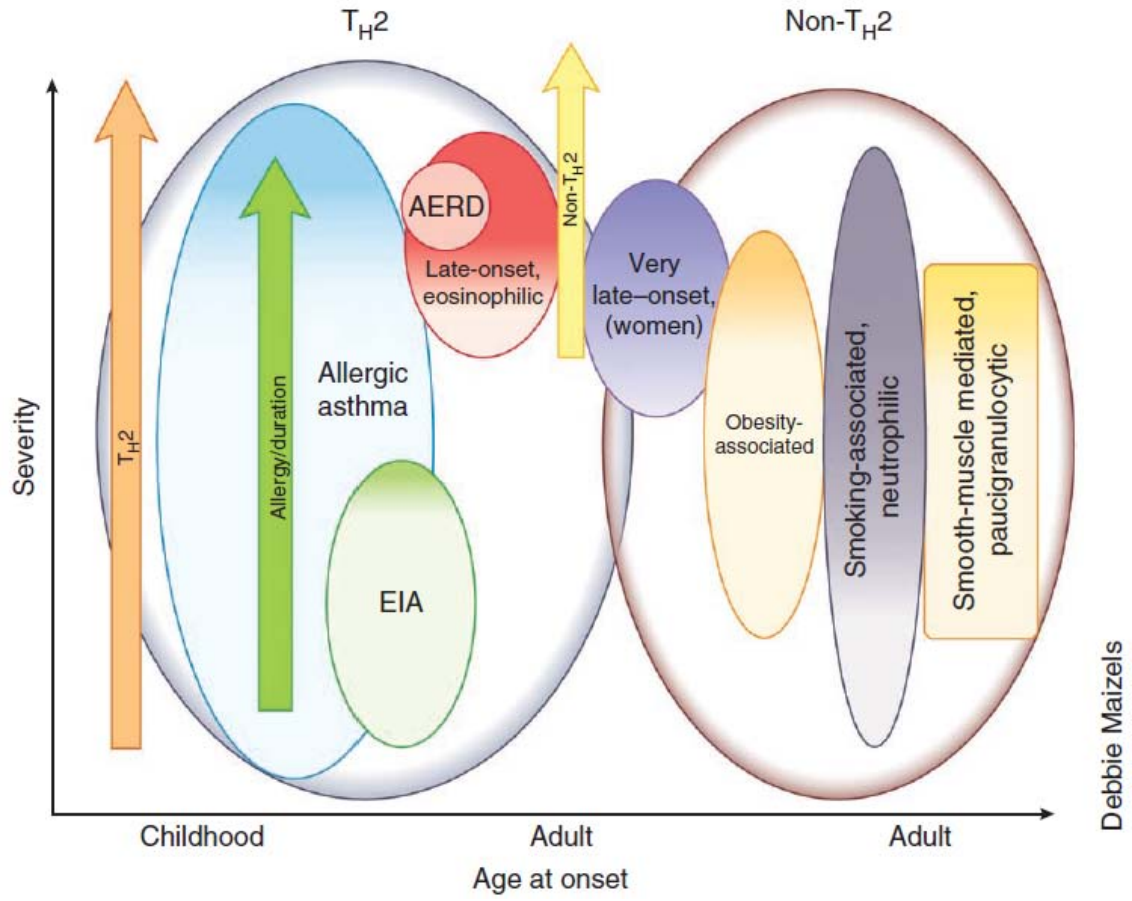
Regarding reversibility of overweight, a systematic review of 15 studies on the effect of weight loss among asthma patients reported a consistent improvement in asthma symptoms, use of medications or hospitalizations, across all studies (218). A prospective study investigated the effect of bariatric surgery among asthma patients, and reported improvements in asthma control (219). A recent randomized controlled trial investigated the effect of weight loss in obese patients with severe asthma, and reported improvements in asthma control in patients who underwent the weight reduction program (220). A recent study, using a novel approach from the field of causal inference, assessed the 10-year risk of adult–onset asthma after hypothetical interventions on BMI and physical activity, and showed a significant reduction in asthma risk associated with weight loss intervention, independently of physical activity level (221). These studies suggested reversibility of the obesity-asthma association, which strengthens the case that obesity is a risk factor for asthma (141).

3.2.2. The Obese-Asthma phenotype

Recent studies have increasingly focused on asthma heterogeneity, promoting the concept that asthma consists of multiple phenotypes or consistent groupings of characteristics (2), and using clustering methods to identify these phenotypes (32–35) (see Figure 2). Overall, these studies found that obesity was an important determinant of asthma phenotype,

playing a more significant role than other commonly assessed clinical, physiologic, or inflammatory variables in determining phenotypic cluster (222), leading to the conclusion that asthma in the obese may represent a unique phenotype (15). Recent studies showed that obesity was associated with more severe asthma, worse asthma control (13) and reduced response to asthma medications such as glucocorticoids (14). Several studies showed that obesity in asthma patients was associated with neutrophilic rather than eosinophilic inflammation (223), especially in women (224). As opposed to asthma in non-obese individuals, which is characterized by T_H2-mediated allergic inflammation, asthma in obese individuals is characterized by a non-allergic mechanism, which might explain the corticosteroid resistance in obese asthma patients (225).

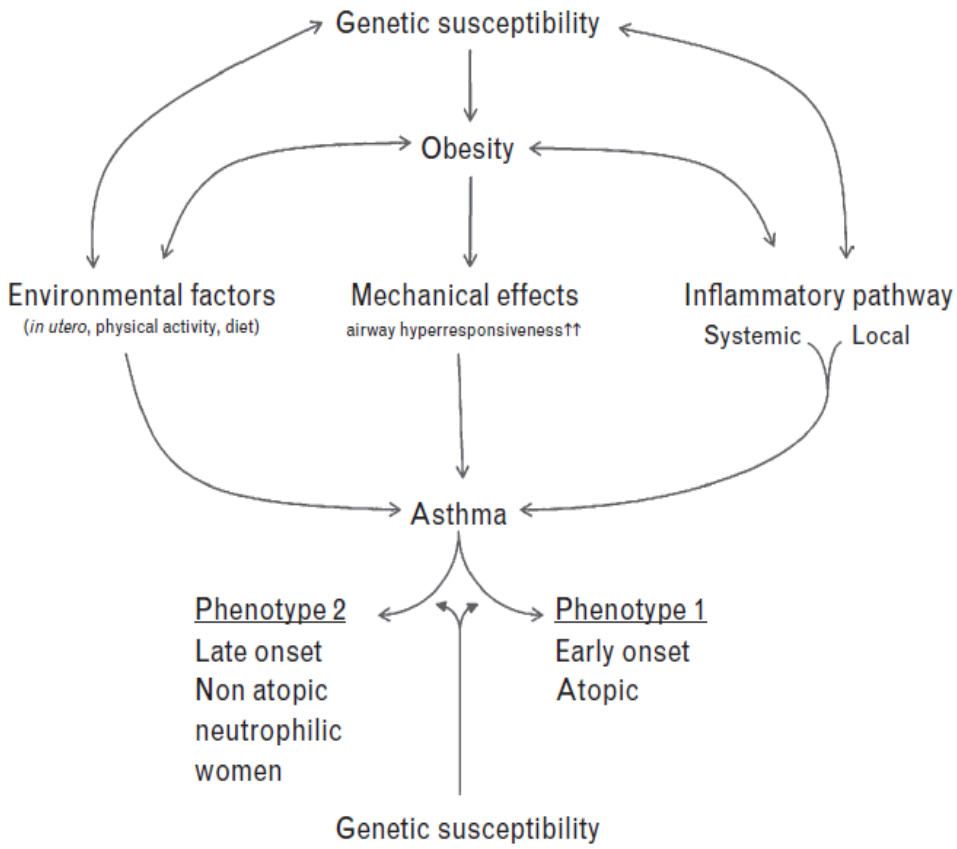
Figure 2. Theoretical grouping of emerging asthma phenotypes based on the distinction between T_H2- and non-T_H2 asthma (reproduced from Wenzel *et al. Nature* 2012 (2))



EIA: exercise-induced asthma, AERD: aspirin-exacerbated respiratory disease

However asthma phenotype is not uniform in obese individuals, with differences observed between obese patient clusters with regard to airway inflammation, symptoms, and control (222). The obese-asthma phenotype further varies with age and according to gender. Recent studies showed a stronger effect of obesity on asthma in females than males (226). A longitudinal study among asthma patients suggested that the greatest effects of obesity on lung function may occur during childhood (227). This heterogeneity within the obese-asthma phenotype represents an active topic of research with cluster analyses aiming to identify sub-phenotypes of obese asthmatics (35). A recent review identified two obese-asthma sub-phenotypes according to age of onset: 1) the "late-onset" obese-asthma phenotype, characterized by late-onset asthma, greater proportion of females, lower prevalence of atopy and eosinophilic inflammation; and 2) the "early-onset" obese-asthma phenotype, characterized by early-onset asthma, greater proportion of males, atopy, eosinophilic inflammation and more severe asthma (228) (see Figure 3). A cross-sectional study assessed the obesity-asthma association according to age of asthma onset and found a higher effect of obesity on lung function and airway obstruction among early-onset asthmatics (age of onset < 12 years-old) than late-onset asthmatics (age of onset ≥12 years-old) (229). This study also showed that early-onset asthmatics, but not late-onset asthmatics, had a steep BMI increase for every year after being diagnosed, suggesting that in early-onset asthma, the association between obesity and increased asthma morbidity is in part the result of more severe asthmatics gaining weight and becoming obese; whereas in late-onset asthma, the association between obesity and increased asthma severity is more likely to be causative (causal effect of obesity on asthma) (229).

Figure 3. Possible mechanisms and pathways between asthma and obesity (reproduced from Rasmussen *et al. Curr Opin Allergy Clin Immunol* 2014 (230))



A recent cross-sectional study among U.S. children assessed the association between indicators of adiposity/obesity (BMI, percent body fat and waist circumference) and asthma outcomes according to their level of fractional exhaled nitric oxide (FeNO), which is a biomarker of eosinophilic airway inflammation (231). This study reported significant associations between adiposity indicators and current asthma only among children with low FeNO, whereas significant associations between adiposity indicators and increased asthma severity or poor asthma control were reported only among asthmatic children with high FeNO. It was thus hypothesized that obesity may play a role in the inception of asthma via non atopic pathways, whereas in children with asthma, obesity and atopy may act synergistically and result in worsened asthma severity and control (231).

3.2.3. Mechanisms

The epidemiologic evidence supporting a meaningful relationship between obesity and asthma is strong, and whereas gaps in knowledge exist, focus has shifted to understanding the

mechanisms for how obesity may cause or worsen asthma (232). Although it is uncertain whether obesity can directly trigger asthma, experts say it is obvious that it can complicate asthma management (233). Several mechanisms have been suggested to explain the effects of obesity on asthma.

Mechanical effect

Obesity, abdominal obesity in particular, compromises lung mechanics by restricting lung volumes, reducing chest wall compliance, and attenuating respiratory muscle efficiency (234,235). Indeed, breathing at lower lung volumes causes an increased respiratory rate to compensate for reduced tidal volume, and reduces breathing-related airway distension, which increases the work of breathing and causes increased exercise-induced dyspnoea (12). Several studies have failed to demonstrate an association between obesity and airflow obstruction or airway hyperresponsiveness (AHR) (236), suggesting that obesity causes restriction not obstruction (232).

Inflammatory effect

The adipose tissue of obese individuals is infiltrated with activated macrophages that interact with adipocytes, leading to an unbalance in concentrations of adipokines, and promoting a state of systemic inflammation. Studies have mainly focused on two adipokines: leptin, which is pro-inflammatory and is markedly elevated in obesity, and adiponectin, which is anti-inflammatory and is decreased in obesity. Changes in many adipose-derived inflammatory moieties, including leptin, adiponectin, and TNF-α, have the capacity to promote airway hyperresponsiveness (AHR) and may thus contribute to asthma in the obese (237).

However, the link between adipokines and asthma seems to be influenced by age and gender and associations have only been found in population subgroups, such as premenopausal women (238) or prepubescent boys and girls (12). Moreover, several studies on the effect of weight loss on asthma suggested that improvements in asthma following weight loss were not mediated by inflammatory effects. Whereas one randomized controlled trial did not report any changes in markers of airway inflammation following weight reduction programme (220), another longitudinal study reported a significant increase in several inflammation markers, following bariatric surgery (219).

Hormonal effect

As previously said, studies showed that the association between obesity and asthma is stronger in females than males (239). It is well known that obesity is associated with earlier sexual maturation, increases estrogen levels, and leads to early menarche in girls (239). Thus, the fact that the male-female asthma prevalence ratio is reversed with the onset of puberty suggests (22) that this sex difference may be explained by hormonal factors, with long-lasting effect of age at menarche on estrogen concentrations during adulthood (226). In the longitudinal Tucson Children's Respiratory Study, a stronger association between childhood obesity and the incidence of wheezing was observed among girls who reached menarche before the age of 11 years (240) while a cross-sectional study among French asthmatic adults from the Epidemiological study on the Genetics and Environment of Asthma (EGEA) study showed a stronger association between BMI and asthma severity among women who reached menarche before the age of 11 years (241). On the other hand, in the RHINE (Respiratory Health in Northern Europe) study, an interaction was found between obesity and oral contraception use in relation to asthma, among Northern European women aged 25-44 years-old (242).

Other hypotheses have been proposed to explain the lack of an association in boys. The first explanation might be that BMI is not an equivalent measure of fatness in boys and girls: in men, BMI has better correlation with lean mass than with percent body fat, whereas the reverse occurs in women. The second explanation might be related to chest wall mechanisms: compliance of the chest wall is reduced by adipose tissue around the rib cage, which typically occurs in obese women (243).

Effect through obesity comorbidities

The effect of obesity on asthma could in part be explained by the presence of its comorbidities. Obesity increases the risk of both gastro-oesophageal reflux disease (GERD) and sleep disordered breathing (SDB), and possible effects of these disorders on the obesity/asthma relationship have been suggested (244). Obesity is associated with several other comorbidities, including hypertension, insulin resistance, diabetes, and hyperlipidemia. Each of these comorbidities alone can increase the oxidative stress burden, and thus may cause or worsen asthma (245). These comorbidities usually occur simultaneously, as is the case of the metabolic syndrome that is characterized by the association of type 2 diabetes,

systemic hypertension, dyslipidemia, and abdominal obesity (assessed using waist circumference). Some studies showed associations between the metabolic syndrome and asthma (246), suggesting that the obesity-asthma relationship might be mediated by the metabolic syndrome (247).

However, a recent longitudinal study suggested that the metabolic syndrome did not explain the BMI-asthma association and that BMI was a stronger predictor of incident asthma among women than the metabolic syndrome, suggesting that other obesity-associated factors may be involved (248).

Genetic factors

On the other hand, some studies suggested that common genetic characteristics may influence obesity and asthma and/or mechanisms influencing the two conditions (249). A cross-sectional study among 1001 monozygotic and 383 dizygotic same-sex twin pairs in the U.S. found that a large part of the phenotypic variation for asthma (53%) and obesity (77%) was due to additive genetic effects and 8% of the genetic component of obesity was shared with asthma (250). A more recent meta-analysis study investigated the genome-wide association study (GWAS) of BMI in a large European population to identify genetic variants that are associated with BMI and showed that the DENND1B gene, which was recently identified as an asthma susceptibility gene in children, may also be associated with BMI in asthmatic children. However, only weak associations were found between DENND1B and BMI in non-asthmatic children and no associations were seen in asthmatic/non-asthmatic adults (251).

Obesity as an epiphenomenon

It is also possible that obesity is an epiphenomenon, and changes in physical activity or diet are responsible for the increases in both asthma and obesity (3,4). Besides these interrelationships, it is also possible that the association between asthma and obesity is explained by common social or environmental factors. The interrelationships between the three nutritional factors (i.e., obesity, diet and physical activity) are complex and poorly studied. These issues are addressed in the next section.

4. Interrelations between nutritional factors and environmental factors

This methodological reflection led to the publication of a methodological note in the journal Allergy in 2012 (182).

For a long time, lifestyle (nutrition/diet, physical activity, smoking and alcohol intake) was identified as one of the most influential health determinants. It was assumed that many forms of behavior that contribute to this determinant are under great influence of individual choice and control and thus are liable to be coped with by educational interventions. Some results to this effect have been reported, though not satisfactorily enough to support the correctness of this approach still insisted upon in many regions. Cognizance is emerging that neither lifestyle, nor smoking or alcoholism, represent an individual choice, but are results of a combined activity of several factors in one's social environment (252). Therefore, understanding the interrelations between lifestyle and environmental determinants for chronic diseases, and especially asthma, is a major challenge for public health. Recent approaches to causal inference offer a framework that may help to address the complex interplay between nutritional and environmental factors in chronic diseases.

Interrelations may occur within nutritional factors, and also between nutritional and environmental factors, leading to the issues of confounding or mediation. This section examines the different interrelations that may occur, first within nutritional factors, and then between nutritional and environmental factors.

4.1 Interrelations within nutritional factors

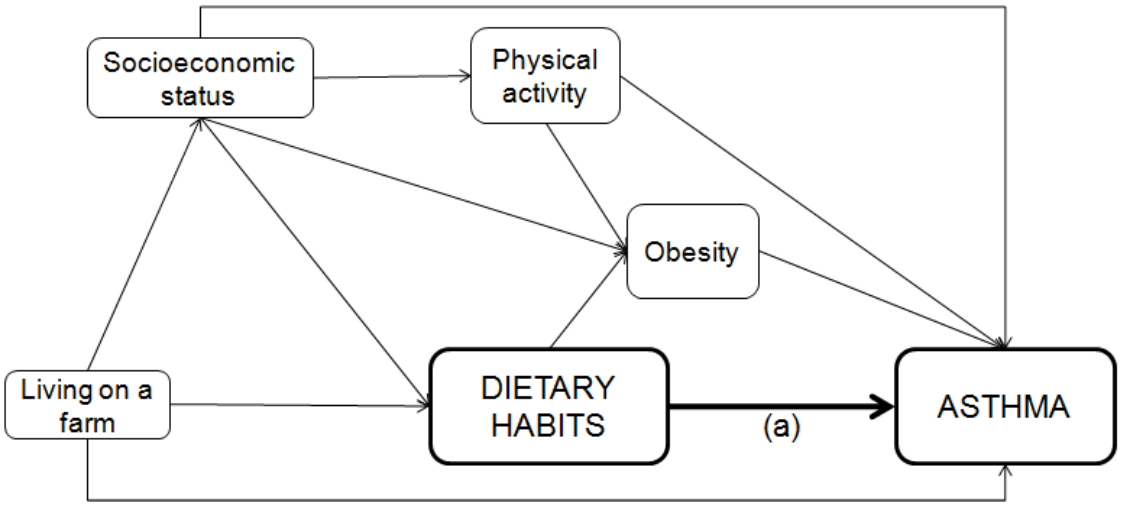
Tit has been suggested that the modification of dietary habits (less fruits/vegetables, more ready to eat meals), the obesity epidemic, and the decrease in physical activity, have all played a role in the increase of asthma worldwide (3,4). Overweight and obesity reflect an imbalance between energy provision (i.e. intake of calories) and expenditure (i.e. physical activity) (253), so the interrelations between these factors (obesity, diet and physical activity) make it difficult to disentangle their separate roles on asthma. Up to now, few studies have investigated the joint roles of diet, physical activity and body composition as determinants of asthma (177,221,254–259) or only the joint roles of physical activity and body composition as determinants of asthma and most of them had methodological limitations (177,254–259).

A recent study compared the prevalence of respiratory outcomes between 1990 and 1998, using the data from 2 cohorts of UK pre-school children (the first cohort included

children born in 1985–1989, the second cohort included children born in 1993–1997). This study showed that the increasing prevalence of wheezing throughout the 1990s was not explained by the generational increase in BMI, suggesting that it could possibly be explained by lifestyle factors that also have been evolving in the last decades such as dietary habits, exercise habits or sedentary lifestyle instead (260).

In a review from 2012, Nurmatov *et al*. highlighted an inadequate handling of confounding and effect modification in most epidemiological studies investigating the role of diet on the development of childhood asthma and allergies (261). Indeed, diet, as well as physical activity and thus obesity, represent essential aspects of lifestyle, with specificities between countries and social groups due to cultural, social and environmental factors. How to properly account for confounders when investigating the effect on nutritional factors on asthma is conceptually challenging (261). First, potential confounders and effect modifiers are numerous and most of them are strongly correlated. Up to now, the method used to control for confounding was to investigate the possible effect of each risk factor adjusted for all the other risks factors, leading to the issue of over-adjustment. Recent approaches to causal inference offer a framework that may help to address these issues. Direct acyclic graphs (DAGs) are causal graphs in which all the arcs are arrows (directed) and no directed path forms a closed loop (acyclic) (262). DAGs may help to decide how to enter variables in a model, to identify potential biases arising from other adjustments, as well as to distinguish confounders from intermediate variables. For example, according to the following DAG (see Figure 4), obesity is a mediator in the effect of diet on asthma, and physical activity is a confounder in the assessment of the effect of obesity on asthma. Previous statistical and epidemiological research has shown that if we adjust for a mediator (e.g., obesity) and a common cause (e.g. physical activity) of the mediator and the outcome, when assessing the causal association between an exposure (e.g. dietary habits) and an outcome (e.g. asthma), we will get biased results (262,263).

Figure 4. Example of the causal association between diet and asthma, taking into account "potential confounders" using Direct Acyclic Graph (DAG)



From a longitudinal perspective, interrelations between nutritional factors are time-dependent. Besides the potential role of each nutritional factors on asthma at a given time t, asthma may modify nutritional factors at time t+1 (for instance, decrease in the practice of physical activity), and each nutritional factor may modify another nutritional factor at time t+1. Thus, there is time-dependent confounding and, in this situation, standard methods of analysis may provide biased results (262,263).

In longitudinal epidemiological studies, the complex situations of time-dependent confounding can be addressed using a novel approach from the field of causal inference, marginal structural models (MSM) (264). These models, applicable only with repeated data, enable the creation of a pseudo-population in which there exists no time-dependent confounding. For that purpose, each subject is assigned a weight which represents the inverse of the calculated probability of receiving the observed history of exposure, given a chosen set of covariates (265). MSM have been developed in the frame of the counterfactual approach to causality (266). Counterfactuals are defined as the outcome that would have been observed, had the exposure differed. MSM have been used in various settings: in survival analysis calculating a censoring weight (267–269), in mediation analysis to disentangle direct and indirect effects (270,271), or to address the healthy worker effect in the occupational context (272). They have also been used in the context of nutritional factors, to study the joint effect of physical activity and body composition on functional limitation (273), or the independent effect of physical activity on COPD development and course (274). MSM are easily

implemented with standard software, designing the model is the most challenging. Thus, MSM might be an appropriate approach to address confounding and effect modification in the context of complex and time-dependent interrelations, such as the diet-asthma association, when repeated data are available.

The g-formula, which was first described in 1986 by Robins (275), is another method that allows adjustment for time-dependent confounding. However, the availability of rich data from large cohort studies and the acceleration of computing speeds have only recently made the method feasible for widespread use. The g-formula is a generalization of standardization for time-dependent confounders and exposures, and can be used to consistently estimate the standardized risk of a health outcome under hypothetical interventions. The standardized risk is then a weighted average of the risks of the health outcome, conditional on the specified intervention values and the observed confounder history. The weights are the probability density functions of the time-varying confounders, which are estimated via parametric regression models (276). A recent study used the parametric g-formula to assess the 10-year risk of adult–onset asthma after hypothetical interventions on BMI and physical activity, and showed a significant reduction in asthma risk associated with weight loss intervention and a non-significant reduction associated with intervention on physical activity level (221).

4.2. Interrelations between nutritional and environmental factors

Besides interrelations within nutritional factors, diet, obesity and physical activity may also interact with environmental factors related to systemic inflammation, such as air pollution or occupational/domestic exposures. Few studies have been published regarding this important issue despite the fact that asthma is considered to be due to a complicated interplay of genetic, environmental, lifestyle and social factors. As obesity is now a well-known risk factor for asthma, trying to understand better how obesity might modify associations between environmental factors and asthma is particularly relevant.

In a recent review taking the example of the occupational setting, conceptual heuristic models have been described examining the role of obesity as both a risk factor for occupational diseases (e.g. injuries and preterm exit from the labor market) and a health outcome from work conditions (e.g. sedentary work, shift work, job stress and exposure to some chemicals), while taking into account interactions with other risk factors (277). Obesity

may thus be defined as a modifying or as mediating variable, depending on the research question that is addressed.

Besides occupational exposures, domestic exposures to cleaning products appear as an emergent risk factor. It has been proposed that inhalation of compounds with respiratory irritant properties may induce bronchial epithelial damage and facilitate allergic sensitization by triggering a pro-inflammatory response, neurogenic inflammation, increased lung permeability, and remodelling of the airways epithelium (278). Non-allergic-mediated bronchial inflammation has also been described, and cleaning and disinfectant exposures may lead to non-eosinophilic bronchial inflammation and the onset or aggravation of asthma through non-allergic pathways (279). Although interaction of overweight/obesity in the effect of domestic exposure to sprays on asthma has biological plausibility, as an underlying state of inflammation, no study has yet assessed the potential modifying role of overweight/obesity in the association between domestic cleaning exposures and asthma.

A recent study reviewed the literature to identify potential response-modifying factors that should be considered when assessing the association between O_3 exposure and health effects. The authors identified, among other factors, obesity for which they stated there was "suggestive" evidence that it may increase the risk of O_3-related health effects (280). A recent review focused on the interrelations between air pollution, obesity and asthma, concluding that obesity increases vulnerability to the harmful effects of air pollutants. Several mechanisms have been proposed to explain it, including inflammatory mechanisms. Indeed, obesity is a pro-inflammatory state and thus, may further amplify the inflammatory response induced by exposure to air pollutants (281). A recent cross-sectional study demonstrated that overweight/obesity increased susceptibility to ambient air pollution among Chinese children (282). Another recent study showed that overweight and obese children with asthma were more susceptible to the pulmonary effects of indoor pollutants among children with asthma (283).

Besides air pollution and occupation exposures, factors of the social and physical environment experienced at home (for example, parental smoking, or housing deterioration) might explain the relationship between asthma and obesity very early in life. A cross-sectional study examining the relationship between obesity and asthma among 3 year-old urban US children, took into account the social context and home environment (including housing characteristics) of the families, to assess the interrelations between the social and physical environment experienced at home, obesity and asthma. This study suggested that the obesity-

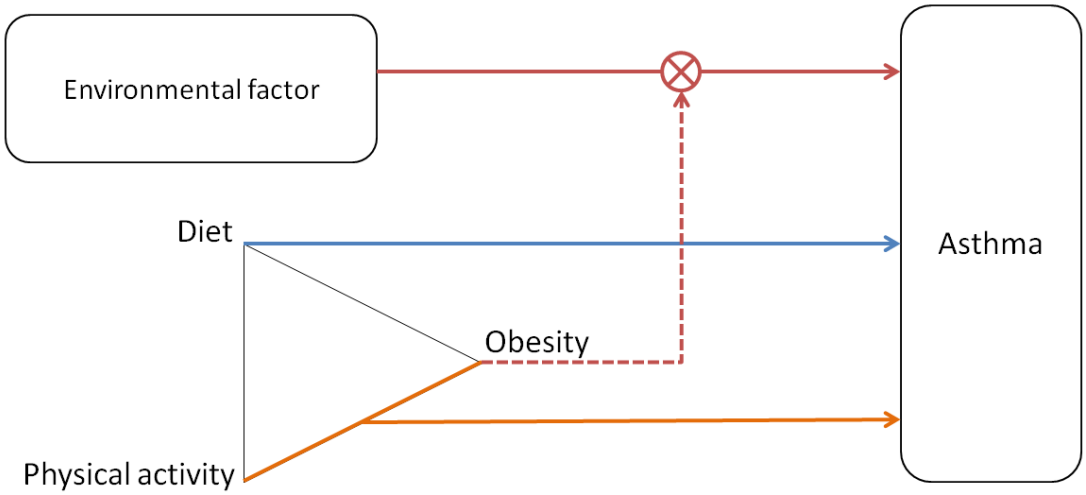
asthma association is not attributable to social or physical factors in the home environment (284). However, the method used to assess these interrelations was to investigate the possible effect of each risk factor adjusted for all the other risks factors, which may thus have led to the issue of over-adjustment.

In conclusion, besides the different mechanisms that could explain the specific effect of obesity on asthma, the association between obesity and asthma may represent an epiphenomenon of more complex interrelations with other nutritional, environmental, behavioral or social factors, that should be addressed as well. Obesity may thus be either considered as a risk factor, and/or a confounder, and/or a mediator, and/or a modifying factor, depending on the research question that is addressed.

OBJECTIVES

The general aim of the thesis is to assess the role of nutritional factors in asthma. Because of complex interrelations within nutritional factors (i.e., obesity, diet and physical activity) and their interaction with social and environmental factors, each nutritional factor may be considered either as a risk factor - either jointly or independently - or as a modifying factor. The first part of the thesis is focused on dietary habits, and the second part is focused on obesity.

Figure 5. Specific objectives of the thesis



The first part of the thesis aims to study the role of dietary habits in asthma (see Figure 5, blue arrow), while addressing nutritional epidemiology issues. Thus, the first part of this thesis has two specific objectives:

1) to compare principal component analysis with confirmatory factor analysis for the identification of dietary patterns

2) to study the effect of these dietary patterns on new adult-onset asthma among French elderly women (E3N cohort study)

The second part of the thesis aims to understand better the role of overweight and obesity in asthma. Thus, the second part of this thesis has two specific objectives:

1) to assess the joint and independent effects of physical activity and body mass index on asthma symptoms (see Figure 5, orange arrow), using marginal structural models to

disentangle the time-dependent interrelations between asthma, obesity, and physical activity (obesity as a risk factor)

2) to investigate the potential inflammatory role of obesity in asthma and its interaction with an environmental inflammatory factor of asthma: domestic exposure to sprays (obesity as a modifying factor) (see Figure 5, red arrow)

MATERIALS AND METHODS

All the analyses conducted in the thesis were performed within the French E3N study (epidemiological prospective cohort study among women of the MGEN - *Mutuelle Générale de l'Education Nationale*), a generalist cohort of epidemiology. Some of the analyses also included specific respiratory information collected through the Asthma-E3N study (pilot study and main study), a nested case-control study on asthma performed within the E3N study.

First, the main E3N study is presented, with a description of all the variables used in the different analyses including nutritional factors, respiratory phenotypes and other potential confounders. Then, the specific respiratory study conducted in the E3N survey is presented, first by detailing the Asthma-E3N pilot survey conducted in 2009, and then by presenting the Asthma-E3N study conducted in 2011-2013.

1. The main E3N study

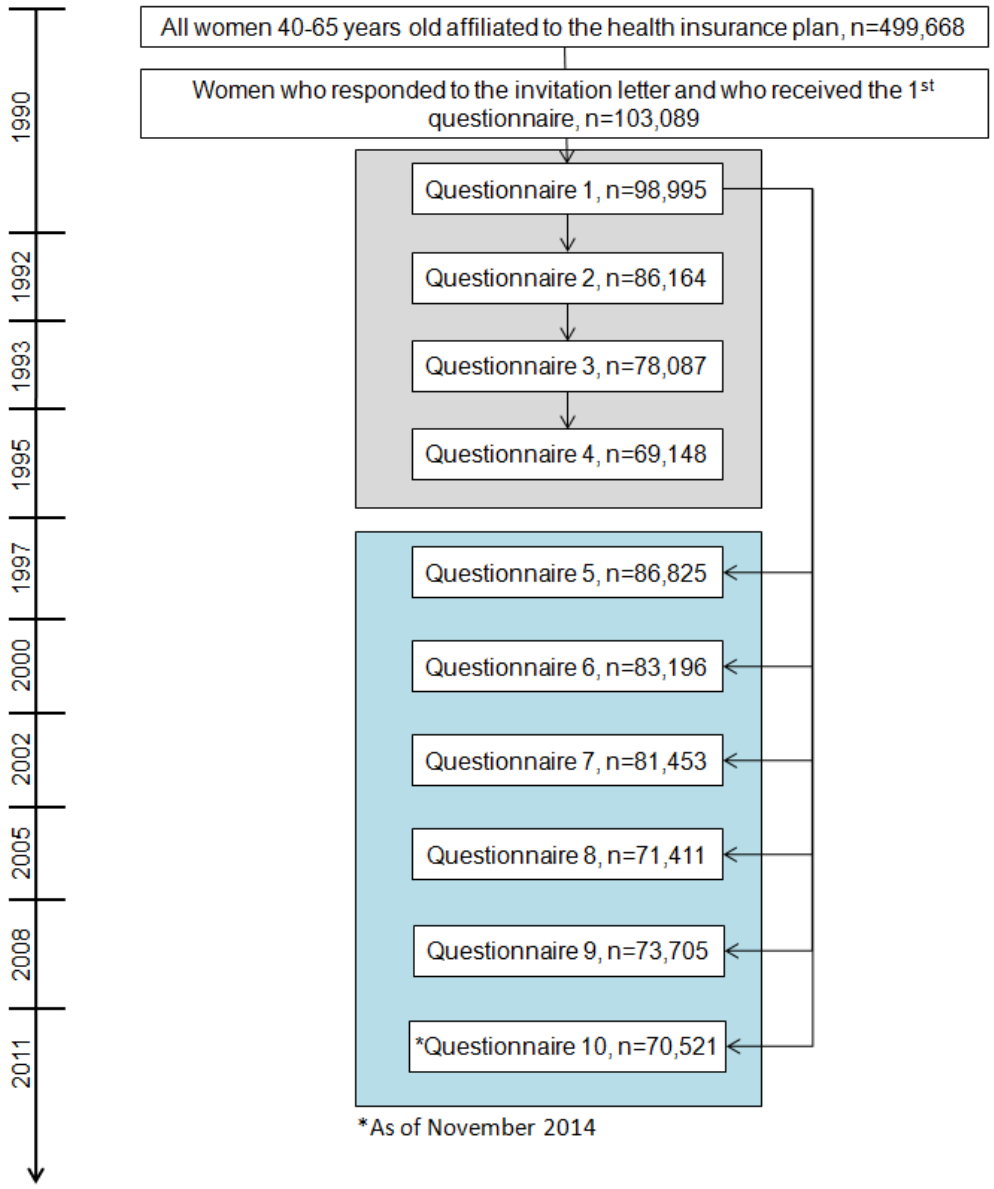
1.1. Study design and follow-up

The E3N study (epidemiological prospective cohort study among women of the MGEN - *Mutuelle Générale de l'Education Nationale*) was undertaken in France in 1990 (285). At that date, half a million women, aged 40-65 years, residing in continental France and insured by the MGEN, a national health insurance plan covering mostly teachers, were invited to participate. The invitation form clearly indicated that the study was planned to last a minimum of 10 years, during which questionnaires would be sent regularly to follow up the health status of the participants. Twenty percent agreed to be volunteers, by filling in the first questionnaire and consent form. The comparison of the distribution of the respondents and the population of women invited to participate according to age and geographic origin showed that the sample was fairly representative of the population insured by the health insurance plan (285). The main E3N study included 98,995 women at baseline, among which 72% were teachers. The E3N study is also the French component of the European Prospective Investigation on Cancer (EPIC) study.

Roughly every two years, information on lifestyle and medical history was collected by self-administered questionnaires. Up to now, ten questionnaires have been sent since 1990 (see Figure 6). From Q2 (1992) to Q4 (1995), follow-up questionnaires were sent only to women who had answered the previous questionnaire. From Q5 (1997) on, a new strategy of follow-up was adopted to increase response rate, and follow-up questionnaires were sent to the entire cohort, except women who asked to be withdrawn from the study or who died between two follow-ups. From Q2 on, response rates were always greater than 85%.

The data cleaning of Q9 was completed in 2012 and the one of Q10 is still under process; therefore, these data were not used in the thesis.

Figure 6. Flow diagram of the E3N cohort study



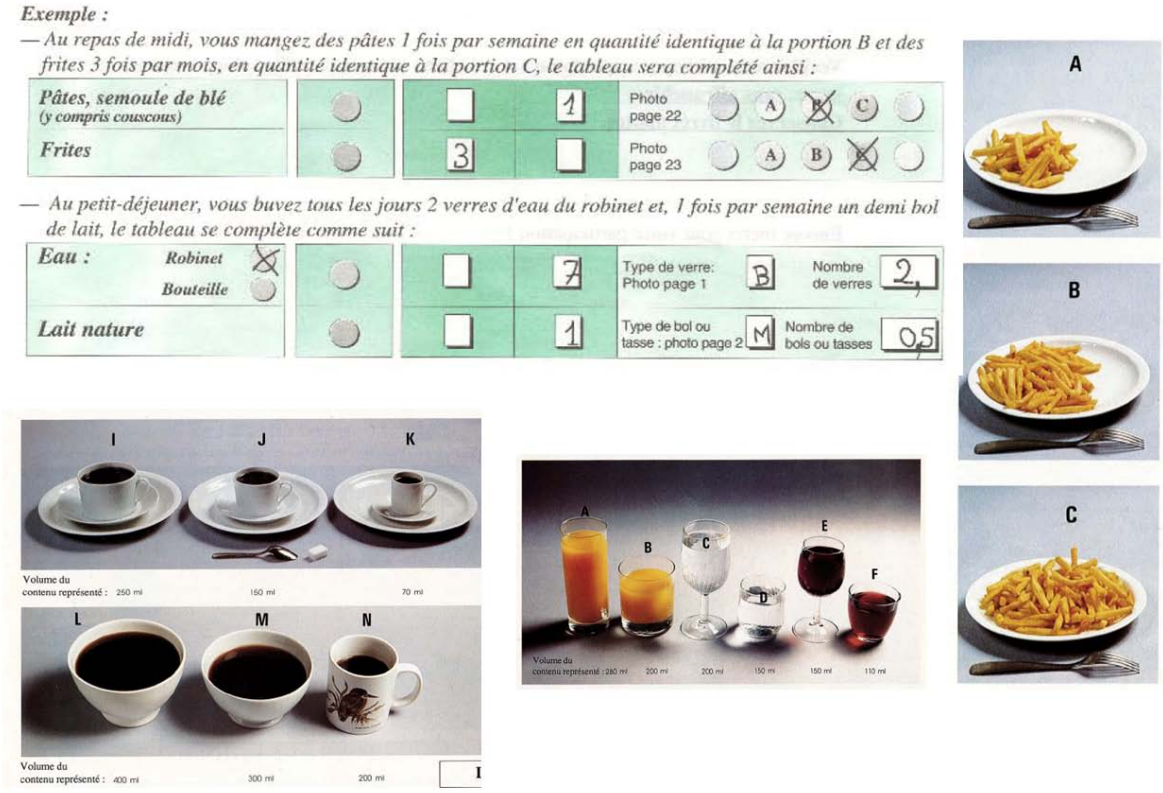
1.2. Data on nutritional factors

1.2.1. Dietary data

Dietary data were collected in 1993 (Q3), using a two-part self-administered food frequency questionnaire. Questions were asked about all consumption occasions from breakfast to after-dinner snacks, including in between meals such as the aperitif before lunch or dinner. Usually two hot meals are eaten per day in France, lunch and dinner, often with similar foods. Another important feature of the questionnaire was the separation into two parts for most food groups of the quantification of food consumption from the description of qualitative aspects of different food items within each food group.

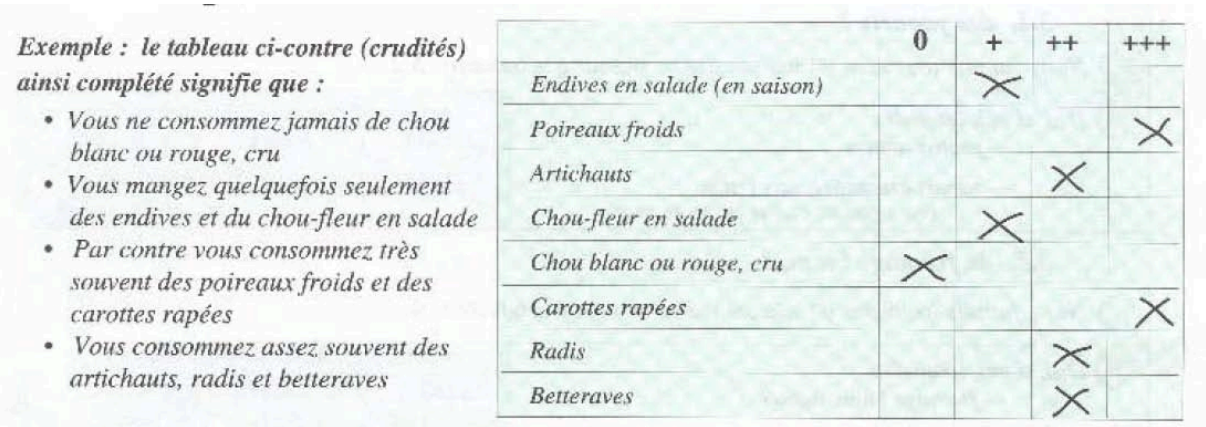
The first part included questions on consumption frequency and portion sizes of 66 food types or items grouped by meal: 38 items for breakfast and in-between snacks, 50 for lunch and dinner, and 13 for aperitifs. For frequency, the following 11 categories were allowed: never or less than once a month, one, two or three times a month, and one to seven times a week. Portion sizes were estimated with the help of an album with photos of 42 food items and dishes. Study subjects could choose portions smaller than, equal to or larger than the three portion sizes shown, and indicate the different types of bread or biscuits consumed, as represented by photos (see Figure 7). Foods that could not be represented by pictures were estimated in natural units (e.g. eggs, biscuits, croissants).

Figure 7. Example from the first part of the food questionnaire



The second part of the questionnaire contained qualitative questions concerning specific food items within one of the generic food groups which were used in the first part (see Figure 8). Study subjects were asked to score their relative consumption frequency for each single food item within the group (four answer categories were allowed: never or seldom, every now and then, regularly, very often). For example, questions in the first part concerned fish as a generic food group, whereas the question in the second part concerned the relative consumption frequency of different types of fish such as mackerel, tuna and cod. A weighting factor can be attributed to the nutrient values of different types of fish consumed and applied to the frequency and quantity of fish consumed as mentioned in part 1 of the questionnaire. In this way, combining the first and the second part of the questionnaire, together with the photo album, permitted an increase in the total number of items on which qualitative and quantitative information was available to a total of 208 food items. Specific attention was paid to the fat and sugar content of dairy products consumed by the study subjects as well as to cooking habits concerning the type and quantity of fat used.

Figure 8. Example from the second part of the food questionnaire



Exemple : le tableau ci-contre (crudités) ainsi complété signifie que :

- *Vous ne consommez jamais de chou blanc ou rouge, cru*
- *Vous mangez quelquefois seulement des endives et du chou-fleur en salade*
- *Par contre vous consommez très souvent des poireaux froids et des carottes rapées*
- *Vous consommez assez souvent des artichauts, radis et betteraves*

	0	+	++	+++
Endives en salade (en saison)		X		
Poireaux froids				X
Artichauts			X	
Chou-fleur en salade		X		
Chou blanc ou rouge, cru	X			
Carottes rapées				X
Radis			X	
Betteraves			X	

The reproducibility and relative validity of the questionnaire were assessed against twelve 24-hour recalls carried out over one year (286). The study showed a good reproducibility for foods (correlations ranged from 0.40 to 0.74) and for nutrients (correlations ranged from 0.54 to 0.75). Relative validity was tested by comparing the first questionnaire with the average of the 24-hour recalls. The crude correlation between questionnaire assessment and mean 24-hour recalls ranged from 0.10 to 0.71 for foods and from 0.28 to 0.78 for nutrients. The lowest correlations were found for foods which are not consumed regularly. Adjustment for total energy intake and for attenuation improved correlation coefficients for nutrients (range: 0.29–0.81).

Dietary supplementation use (yes/no) was first investigated in 1995. Participants reported the use of calcium, vitamins A, B, C, D and E, β-carotene, minerals/trace elements and other vitamins (287). Dietary supplementation use was then recorded in 2000, 2002 and 2005, with an extensive list of supplements.

1.2.2. Body composition

Since 1990, self-reported weight (expressed in kilograms) has been collected at each questionnaire. Self-reported height (expressed in meters) was collected at baseline (1990), in 1995, in 2000, in 2002, and in 2005. Body mass index has been calculated at each questionnaire and expressed in kg/m². Besides weight and height, other anthropometric measurements have been collected such as waist circumference (cm) and hip circumference (cm) in 1995, 2002 and 2005, sitting height (cm) and bust circumference (cm) in 1995, and

body silhouettes, as first proposed by Sørensen *et al.* (206) in 1990 and 2002 (see Appendix 1).

A validation study has been performed to evaluate these self-reported measurements against objective measurements in a sub-sample of women (288). The differences observed between the two measurements (self-reported or taken by technicians) were small and the correlation coefficients ranged from 0.8 to 0.9 showing that self-reported measurements for these variables can be considered accurate and unbiased.

1.2.3. Physical activity

In 1990 (Q1), 1993 (Q3), 1997 (Q5), 2002 (Q7) and 2005 (Q8), several questions on physical activity were asked, but they differ from one questionnaire to another.

In 1990, questions on physical activity included the usual distance walked daily (<500, [500-2,000[, and ≥2,000 m), the average number of flig hts of stairs climbed daily (0, [1-4], and ≥5), the average amount of time spent weekly doing light household activity (0, [1-4], [5-13], and ≥14 hours) and heavy household activity (0, [1 -4], and ≥5 hours), and the average amount of time spent weekly doing moderate recreational activity (0, [1-4], [5-13], and ≥14 hours) and vigorous recreational activity (0, [1-4], and ≥5 hours).

In 1993, questions on physical activity included the duration (hours/week) of physical activity habits in winter/summer including walking, cycling, gardening, home do-it-yourself activities, and sports, the number of stairs climbed per day and physical habits at work (almost seated all the working day, standing during the day but the job does not require physical effort, the job requires physical efforts).

In 1997, questions on physical activity included the duration (hours/week) of physical activity habits in winter/summer including walking, cycling, gardening, home do-it-yourself activities, sports and cleaning tasks, and physical habits at work (almost seated all the working day, standing during the day but the job does not require physical effort, the job requires physical efforts).

In 2002, questions on physical activity included the duration (hours and minutes/week) of physical activity habits in winter/summer including walking, cycling, gardening, home do-it-yourself activities, sports and cleaning tasks.

In 2005, questions on physical activity included the duration (hours/week) of physical activity habits including walking, vigorous sports and moderate sports, vigorous cleaning tasks and moderate cleaning tasks, and habits regarding napping (never or less than once/week, ≥1/week) and sleeping (hours/day).

In 1993, 1997 and 2002, distinction between winter and summer was made. The mean of the two answers was taken for each physical activity variable. If one was missing, the non missing value was taken (assuming winter and summer values were similar). For each questionnaire, the following rule was applied for each woman (E3N internal decision): if she answered to at least one question on physical activity, the missing values corresponding to the "non answered" questions were considered as null and transformed into 0.

A physical activity score was estimated by multiplying the metabolic equivalent (MET) cost of each activity by their frequency and duration, according to the Compendium of Physical Activities (289). A value of 3 METs for walking, 6 METs for moderate recreational activities, 9 METs for vigorous recreational activities, 8 METs for climbing stairs, 2.5 METs for light household activities and 4 METs for heavy household activities were assigned. As different questions were asked in questionnaires, specific physical activities expressed in METS/week also differ from one questionnaire to another. In 1990 and 1993, we generated two variables for total physical activity: one taking into account climbing stairs and one without. In Table 9, the distribution of each source variables (from the main questionnaire) and generated variables (expressed in METS/week) are presented for each questionnaire.

Table 9. Physical activity score (METs/week) in each questionnaire

METS/week, mean (SD)	Q1 (1990) n=97,559	Q3 (1993) n=73,983	Q5 (1997) n=83,568	Q7 (2002) n=78,024	Q8 (2005) n=69,639
Walking (distance per day)	5.7 (4.6)				
Walking (hours per week)		16.1 (18.5)	18.1 (17.0)	15.7 (15.0)	19.5 (23.4)
Cycling		4.2 (13.8)	3.5 (9.7)	3.4 (10.4)	
Gardening		9.0 (15.6)	7.8 (12.3)	10.3 (15.6)	
Home do-it-yourself activities		8.1 (17.8)	5.5 (13.5)	6.1 (14.7)	
Sports (all)		9.1 (18.8)	8.4 (14.4)	8.6 (15.6)	
Vigorous	6.5 (10.8)				10.2 (21.1)
Moderate intensity	12.0 (13.8)				11.6 (16.8)
Cleaning tasks (including cooking)			28.4 (22.4)		
Cleaning tasks (all)				23.5 (21.0)	
Vigorous	6.3 (6.4)				6.7 (10.2)
Moderate intensity	10.5 (9.6)				11.8 (12.3)
Number of stairs climbed per day	1.4 (1.1)	3.0 (3.9)			
Total physical activity without stairs	43.1 (28.2)	46.5 (50.4)	71.7 (45.8)	67.7 (49.7)	59.8 (50.3)
Total physical activity with stairs	44.5 (28.3)	49.5 (50.8)	71.7 (45.8)	67.7 (49.7)	59.8 (50.3)

1.3. Data related to the respiratory health in the main E3N study

In the main E3N questionnaires, simple but repeated questions were available regarding asthma. From 1992 to 1995, women were asked if they have had asthma attacks (yes/no) since the date of the previous questionnaire. In 1997, they were asked if they have had asthma attacks since 1990 (Q1). In 2000, they were asked if they had had asthma attacks since 1997 (Q5) or the last answered questionnaire. In 2002 and 2005, they were asked if they had ever had asthma attacks. Moreover, a question on asthma in 1992 (Q2) distinguished asthma before and after 1990 (Q1). Therefore ever asthma at baseline could also be assessed.

Supplementary questions regarding asthma were also asked to E3N women (see Table 10). In 1992, age at first attack was collected and in 1993, 1995, 1997 and 2000, date of diagnosis was collected. More detailed questions were asked in 2002 and 2005. In 2002, women were asked if (1) they ever had attacks of breathlessness at rest with wheezing, (2) their asthma diagnosis was confirmed by a physician, (3) they ever received a treatment for asthma attacks, (4) age at first attack, (5) they had had an asthma attack in the last 12 months, and (6) the frequency of these attacks in the last 12 months. They were also asked if they were currently taking inhaled corticosteroids or inhaled bronchodilators at least three times per week. In 2005, women were asked if (1) their asthma diagnosis was confirmed by a physician, (2) age at first asthma attack, (3) age at last asthma attack, (4) they had had an asthma attack in the last 12 months, and if yes, (5) how many, and (6) if they were currently taking medication for asthma.

Table 10. Available data on asthma in the E3N questionnaires

	Q_1 1990	Q_2 1992	Q_3 1993	Q_4 1995	Q_5 1997	Q_6 2000	Q_7 2002	Q_8 2005
Asthma attack(s) (ever), yes/no	x	x	x	x	x	x	x	x
Age at first attack		x					x	x
Age at last attack								x
Date of diagnosis			x	x	x	x		
Attacks of breathlessness at rest with wheezing (ever), yes/no							x	
Diagnosis of asthma confirmed by a physician, yes/no							x	x
Treatment for asthma attacks (ever), yes/no							x	
Current use of inhaled corticosteroids ≥3 times/week, yes/no							x	
Current use of inhaled bronchodilators ≥3 times/week, yes/no							x	
Current use of medication for asthma, yes/no								x
Asthma attack(s) in the last 12 months, yes/no							x	x
Frequency of asthma attacks in the last 12 months							x	x

Using these data, we were able to define childhood asthma (less than 16 years old) and adulthood asthma (≥16 years), as previously described in respiratory surveys (68,290). In 2002 and 2005, we were also able to classify women according to definition used in the American Thoracic Society standardization project, i.e., “Did you ever have an asthma attack?” and if yes, “Was this diagnosis confirmed by a doctor?’’ (291). In 2002, we were also able to classify women according to the British Medical Research Council (BMRC) definition, i.e., “Did you ever have an asthma attack or an attack of breathlessness at rest with wheezing’’ (292). The prevalence of ever asthma was almost stable based on questionnaires from 1990 till 2000 (see Table 11), ranging between 2.3% and 4.4%. However, the prevalence was quite larger in 2002 and 2005, when specific questions on asthma were asked in the main questionnaire. In 2002, the prevalence of asthma according to the ATS was 7.1%, and 9.7%

according to the BMRC definition. In 2005, the prevalence of asthma according to the ATS was 8.7%.

Table 11 . Asthma prevalence in each questionnaire

	Q_1 1990	Q_2 1992	Q_3 1993	Q_4 1995	Q_5 1997	Q_6 2000	Q_7 2002	Q_8 2005
All women								
Asthma attack(s) (ever) (%)	3.9	4.4	2.9	2.3	2.5	2.4	7.8	9.8
Asthma confirmed by a physician (ATS definition) (%)							7.1	8.7
Asthma attacks/attacks of breathlessness at rest with wheezing (BMRC definition) (%)							9.7	
Adulthood asthma (≥16 years) (%)		2.6					4.8	5.8
Among women with ever asthma								
Age at first attack, m (SD)		25.4 (16.3)					29.6 (19.4)	31.2 (20.4)
Treatment for asthma attacks (ever) (%)							92.2	
Current use of inhaled corticosteroids ≥3 times/week (%)							19.8	
Current use of inhaled bronchodilators ≥3 times/week (%)							27.6	
Current use of medication for asthma (%)								48.8
Asthma attack(s) in the last 12 months (%)							29.1	27.2
Frequency of asthma attacks ≥ 1/week in the last 12 months (%)							22.4	
Number of asthma attacks in the last 12 months, m (SD)								3.9 (7.0)

m (SD): mean (standard deviation)

All asthma medications dispensed by the French health insurance MGEN have been collected every year since 2004. The MGEN database contains comprehensive information on

asthma medications dispensed to all of the E3N women. Ethics have been granted to use this dynamic database for this research. All dispensed anti-asthma medications were identified using the Anatomical Therapeutic Chemical (ATC) classification available in the database (293). We considered in particular inhaled corticosteroids (ICS) alone or combination (ATC codes R03BA02, R03BA03, R03BA05, R03AK06 and R03AK07) and inhaled bronchodilators (ATC codes R03AC02, R03AC03, R03AC08, R03AC12, R03AC13, R03CC03, R03AK03 and R03AK04). Inhaled corticosteroids and inhaled bronchodilators were considered separately. Dispensed medications were considered as continuous variable (mean of dispensed canisters per year) and qualitative variable (0, 1-3, ≥4 canisters per year for inhaled corticosteroids and 0, 1, 2, 3, ≥4 canisters per year for inhaled bronchodilators).

Within the E3N study, temporal asthma patterns have been defined and validated (294). Using these seven repeated answers to the asthma question from 1922 till 2005, three temporal asthma patterns were defined. The first pattern was labeled ‘‘Never asthma’’, due to the absence of positive answers over time. The second was labeled ‘‘Inconsistent answers’’ and included women with at least one ‘‘yes’’ to the asthma question, followed by a ‘‘no’’ in subsequent questionnaires. The third pattern, labeled ‘‘Consistent answers’’, included women with fully consistent positive answers to the asthma question. The reliability of the three patterns was evaluated using standardized questions on asthma and the dispensed drug database. The sound reliability of the patterns has been confirmed, considering the questionnaires as well as the reimbursement of asthma drugs. Three or more repeated positive asthma answers from 1992 to 2005 ensured an almost perfect agreement with the standardized asthma definitions (ATS and BMRC). It was shown that asthma patterns with ‘‘Inconsistent answers’’ and ‘‘Consistent answers’’ corresponded to asthma with different characteristics regarding age of onset and activity. In this study (294), it was shown that women with less severe, more variable asthma were more likely to be inconsistent in their responses, suggesting that the pattern labeled ‘‘Inconsistent answers’’ is a phenotype which may capture the variable expression of asthma. Furthermore, it was shown that the repetition of positive answers is an indicator of disease severity (294).

1.4. Other potential confounders

A lot of variables related to social, environmental, lifestyle, and reproductive factors were recorded in the E3N study throughout the questionnaires. In the analyses conducted

during the thesis, several variables were used, usually considered as time-dependent confounders; they are presented below.

Age was calculated at each questionnaire based on date on birth and date at which the questionnaire was filled out.

In 1990, women provided information regarding their education level achieved. This variable was categorized in 6 classes: no diploma, “Certificat d’études”, “BEPC/CAP”, high school to 2-level university diploma, 3-/4-level university diploma, ≥5-level university diploma.

In 2002, women were asked whether they had lived continuously on a farm for at least 3 months during childhood, and, if answering yes, whether their parents were farmers.

Smoking status was provided at each questionnaire, i.e., regular smoker, occasional smoker (less than one cigarette/day), former smoker, and current smoker. For current smokers, the number of cigarettes smoked was recorded, and for former smokers, the number of years since quitting. An important work has been conducted by the E3N team to harmonize the smoking status throughout the questionnaires, and to provide an optimal definition of smoking.

Extensive data have been recorded regarding reproductive factors such as parity, age at first full-term pregnancy, age at menarche and menopause. In the analyses conducted during the thesis, menopause was taken into account as a potential risk factor. To ensure that the constructed menopause variables were as accurate as possible, the whole set of answers on date and type of menopause (natural or the result of bilateral oophorectomy, chemotherapy, radiotherapy, or other treatments), date of last menstruation, date of start of menopausal symptoms, and date of hysterectomy, if appropriate, were taken into account. Menopause was defined as the cessation of periods for natural or other reasons. Women for whom age at menopause could not be determined (e.g., women that reported a hysterectomy but gave no information on oophorectomy or menopausal symptoms, or women that indicated they were postmenopausal without any other information) were considered as menopausal at age 47 if menopause was artificial and at 51 otherwise, ages that corresponds to the median age at menopause when artificial or natural, in the E3N cohort. Detailed information was also available regarding lifetime use of hormonal treatments throughout the questionnaires. For each episode of treatment (defined as the non-stop use of the same hormonal brand or

combination), brand name, age at initiation of use and duration were recorded. The information was updated in each of the subsequent questionnaires. The complete history of hormone replacement therapy (HRT) use was established using data from all the questionnaires.

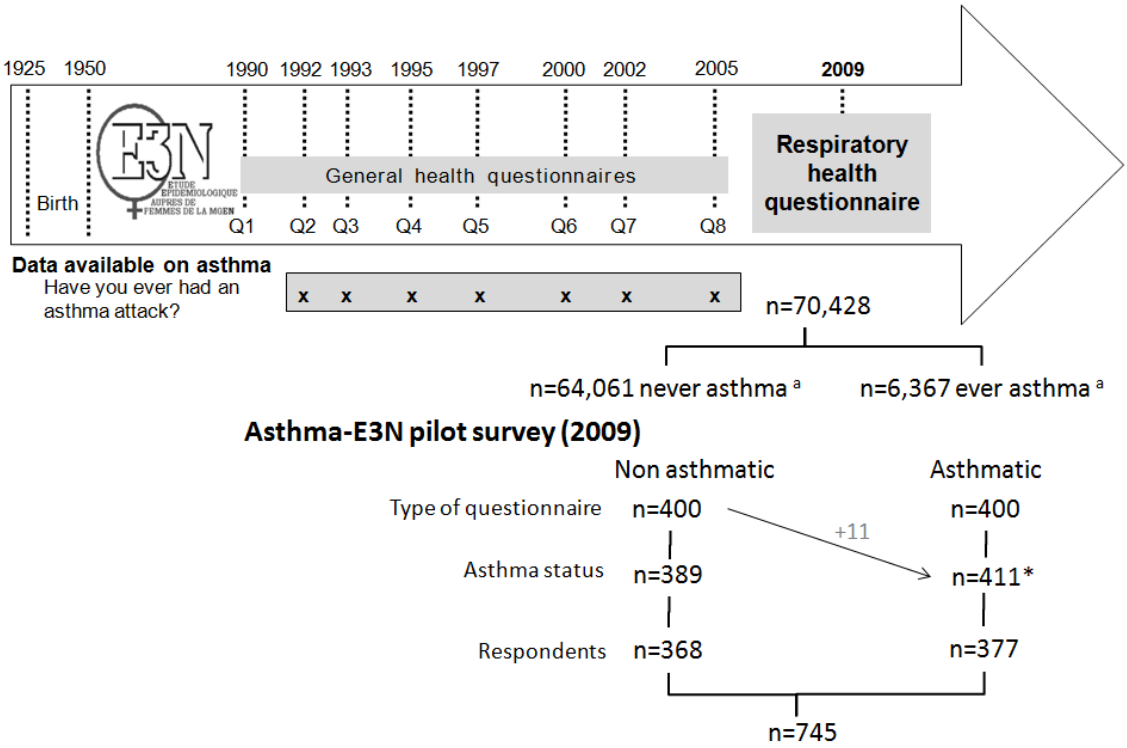
2. The specific respiratory survey in the E3N study

In order to improve the characterization of asthma phenotypes in the E3N study, a nested case-control study on asthma has been set up. Firstly, a pilot respiratory survey has been conducted in 2009 in a random sample of roughly 800 women, and in 2011, the Asthma-E3N has been conducted.

2.1. The Asthma-E3N pilot survey

In 2009, the Asthma-E3N pilot survey was conducted to improve asthma characterization among participants from the E3N study. Among the 70,428 women who returned the 8th questionnaire in 2005 and still alive in 2009, 6,367 women reported at least once asthma in main questionnaires from 1992 to 2005, and 64,061 women never reported asthma (see Figure 9). In each group, we randomly selected 400 women (1 control per case, no matching of cases and controls). All these women received a very detailed questionnaire on respiratory health based on international standardized recommendations with adapted questions from the British Medical Research Council (BMRC) (292), the American Thoracic Society and the Division of Lung Diseases (ATS) (291), and the European Community Respiratory Health Survey (ECRHS) (295). Questionnaires were self-completed and returned by mail. No pulmonary function tests were performed. A 93% response rate was obtained (n = 745).

Figure 9. Selection of the Asthma-E3N pilot survey population



[a] Never asthma was defined by the absence of positive answer to the asthma question from 1992 till 2005, and ever asthma by the presence of at least one positive answer to the asthma question from 1992 to 2005

* 411 asthmatics at the respiratory health pilot survey: 400 who received an asthmatic questionnaire + 11 who received a non-asthmatic questionnaire (because they had a missing answer to the asthma question in 2005)

Regarding asthma, the Asthma-E3N pilot questionnaire included questions on respiratory symptoms, asthma attacks, asthma-triggers, obstructive pulmonary diseases, nasal symptoms, allergy, drug consumptions, hospitalizations and standardized tools to assess asthma quality of life (the Asthma Quality of Life Questionnaire) (296). Using this detailed information, we have defined two asthma phenotypes in the thesis: 1) ever asthma: report of "ever asthma attacks" or "attacks of breathlessness at rest with wheezing"; 2) current asthma: ever asthma and the report of asthma attacks or asthma treatment or asthma-like symptoms in the last 12 months (i.e., breathlessness while wheezing, woken up with a feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, or woken by attack of shortness of breath). The description of women according to ever asthma status is presented in Table 12.

Table 5. Comparison of respondents according to ever asthma status

	All women n=745	**Never asthma** n=377	**Asthma ever** n=368	**p**
Age (years), mean ± SD	68.5 ± 6.4	68.7 ± 6.7	68.4 ± 6.2	0.58
BMI (kg/m²), mean ± SD	23.9 ± 3.8	23.7 ± 3.9	24.1 ± 3.8	0.14
BMI (kg/m²), %				
<20	11.2	12.2	10.2	
[20-25[	57.8	59.9	55.6	0.08
≥ 25	31.0	27.8	34.2	
Smoking status (%)				
Never smoker	57.5	60.0	54.9	
Past smoker	35.2	32.2	38.2	0.23
Current smoker	7.4	7.8	6.9	
Educational level (%)				
< High school diploma	11.6	13.6	9.6	
High school to 2-level university diploma	52.2	54.0	50.4	0. 03
3-level or 4-level university diploma	17.5	15.2	19.7	
≥ 5-level university diploma	18.7	17.2	20.3	
Allergic rhinitis (%)	47.4	32.4	62.5	<0.0001
Dispensed inhaled corticosteroids (%)	23.0	6.1	40.2	<0.0001

The questionnaire also included a specific questionnaire regarding domestic exposure in the past twelve months as the one used in the French EGEA study (68) and in the ECRHS study (67). The frequency of 4 household tasks, 5 specific cleaning tasks, 7 cleaning products and 7 sprays were provided and classified in four categories: never, less than 1 day/week, 1-3 days/week, 4-7 days/week. The description of women regarding domestic exposures and cleaning tasks is presented in Table 13. In this population, 41.3% of the women did not report household help.

Table 13. Specific questionnaire on domestic exposures

Performing the following tasks (%)	Never	<1 day /week	1-3 days /week	4-7 days /week
Cleaning the house	5.2	28.1	49.2	17.5
Washing clothes by hand	45.1	47.6	6.9	0.4
Washing clothes by machine	1.9	14.0	74.6	9.5
Dusting, sweeping, hoovering, rug beating	6.9	31.9	47.7	13.6
Mopping, wet cleaning, damp wiping	8.6	32.7	46.6	12.1
Cleaning the toilet bowl	6.0	18.2	49.1	26.7
Polishing, waxing, shampooing	36.3	60.8	2.8	0.1
Cleaning windows or mirrors	16.1	76.9	6.3	0.7
Cleaning the kitchen	5.8	29.4	39.1	25.7
Use of the following cleaning products (%)	**Never**	**<1 day /week**	**1-3 days /week**	**4-7 days /week**
Washing powders (detergents)	12.1	29.2	39.2	19.5
Liquid multi-use cleaning products	12.1	39.8	33.0	15.1
Polishes, waxes (floor, furniture)	35.2	60.8	3.6	0.3
Ammonia	83.0	15.7	1.0	0.3
Decalcifiers, acids (liquid scale removers)	43.3	51.0	5.0	0.7
Solvents, stain removers	38.7	57.7	3.6	0.0
Perfumed or scented cleaning products	48.8	36.7	12.7	1.7
Bleach	6.9	54.2	29.3	9.7
Use of the following sprays (%)	**Never**	**<1 day /week**	**1-3 days /week**	**4-7 days /week**
Furniture sprays	61.5	34.2	3.8	0.6
Glass cleaning sprays (windows, mirrors)	36.3	56.1	7.1	0.6
Sprays for carpets, rugs or curtains	79.6	19.8	0.4	0.1
Sprays for mopping the floor	94.2	4.8	0.9	0.1
Oven sprays	71.2	27.7	1.0	0.1
Ironing sprays	84.0	14.0	2.0	0.0
Air refreshing sprays	54.2	32.8	8.5	4.5
Degreasing sprays	63.5	27.8	7.5	1.3
Pesticide, insecticide or acaricide sprays	44.6	52.0	2.9	0.6

2.2. The Asthma-E3N study

In order to improve the respiratory characterization of women from the E3N study, a nested case-control study on asthma (Asthma-E3N) was performed in 2011. Among the 76,796 women who answered to the main E3N questionnaires in 2005 (8th questionnaire) or in 2008 (9th questionnaire), and who were still alive in 2011, all women who previously reported at least once “asthma” on the main questionnaire (from 1990 to 2008) were selected; this group was labeled “women with asthma” (n=7,100). Then, 14,200 aged-matched “women without asthma” were randomly selected (among the remaining). In September 2011, they both received a very detailed questionnaire on respiratory health (similar to the one used in the pilot study). In addition to the Asthma-E3N pilot questionnaire, the Asthma-E3N questionnaire included standardized tools to assess asthma control (the Asthma Control Test) (297). Overall, 19,398 questionnaires were returned, with a response rate of 92%. The final study population included 6,268 women with asthma, and 13,130 women without asthma. The description of women according to ever asthma status is presented in Table 14.

Table 14. Comparison of respondents according to ever asthma status

	All women n=19,398	**Never asthma** n=13,130	**Asthma ever** n=6,268	**p**
Age (years), mean ± SD	70.1 ± 6.3	70.1 ± 6.3	70.0 ± 6.2	0.38
BMI (kg/m²), mean ± SD	23.9 ± 3.9	23.7 ± 3.7	24.4 ± 4.2	<0.0001
BMI (kg/m²), %				
<20	12.4	13.1	10.9	
[20-25[	55.2	56.6	52.4	<0.0001
[25-30[	24.9	24.0	26.8	
≥ 30	7.5	6.3	9.9	
Smoking status (%)				
Never smoker	59.9	61.2	57.3	
Past smoker	33.9	32.4	36.9	<0.0001
Current smoker	6.2	6.4	5.9	
Educational level (%)				
< High school diploma	12.1	12.3	11.7	
High school to 2-level university diploma	50.8	51.6	49.0	<0.0001
3-level or 4-level university diploma	18.7	18.4	19.3	
≥ 5-level university diploma	18.4	17.6	20.0	
Allergic rhinitis (%)	39.8	28.2	65.4	<0.0001
Dispensed inhaled corticosteroids (%)	13.6	5.4	30.7	<0.0001

RESULTS AND CONCLUSION

Main results of the thesis are presented below, first regarding the assessment of dietary patterns and their association with asthma, and then regarding the role of obesity, first as a risk factor for asthma, and then as a modifying factor in the association between the domestic use of sprays and asthma.

1. Dietary habits and asthma

This work has been presented at the American Thoracic Society congress in Philadelphia in May 2013 (298) *and at the Lungstorming Meeting in June 2014, and led to the writing of an article which is in second revision after reviewers' comments in the Journal of Nutrition.*

INTRODUCTION

In the last years, there has been a growing interest in dietary patterns to evaluate overall diet (5,85,97,119), leading to methodological developments in nutritional epidemiology. Among several exploratory methods, principal component analysis (PCA) is the most frequently used method to derive *a posteriori* dietary patterns (119). The alternative use of structural equation modeling (SEM), which allows to test a statistical model specifying dietary patterns as latent variables, has been proposed (131). SEM methods include, among others, confirmatory factor analysis (CFA), which is the SEM equivalent of PCA.

The terminology of CFA (i.e., confirmatory) is misleading because CFA has mainly been used as a secondary step to "confirm" dietary patterns derived using PCA (132) or derived using *a priori* hypotheses from the literature (137). Up to now, only one study used CFA as a one-step approach, in the same context as PCA, i.e., by specifying that latent variables might depend on all the available food groups, thus defining a model in which a parameter is estimated for each food group, for each pattern; this study showed that patterns derived using CFA were more statistically meaningful in terms of stability and relevance than dietary patterns derived using PCA (6). In a recent simulation study, the routine use of PCA to derive dietary patterns when investigating the association between diet and a health outcome

was questioned (7). Up to now, no study was performed to compare dietary patterns derived using PCA and CFA regarding their associations with socio-economic characteristics and diseases.

Dietary patterns derived using PCA have been studied in relation to many chronic diseases (103,299). Regarding asthma, changes in diet with an increase of a calorically dense and nutrient-poor Western diet have been evoked to explain the increase of its prevalence over the last forty years (164). Studies on dietary patterns derived using PCA in relation to adulthood asthma showed conflicting results according to the study design (8–11,121,124,125,191–193). Associations between dietary patterns and asthma have been reported in case-control and cross-sectional studies (121,124,125,191–193), and two studies reported an increased risk of asthma or wheeze with a Western diet (191,193). Up to now, only four longitudinal studies were conducted and none of them reported significant associations between dietary patterns derived using PCA and new adult-onset asthma (8–11). It is possible that the use of innovative methods to derive dietary patterns led to conflicting findings when investigating their associations with chronic diseases, especially with diseases such as asthma, for which the existence of an effect of dietary habits is still unclear.

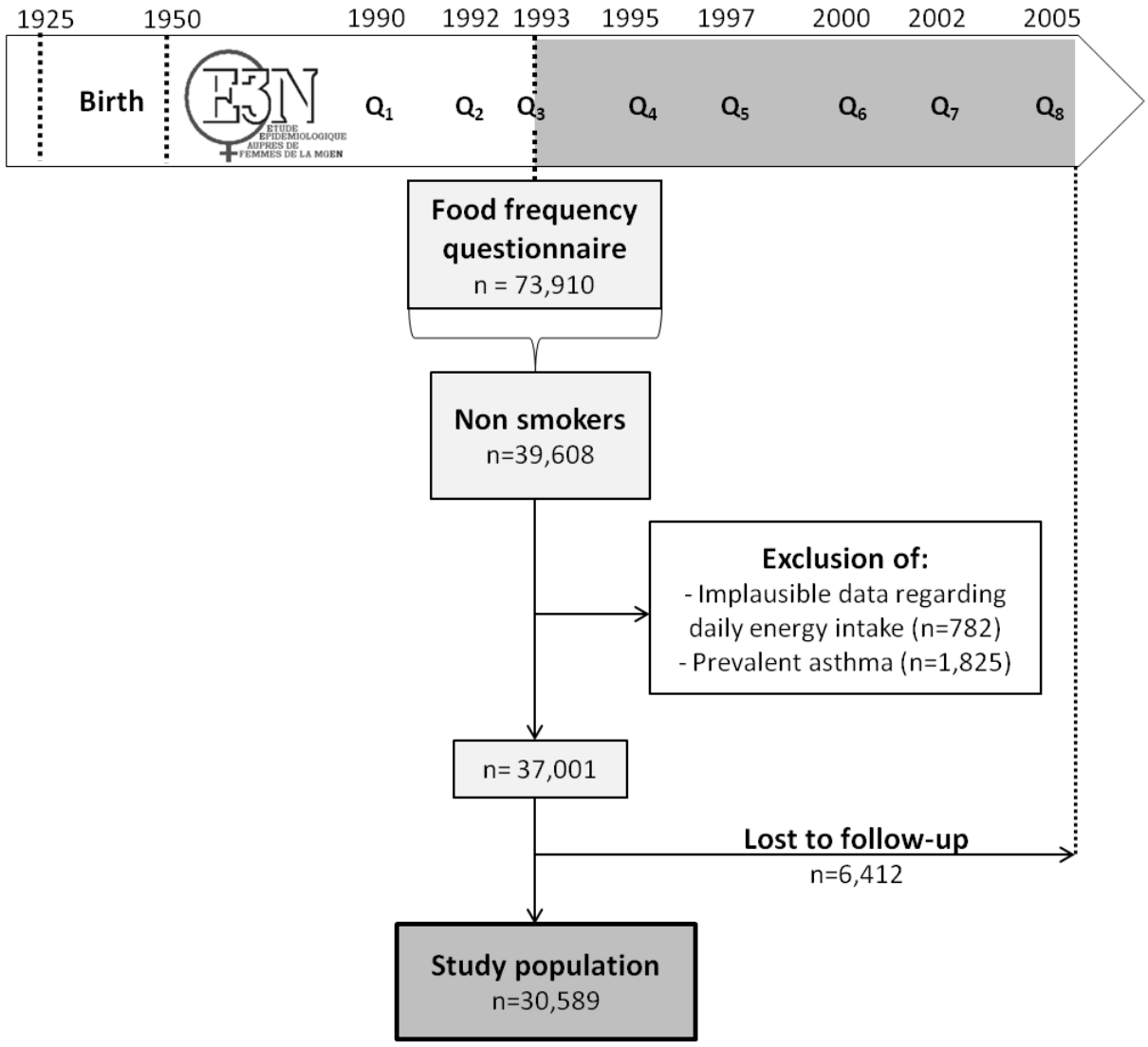
We defined two aims in our study: 1) the first one was methodological and was to compare dietary patterns derived using PCA and CFA, used as equivalent approaches (i.e., by defining a model in which a parameter is estimated for each food group, for each pattern), 2) and the second one was to study the effect of these dietary patterns on new adult-onset asthma among a large population of French women.

MATERIALS AND METHODS

Study population

The study population was selected among the E3N cohort study. Information on asthma was available until 2005. In 1993, information on diet was collected through a food frequency questionnaire. Thus, our study period starts in 1993, up to 2005. Among the 73,910 respondents of the 1993 food frequency questionnaire, analyses were restricted to never smokers (n=39,608), due to the potential overlap between the diagnosis of chronic obstructive pulmonary disease and asthma. Moreover, since smoke exposure is a well known trigger of asthma exacerbations (3), asthma worsening makes people quit smoking, and one might find that smoking is a protective factor for asthma. Thus, restricting our analyses to never smokers allows avoidance of potential reverse causation. Women with extreme values (in the bottom or top 1%) of the ratio between energy intake and required energy calculated after taking age, weight and height into account (n=782) and women with prevalent asthma at baseline (n=1,825) were excluded. Among the 37,001 remaining women, 6,412 were lost to follow-up. In the end, 30,589 women were included, among whom 1,177 reported adult-onset asthma between 1993 and 2005 (see Figure 10).

Figure 10. Selection of the study population



In comparison with included women, the 6,412 women lost to follow-up were significantly older and thus, had more frequently a postmenopausal status (even after adjustment for age). They were also less likely to use menopausal hormone therapy (MHT) after menopause, had a lower educational level, were more frequently overweight, and had less frequently farmer parents. They were however comparable in terms of physical activity and supplements use (see Table 15).

Table 6. Comparison of included women versus women lost to follow-up

	Included (n=30,589)	**Lost to follow-up** (n=6,412)	**p***	**p****
Age (years), mean ± SD	53.4 ± 6.6	55.1 ±7.5	<.0001	-
Post menopausal women (%)	59.8	74.7	<.0001	<.0001
Use of MHT among post menopausal women (%)	71.8	56.7	<.0001	<.0001
BMI (kg/m²), mean ± SD	22.8 ± 3.1	23.4 ± 3.6	<.0001	<.0001
BMI (%°)			<.0001	<.0001
< 20 kg/m²	15.5	13.3		
20 to 25 kg/m²	65.2	59.5		
≥ 25 kg/m²	19.3	27.2		
Physical activity (METS/week), mean ± SD	49.6 ± 48.3	50.2 ± 57.5	0.38	0.40
Years of education (%)			<.0001	<.0001
< 12	13.6	19.1		
12-14	55.2	51.1		
15-16	15.8	15.3		
≥ 17	15.5	14.5		
Supplements use (%) †	26.4	27.0	0.41	0.66
Farmer parents (%)	14.6	13.2	0.03	0.02

SD: standard deviation

† Supplements use was recorded in 1995

* p-value. Chi-squared tests were conducted for categorical variables and t-tests were conducted for continuous variables

** p-value after adjustment on age. Logistic regression models were used for categorical variables and generalized linear models were used for continuous variables

Assessment of new adult-onset asthma

All questionnaires from 1992 to 2005 included a simple question regarding asthma: "Have you ever had an asthma attack?". Women were considered to have adult-onset asthma between 1993 and 2005 if they: 1) did not report ever having asthma attacks in the 1992 and 1993 questionnaires; and 2) replied at least once "yes" to the asthma question during the follow-up period (between the 1995 and the 2005 questionnaires). Women who did not report ever having asthma attacks in any of the 8 questionnaires were considered as women without asthma (reference group).

Assessment of dietary patterns

Using the 1993 food frequency questionnaire, the average daily intake of 208 foods, expressed in grams per day, was assessed for each woman. These 208 food items were grouped *a priori* into 27 separate food groups (see Table 16). Two methods were used to derive dietary patterns: principal component analysis (PCA) and confirmatory factor analysis (CFA). PCA is a descriptive method of data reduction where components (dietary patterns) are linear combinations of observed variables (food groups intakes). CFA is a modeling method that allows specification and testing of a latent variable model where latent variables are factors (dietary patterns) and measures are food group intakes assessed via their variance-covariance matrix. Regarding the method of estimation, singular value decomposition is used for PCA, whereas CFA is based on maximum likelihood estimation. PCA can be applied when one knows little or nothing about the data, whereas CFA allows previous knowledge to be taken into account to decide how many factors will be extracted. One frequent criticism regarding the use of PCA is the low proportion of variance that is usually explained. Although the proportion of variance explained with PCA is inversely related to the number of variables that is used, CFA allows more variability to be taken into account than does PCA through residuals that are specified in the statistical model (144–146). We used CFA in the same context of PCA, by using the 27 food groups available. For each of the 2 methods: a factor score was attributed to each woman for each pattern by summing up observed intakes of the component food items weighted by the factor loading, and each factor score was divided into quintiles.

Assessment of other variables

Because the population of the present study was mostly composed of teachers (roughly 70%), years of education were used as a proxy for socio-economic status. Total energy intake was estimated in 1993 using the diet questionnaire and expressed in kilocalories per day (kcal/day). Physical activity and menopausal status were investigated in 1993 and in each follow-up questionnaire. Physical activity was measured in metabolic equivalents (METs)/week (289) and then categorized into tertiles (low, medium, high level). BMI at baseline was calculated based on height and weight, and was used as a categorical variable (<20, [20-25[, ≥25 kg/m²). Regarding menopause, participants were classified as pre-menopausal women or post-menopausal, and post-menopausal women were classified according to hormone replacement therapy (HRT) use (yes/no), which has been associated with an increased rate of newly diagnosed asthma in the E3N study (300). Dietary supplementation use (yes/no) was first investigated in 1995: participants reported the use of calcium, vitamins A, B, C, D and E, beta carotene, minerals/trace elements and other vitamins (287). In 2003, women were asked whether they had lived continuously on a farm for at least 3 months during childhood, and, if answering yes, whether their parents were farmers. Having farmer parents, as proxy of farming lifestyle during childhood, has been found to have a protective role on adult-onset asthma in the E3N study (301). Retirement status at baseline (yes/no) was assessed based on information on working status and date of retirement, which was collected in the 2005 questionnaire.

Statistical analyses

For PCA, the number of retained factors (dietary patterns) was graphically assessed using the Scree plot, while taking into account interpretability. The factors were rotated using the varimax rotation (i.e.an orthogonal transformation of axis) in order to obtain a more interpretable structure. For CFA, which offers the possibility to define a correlation between latent variables, 4 models were tested, taking into account previous knowledge (9,11,124,192): a 3-factor model with correlated latent variables, a 3-factor model with independent latent variables, a 2-factor model with correlated latent variables, and a 2-factor model with independent latent variables. Three measures of global fit were retained: the Chi-square, the goodness of fit (GFI) and the root mean square error of approximation (RMSEA), with its 90% confidence interval. The conventional overall Chi-square test of fit in covariance structure analysis assesses the magnitude of the discrepancy between the sample and fitted

covariance matrices. A cutoff value of 0.05 has been proposed to indicate the fit of RMSEA (<0.05: close fit, 0.05-0.08: fit fit, >0.10: poor fit), and for GFI, a cutoff of 0.90 has been proposed (130). As PCA factors (components) are not directly comparable to CFA factors, we calculated and compared their correlations with the 27 food groups. In this specific case (correlations), absolute values are directly comparable.

Associations between factors and adult-onset asthma were evaluated using Cox proportional hazards models, using age as the time-scale, as previously recommended in the E3N cohort (302). Further stratification on 5-year intervals birth cohort was made in order to control for cohort effects (303). Associations were adjusted for physical activity and menopausal status, treated as time-dependent variables, and years of education, total energy intake and having farmer parents, treated as fixed variables. Associations were not adjusted for BMI. As obesity reflects an imbalance between diet and physical activity, obesity may act as a mediator in the association between diet and asthma, and thus, adjusting for obesity when studying the effect of diet on asthma could introduce bias.

Various sensitivity analyses were performed. In order to avoid potential for preclinical asthma leading to reverse causation, we performed a first sensitivity analysis by excluding women who developed asthma in the first 24 months of follow-up, i.e. between 1993 and 1995. In the E3N study, supplements use has been found to influence dietary habits (287). As women taking supplements might modify their diet in relation to their disease, analyses were further performed among women who did not use supplements. Obesity is a well known risk factor for asthma, especially in women (12) and thus, may act as an effect-modifier in the association between diet and asthma. In order to evaluate a potential interaction with diet on adult-onset asthma, analyses were stratified on BMI at baseline. Dietary habits highly depend on the social context: the same foods, especially in terms of quality, are not consumed according to the socioeconomic level. Therefore, analyses were stratified on years of education ($<12, \geq 12$), in order to evaluate a potential interaction of socioeconomic level with diet on adult-onset asthma. Retirement from work is one of the last transitional life events involving important lifestyle changes such as a modification of dietary habits (304). In order to assess a potential cohort effect in dietary habits, dietary patterns were independently derived in different strata of our population, according to date of retirement: women retired at baseline, women not retired at baseline. Moreover, to take into account window of exposure, analyses of the associations between dietary patterns and adult-onset asthma were also

stratified on women's retirement status at baseline. All analyses were conducted using SAS statistical software, version 9.1.

Table 16. Food groupings for factor analysis

Food groups	Food items
Vegetables	Green salad, endives as salad, chicory, spinach, artichoke, tomatoes as salad, avocado, cucumber, tomato (pizza, salty pie, salty pancake), cooked tomatoes, green beans, eggplant, bell pepper, zucchini, grated carrots, radish, beetroot, celeriac, cooked carrots, salsify, cauliflower as salad, white or red cabbage raw, brussels sprouts, cauliflower, cabbage, mushrooms (pizza, salty pie, salty pancake), mushrooms, maize as salad, peas, onions (pizza, salty pie, salty pancake), onions (sandwich, hamburger), leek as salad, leek (pizza, salty pie, salty pancake), celery, beet, fennel, soups, olives
Condiments and sauces	Mayonnaise, unspecified salad dressing, commercial plain salad dressing, commercial low-fat salad dressing, home-made salad dressing with peanut oil, home-made salad dressing with olive oil, home-made salad dressing with corn oil, home-made salad dressing with sunflower oil, home-made salad dressing with cole seed oil, home-made salad dressing with soybean oil, béchamel sauce (pizza, salty pie, salty pancake), ketchup (sandwich, hamburger), béchamel sauce (sandwich, hamburger)
Fish (fresh/frozen)	Fresh sardines, mackerel fresh, fresh salmon, unspecified fish, hake, julienne, dab, haddock, sole, pollock, whiting, codfish, trout, other fish
Fresh dairy products	Yoghurt, ordinary yoghurt, ordinary yoghurt 0% fat, ordinary yoghurt sweetened, flavoured yoghurt, flavoured yoghurt 0% fat, flavoured yoghurt light, cottage cheese, ordinary cottage cheese, cottage cheese 0% fat, cottage cheese 10–20% fat, cottage cheese 30–40% fat, flavoured cottage cheese 0% fat, flavoured cottage cheese 10–20% fat, flavoured cottage cheese 30–40% fat, sour cream (pizza, salty pie, salty pancake), plain sour cream, sour cream (15% fat)
Fruits	Orange, grapefruit, mandarin, kiwi, peach, melon, apricot, unspecified fresh fruits, apple, pear, banana, pineapple, strawberries or raspberries, cherries, grapes, plums, compote fruits, fruits on syrup
Olive oil	Olive oil
Sunflower oil	Sunflower oil
Breakfast cereals	Breakfast cereals
Milk	Unspecified milk, whole milk, skimmed milk, semi-skimmed milk, sweetened concentrated milk
Pasta, rice, grain	Pasta, couscous, unspecified rice, normal rice, whole rice
Potatoes	Potato salad, potatoes deep fried, mashed potatoes
Processed meat	Sausage, pate, potted meat, cooked ham (pizza, salty pie, salty pancake), smoked lard (pizza, salty pie, salty pancake), sausages, blood sausage, andouillette, cooked ham (hamburger, sandwich)
Red meat and offal	Unspecified red meats, beef, beef 15% fat (sandwich, hamburger), pork, lamb, veal, horse, liver, other offal
Bread	Unspecified bread, white bread, bread whole flour, white bread slices, biscotti, unleavened bread, crackers, toasted bread, wasa bread, small toasted bread, hamburger bread, white bread (sandwich, hamburger)

Fats except olive and sunflower oils	Peanut oil, corn oil, butter, low-fat butter, normal margarine, low-fat margarine, duck fat, other fat
Dough and pastry	Pizza dough, puff pastry
Cakes, biscuits and sweets	Sugar, honey, jam, andy bars, chocolate bars, sweets, croissant, brioche, cakes, pie (pizza, salty pie, salty pancake), cream cakes, fruit pie, dry biscuits, sweetener
Poultry	Poultry, rabbit
Legumes	Lentils as salad, légumes
Cheeses	Unspecified cheese, camembert, St Marcellin, Brie, munster, soft cheeses, blue cheese, Gruyere, Cantal, Goat cheeses, other cheeses, low-fat cheeses, mozzarella (pizza, salty pie, salty pancake), gruyere (pizza, salty pie, salty pancake), gruyere (sandwich, hamburger)
Milk beverages and cream desserts	Chocolate drink, cream dessert, cream dessert with rice, ice cream
Salty biscuits, aperitif biscuits	Salted biscuits
Nuts and seeds	Nuts and seeds
Alcoholic beverages	Wine or champagne, muscat, porto, vermouth, unspecified beer, beer, special beer, cider, whisky, gin, vodka, digestive, alcohol with anis, punch, aperitif made of cassis liqueur and white wine
Canned fish and sea fruits	Canned fish, sea fruits
Egg	Boiled eggs, fried eggs, scrambled eggs, egg (pizza, salty pie, salty pancake)
Non-alcoholic beverages	Fruits juice, soft drinks, sweetened soft drinks, light soft drinks

RESULTS

In 1993, women were aged 53 years-old on average and 34% were retired. They had an average BMI of 23 kg/m². A high majority (86%) had at least 12 years of education, 26% used supplements and 15% had farmer parents during childhood. When PCA was performed, the Scree plot showed a clear break in the curve after the third component (see Figure 11), explaining 24% of the variance. When CFA was performed, the 3-factor model without correlation between latent variables was retained on the basis of both previous knowledge and measures of global fit (highest Goodness of fit index and lowest Root mean square error of approximation, see Table 17).

Figure 51. Screeplot for the principal component analysis

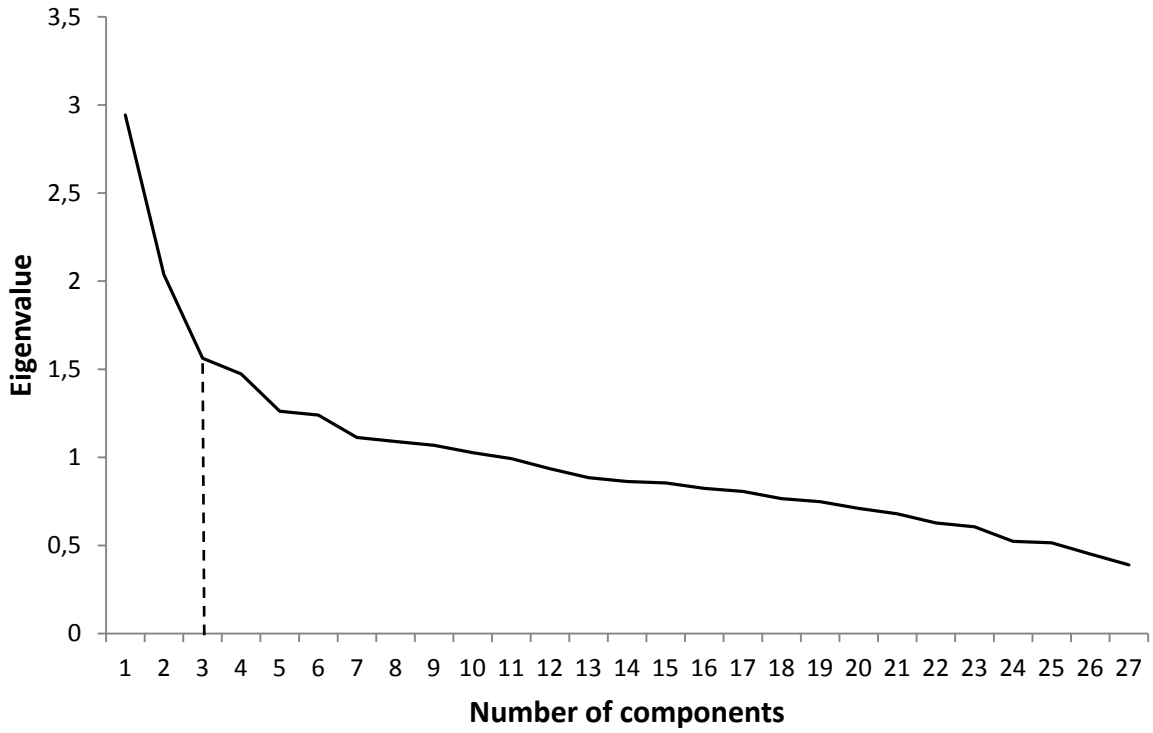


Table 17. Measures of global fit for confirmatory factor analyses according to the numbers of latent variables

	Two-factor model		**Three-factor model**	
	No correlation between dietary patterns	Correlation between dietary patterns	No correlation between dietary patterns	Correlation between dietary patterns
χ^2 [df] (*P*)[2]	41116 [295] (<0.0001)	39651 [294] (<0.0001)	34396 [287] (<0.0001)	37230 [271] (<0.0001)
Goodness of fit index	0.909	0.910	0.922	0.916
Root mean square error of approximation (90% confidence interval)	0.067 (0.067-0.068)	0.066 (0.066-0.067)	0.062 (0.062-0.063)	0.067 (0.066-0.067)
Correlation between factors		Corr (F1,F2) = 0.71		Corr (F1,F2) = -0.78 Corr (F1,F3) = -0.81 Corr (F1,F2) = 0.57

* Chi-square [degree of freedom] (*P*-value).

Three measures of global fit were retained: the Chi-square, the GFI (goodness of fit) and the RMSEA (root mean square error of approximation), with its 90% confidence interval. The conventional overall test of fit in covariance structure analysis assesses the magnitude of the discrepancy between the sample and fitted covariance matrices. A cutoff value of 0.05 has been proposed to indicate the fit of RMSEA (<0.05: close fit, 0.05-0.08: fit fit, >0.10: poor fit), and for GFI, a cutoff of 0.90 has been proposed (130)

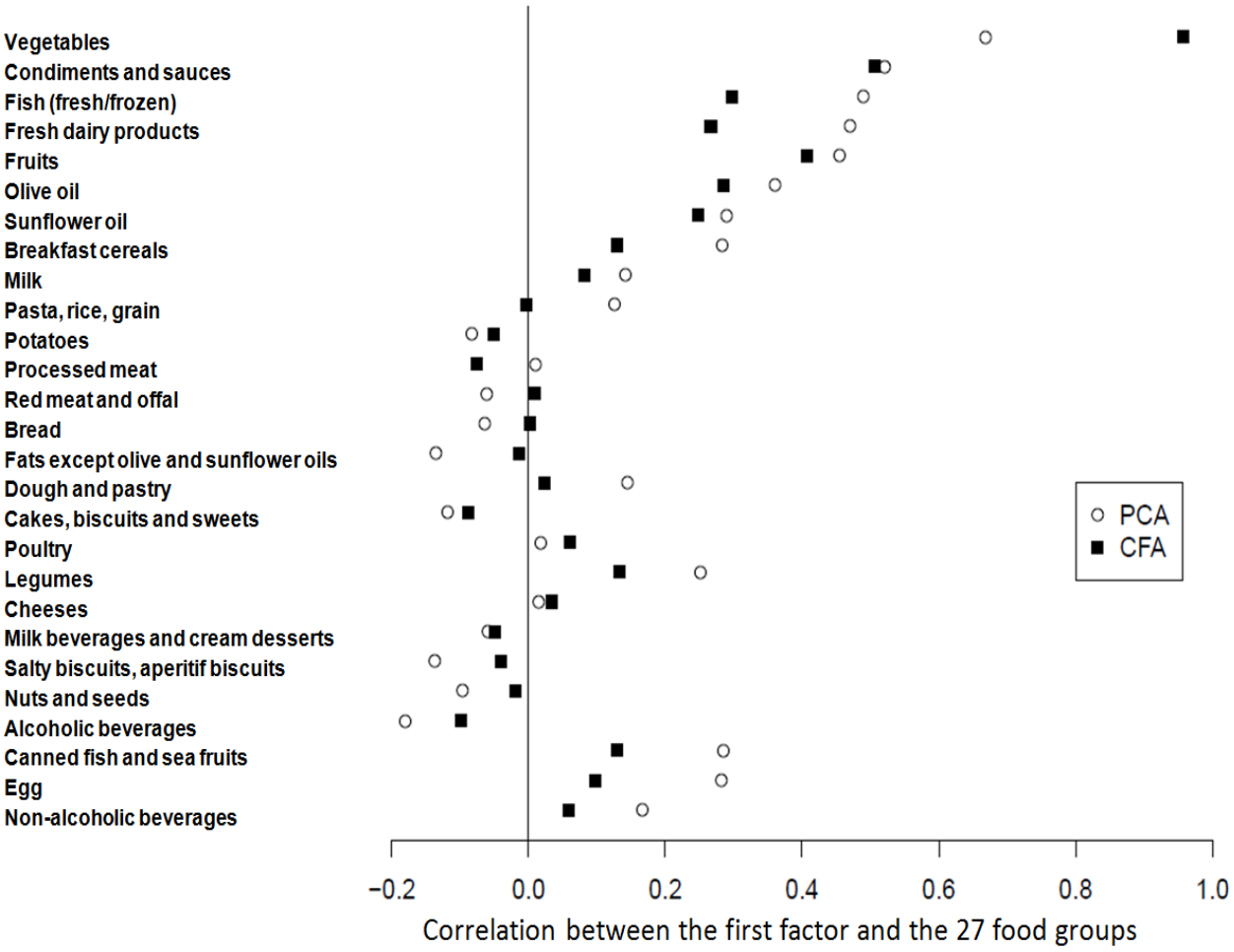
Factors derived using PCA and CFA

Correlations between the 3 factors derived using PCA and the 3 factors derived using CFA were calculated. A correlation of 83% was found between the first factor derived using CFA and the first factor derived using PCA. A correlation of 84% was found between the second factor derived using CFA and the second factor derived using PCA. A correlation of 87% was found between the third factor derived using CFA and the third factor derived using PCA. A correlation of 35% was found between the second factor derived using CFA and the third factor derived using PCA. All the other correlations were lower than |16%|.

Comparison of Factor 1 according to PCA and CFA

Factor 1 was characterized by high correlations with the food groups “Vegetables”, “Condiments/sauces”, “Fish”, “Fresh dairy products”, “Fruits” and “Olive oil”. Whereas similar correlations were observed with the food groups “Condiments and sauces” and “Fruits”, higher correlations were observed, for PCA compared to CFA, with the food groups “Fish”, “Fresh dairy products” and “Olive oil”, and a lower correlation was observed with the food group “Vegetables” (see Figure 12). When dietary patterns were independently derived among women retired at baseline and among women not retired at baseline, similar dietary patterns were found for both PCA and CFA (results not shown).

Figure 12. Factor-loading matrix for the first factor identified using both PCA and CFA methods



Whether PCA or CFA was used, women in the highest quintile of Factor 1 (with the highest score) were significantly older than women in the lowest quintile. After adjustment for age, they significantly had a higher BMI, a higher physical activity level, a higher energy intake and used more supplements as compared to women in the lowest quintile. Women in the highest quintile of Factor 1 derived using PCA had also significantly more frequently a postmenopausal status, used more frequently MHT after menopause and had a lower educational level than women in the lowest quintile. Women in the highest quintile of Factor 1 derived using CFA had also significantly more frequently farmer parents as compared to women in the lowest quintile (see Table 18).

No association was found between Factor 1 and adult-onset asthma when CFA was used. When PCA was used, a positive association, borderline significant after adjustment for potential confounders, was found between Factor 1 and adult-onset asthma (multivariate Risk ratio (RR) [95% Confidence Interval (CI)] for highest vs. lowest quintile: 1.24 [1.03-1.51]; p for trend=0.06) (see Table 19).

When sensitivity analyses were performed, still no association was found between Factor 1 identified using CFA and adult-onset asthma. When PCA was used, the positive association was no longer observed, neither after restricting the study population to the 28,073 women who did not develop asthma in the first 24 months of follow-up (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.10 [0.89-1.36], 0.98 [0.79-1.22], 0.99 [0.80-1.24] and 1.20 [0.97-1.49], respectively; p for trend=0.27), nor after restricting the study population to the 20,853 women without supplements use (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.09 [0.87-1.37], 1.01 [0.80-1.28], 0.93 [0.73-1.19] and 1.21 [0.95-1.53] , respectively; p for trend=0.45). No association was found after stratification on BMI. After stratification on years of education, the association remained similar among the 25,419 women with at least a high school diploma (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.04 [0.84-1.28], 1.06 [0.86-1.31], 1.07 [0.87-1.32] and 1.24 [1.00-1.52], respectively; p for trend=0.06), whereas no association was observed among the 3,987 women who did not complete high school (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.24 [0.76-2.04], 0.98 [0.58-1.66], 0.93 [0.54-1.58] and 1.27 [0.77-2.11], respectively; p for trend=0.71). However, the formal test for interaction between the first pattern and years of education was not statistically significant (p=0.58). After stratification on retirement status, a non significant positive association was found among the 18,372 women not retired at baseline (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.04

[0.81-1.32], 1.01 [0.79-1.28], 0.98 [0.77-1.26] and 1.26 [1.00-1.60], respectively; p for trend=0.11), whereas no association was observed among the 9,482 women retired at baseline (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.24 [0.84-1.83], 1.20 [0.82-1.77], 1.27 [0.86-1.86] and 1.15 [0.77-1.71], respectively; p for trend=0.56).

Table 18. Baseline characteristics of the population according to the first factor identified using both PCA and CFA methods

	PCA					CFA				
	Q1	**Q3**	**Q5**	***p****	***p****	**Q1**	**Q3**	**Q5**	***p****	***p****
Age (years), m(SD)	52.7 (6.7)	53.5 (6.6)	53.9 (6.5)	<.0001	/	52.2 (6.5)	53.4 (6.6)	54.5 (6.6)	<.0001	/
Post menopausal women (%)	54.9	60.1	63.9	<.0001	0.01	52.3	59.7	67.4	<.0001	0.14
Use of HRT (%)	70.6	73.7	71.9	0.04	0.02	71.6	73.5	70.3	0.08	0.40
BMI (kg/m²), m(SD)	22.5 (3.0)	22.8 (3.1)	23.3 (3.3)	<.0001	<.0001	22.5 (3.1)	22.7 (3.1)	23.2 (3.3)	<.0001	<.0001
BMI (%)										
< 20 kg/m²	18.5	15.2	12.5			18.2	16.0	12.8		
20 to 25 kg/m²	64.5	66.0	63.9	<.0001	<.0001	64.3	65.6	63.7	<.0001	<.0001
≥ 25 kg/m²	17.0	18.8	23.6			17.5	18.4	23.5		
Physical activity (METS/week), m(SD)	44.1 (44.4)	49.0 (42.9)	56.7 (56.3)	<.0001	<.0001	43.5 (47.3)	49.4 (43.1)	55.5 (54.8)	<.0001	<.0001
Physical activity level (%)										
Low	39.4	31.4	27.0			40.3	31.6	27.9		
Medium	32.9	35.1	32.7	<.0001	<.0001	32.5	34.4	32.9 39.3	<.0001	<.0001
High	27.8	33.6	40.4			27.2	34.1			
Total energy intake (kcal/day), m(SD)	2068 (534)	2181 (524)	2416 (576)	<.0001	<.0001	2029 (533)	2205 (523)	2390 (568)	<.0001	<.0001
Years of education (%)										
< 12	14.8	13.0	13.9			14.6	12.8	14.5		
12-14	53.4	55.3	54.7	0.28	0.03	53.4	56.7	55.1	0.02	0.29
15-16	15.8	16.2	15.7			16.4	15.1	15.0		
≥ 17	16.0	15.6	15.8			15.6	15.4	15.5		
Supplements use (%) †	21.6	25.7	33.1	<.0001	<.0001	22.7	26.2	30.7	<.0001	<.0001
Farmer parents (%)	13.4	15.3	14.4	0.10	0.11	12.1	15.3	15.8	<.0001	<.0001

Abbreviations: m (SD), mean (standard deviation); Q1, 1st quintile; Q3, 3rd quintile; Q5, 5th quintile.

* p for trend across quintiles of dietary patterns. Chi-squared tests were used for categorical variables and t-tests were used for continuous variables

** p for trend across quintiles of dietary patterns after adjustment on age. Generalized linear models were used for continuous variables and logistic regression models for categorical variables

† Supplements use was recorded in 1995

Table 19. Association between dietary patterns and adult-onset asthma (n=30,589)

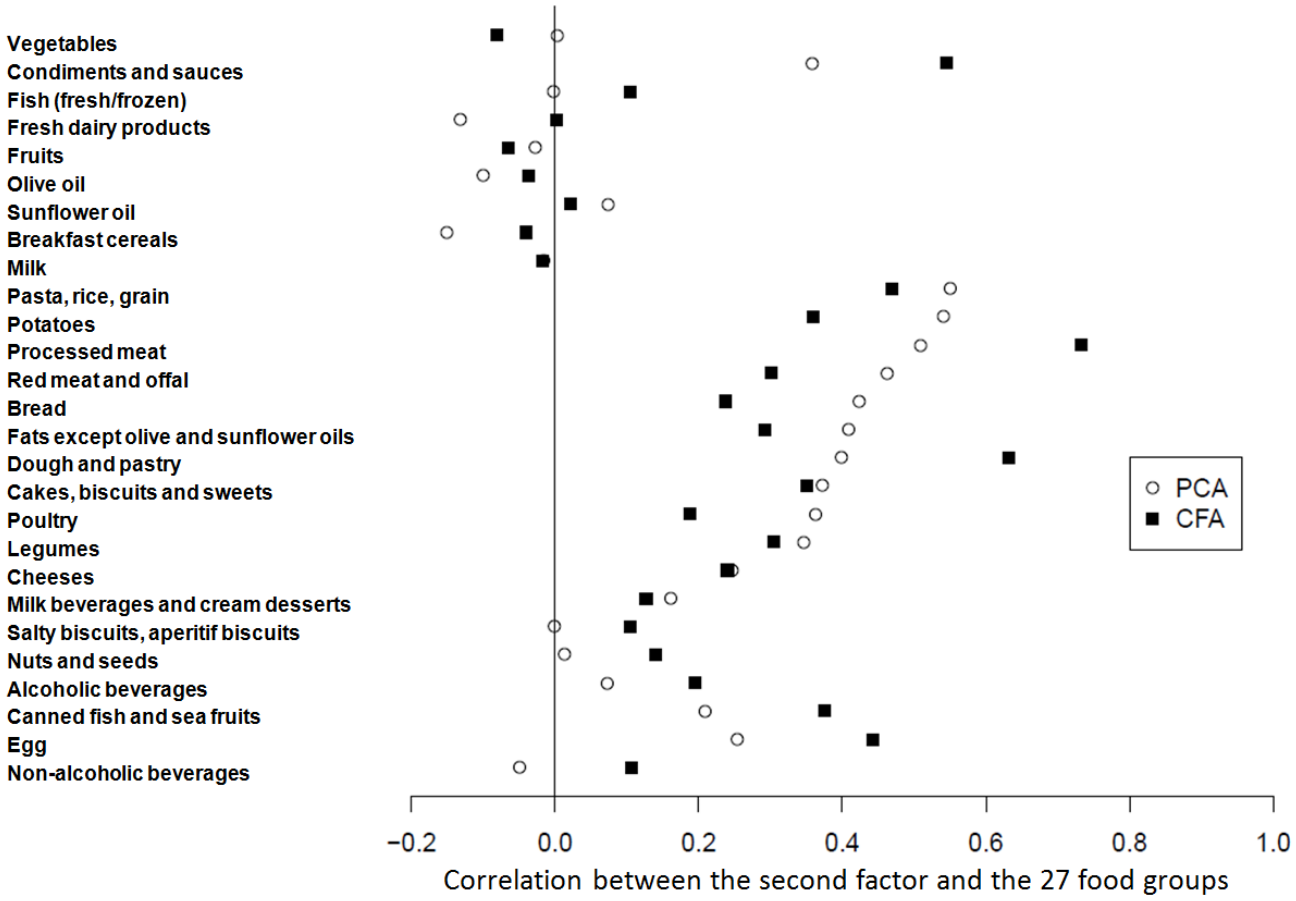
		Intake					
		Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**p for trend**
Factor 1							
PCA	n incident asthma/never asthma	221/5896	230/5888	229/5889	227/5891	270/5848	
	Univariate RR(95% CI)	1.00	1.03 [0.86-1.24]	1.02 [0.85-1.22]	1.01 [0.84-1.21]	1.19 [1.00-1.42]	0.10
	Multivariate RR(95% CI)*	1.00	1.07 [0.88-1.30]	1.05 [0.87-1.28]	1.05 [0.86-1.28]	1.24 [1.03-1.51]	0.06
CFA	n incident asthma/ never asthma	237/5880	227/5891	235/5883	220/5898	258/5860	
	Univariate RR(95% CI)	1.00	0.94 [0.79-1.13]	0.95 [0.80-1.14]	0.88 [0.73-1.06]	1.02 [0.85-1.22]	0.92
	Multivariate RR(95% CI)*	1.00	0.99 [0.81-1.20]	1.00 [0.83-1.22]	0.95 [0.78-1.15]	1.14 [0.94-1.38]	0.30
Factor 2							
PCA	n incident asthma/ never asthma	228/5889	229/5889	225/5893	240/5878	255/5863	
	Univariate RR(95% CI)	1.00	1.03 [0.86-1.24]	1.04 [0.86-1.25]	1.13 [0.94-1.36]	1.26 [1.05-1.50]	0.01
	Multivariate RR(95% CI)*	1.00	1.04 [0.85-1.26]	0.95 [0.77-1.16]	1.05 [0.84-1.30]	1.14 [0.89-1.47]	0.40
CFA	n incident asthma/ never asthma	211/5906	213/5905	242/5876	248/5870	263/5855	
	Univariate RR(95% CI)	1.00	1.06 [0.88-1.29]	1.25 [1.04-1.51]	1.33 [1.10-1.60]	1.47 [1.22-1.77]	<.0001
	Multivariate RR(95% CI)*	1.00	1.00 [0.82-1.23]	1.12 [0.91-1.38]	1.13 [0.91-1.40]	1.30 [1.02-1.67]	0.03
Factor 3							
PCA	n incident asthma/ never asthma	209/5908	215/5903	240/5878	260/5858	253/5865	
	Univariate RR(95% CI)	1.00	1.05 [0.87-1.27]	1.20 [0.99-1.44]	1.32 [1.10-1.58]	1.30 [1.08-1.57]	0.0003
	Multivariate RR(95% CI)*	1.00	1.06 [0.87-1.29]	1.16 [0.96-1.41]	1.19 [0.98-1.45]	1.11 [0.91-1.36]	0.15
CFA	n incident asthma/ never asthma	237/5880	233/5885	237/5881	224/5894	246/5872	
	Univariate RR(95% CI)	1.00	0.98 [0.81-1.17]	1.01 [0.84-1.20]	0.96 [0.80-1.15]	1.08 [0.90-1.29]	0.53
	Multivariate RR(95% CI)*	1.00	0.98 [0.81-1.19]	0.95 [0.79-1.15]	0.89 [0.73-1.08]	0.94 [0.78-1.14]	0.33

* Risk ratios [95% Confidence Interval] (RR [95% CI]) were adjusted for age (as time-scale), menopause, years of education, total energy intake, farmer parents and physical activity

Comparison of the second dietary pattern according to PCA and CFA

Factor 2 was characterized by high correlations with the food groups "Pasta/rice/grain", "Potatoes", "Processed meats", "Red meat and offal", "Bread", "Fats except olive and sunflower oils" and "Dough and pastry". Higher correlations were observed, for PCA compared to CFA, with the food groups "Pasta/rice/grain", "Potatoes", "Red meat and offal, "Bread" and "Fats except olive and sunflower oils". Lower correlations were observed, for PCA compared to CFA, with the food groups "Processed meats" and "Dough and pastry" (see Figure 13). When dietary patterns were independently derived among women retired at baseline and among women not retired at baseline, similar dietary patterns were found for both PCA and CFA (results not shown).

Figure 6. Factor-loading matrix for the second factor identified using both PCA and CFA methods



Whether PCA or CFA was used, women in the highest quintile of Factor 2 were significantly younger than women in the lowest quintile. After adjustment for age, they significantly had a higher BMI, a higher energy intake and used less supplements as compared to women in the lowest quintile. Women in the highest quintile of Factor 2 derived using PCA had also significantly less frequently a postmenopausal status than women in the lowest quintile. Women in the highest quintile of Factor 2 derived using CFA had also a significantly lower physical activity level as compared to women in the lowest quintile. When PCA was used, women in the highest quintile of Factor 2 had significantly more frequently farmer parents than women in the lowest quintile, whereas when CFA was used, they had significantly less frequently farmer parents than women in the lowest quintile (see Table 20).

When PCA was used, a positive significant association was found between Factor 2 and adult-onset asthma, but the association was no longer observed after adjustment for potential confounders (p for trend=0.40). When CFA was used, a positive significant association, that remained significant after adjustment for potential confounders, was found between Factor 2 and adult-onset asthma (p for trend=0.03) (see Table 19).

When sensitivity analyses were performed, still no association was found between Factor 2 identified using PCA and adult-onset asthma. When CFA was used, the magnitude of the association slightly decreased when restricting the study population to the 28,073 women who did not develop asthma in the first 24 months of follow-up (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 0.94 [0.75-1.18], 1.13 [0.90-1.42], 1.08 [0.85-1.38] and 1.20 [0.91-1.58], respectively; p for trend=0.12). Restricting the study population to the 20,853 women without supplements use attenuated the association (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 0.92 [0.71-1.19], 1.14 [0.88-1.46], 1.09 [0.83-1.42] and 1.18 [0.87-1.61], respectively; p for trend=0.17). No association was found after stratification on BMI. After stratification on years of education, a strong significant association was observed among the 3,987 women who did not complete high school (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.30 [0.75-2.25], 1.46 [0.83-2.58], 1.68 [0.92-3.07] and 2.13 [1.10-4.12], respectively; p for trend=0.02), whereas a non significant positive association was found among the 25,419 women with at least a high school diploma (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile:0.96 [0.77-1.19], 1.07 [0.86-1.34], 1.06 [0.84-1.34] and 1.20 [0.92-1.56], respectively; p for trend=0.16). However, the formal test for interaction between Factor 2 and years of education was not statistically significant (p=0.29). After stratification on retirement status, a significant positive association was found among the

18,372 women not retired at baseline (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 0.89 [0.68-1.17], 1.13 [0.87-1.48], 1.23 [0.94-1.62] and 1.29 [0.95-1.76], respectively; p for trend=0.02), whereas a borderline significant positive was observed among the 9,482 women retired at baseline (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.14 [0.81-1.60], 1.16 [0.80-1.68], 1.09 [0.71-1.67] and 1.81 [1.14-2.89], respectively; p for trend=0.06).

Table 20. Baseline characteristics of the population according to the second factor identified using both PCA and CFA methods

	PCA					CFA				
	Q1	**Q3**	**Q5**	***p****	***p****	**Q1**	**Q3**	**Q5**	***p****	***p****
Age (years), m(SD)	55.2 (6.7)	53.4 (6.6)	51.4 (6.1)	<.0001	/	56.0 (6.7)	53.2 (6.4)	51.1 (5.9)	<.0001	/
Post menopausal women (%)	70.3	59.5	48.7	<.0001	0.03	74.0	59.0	46.8	<.0001	0.10
Use of HRT (%)	69.2	72.9	75.0	<.0001	0.46	67.3	73.3	75.4	<.0001	0.23
BMI (kg/m²), m(SD)	22.6 (3.0)	22.7 (3.0)	23.1 (3.4)	<.0001	<.0001	22.6 (3.0)	22.8 (3.1)	23.2 (3.4)	<.0001	<.0001
BMI (%)										
< 20 kg/m²	17.4	15.5	14.2			18.2	15.4	13.4		
20 to 25 kg/m²	64.4	66.2	63.0	<.0001	<.0001	64.0	65.7	63.1	<.0001	<.0001
≥ 25 kg/m²	18.3	18.2	22.8			17.8	19.0	23.4		
Physical activity (METS/week), m(SD)	51.7 (51.4)	49.0 (46.1)	47.7 (44.2)	<.0001	0.44	50.4 (46.6)	49.8 (50.8)	49.2 (47.3)	0.16	0.04
Physical activity level (%)										
Low	31.4	32.1	34.7			32.4	32.9	33.5		
Medium	32.4	34.8	33.5	<.0001	0.12	32.3	33.7	33.3	0.01	0.01
High	36.2	33.2	31.8			35.3	33.4	33.1		
Total energy intake (kcal/day), m(SD)	1712 (388)	2159 (371)	2814 (475)	<.0001	<.0001	1729 (376)	2166 (387)	2783 (498)	<.0001	<.0001
Years of education (%)										
< 12	15.3	12.6	13.6			15.3	13.3	13.2		
12-14	55.0	56.5	53.6	0.0002	0.64	55.8	55.4	52.7	<.0001	0.83
15-16	14.6	16.1	17.5			13.7	16.2	18.2		
≥ 17	15.1	14.9	15.4			15.2	15.1	15.9		
Supplements use (%) †	29.8	25.6	24.2	<.0001	<.0001	29.3	26.4	25.0	<.0001	0.002
Farmer parents (%)	12.5	15.1	16.1	<.0001	<.0001	15.1	14.8	13.8	0.03	0.05

Abbreviations: m (SD), mean (standard deviation); Q1, 1st quintile; Q3, 3rd quintile; Q5, 5th quintile.

* *p* for trend across quintiles of dietary patterns. Chi-squared tests were used for categorical variables and t-tests were used for continuous variables

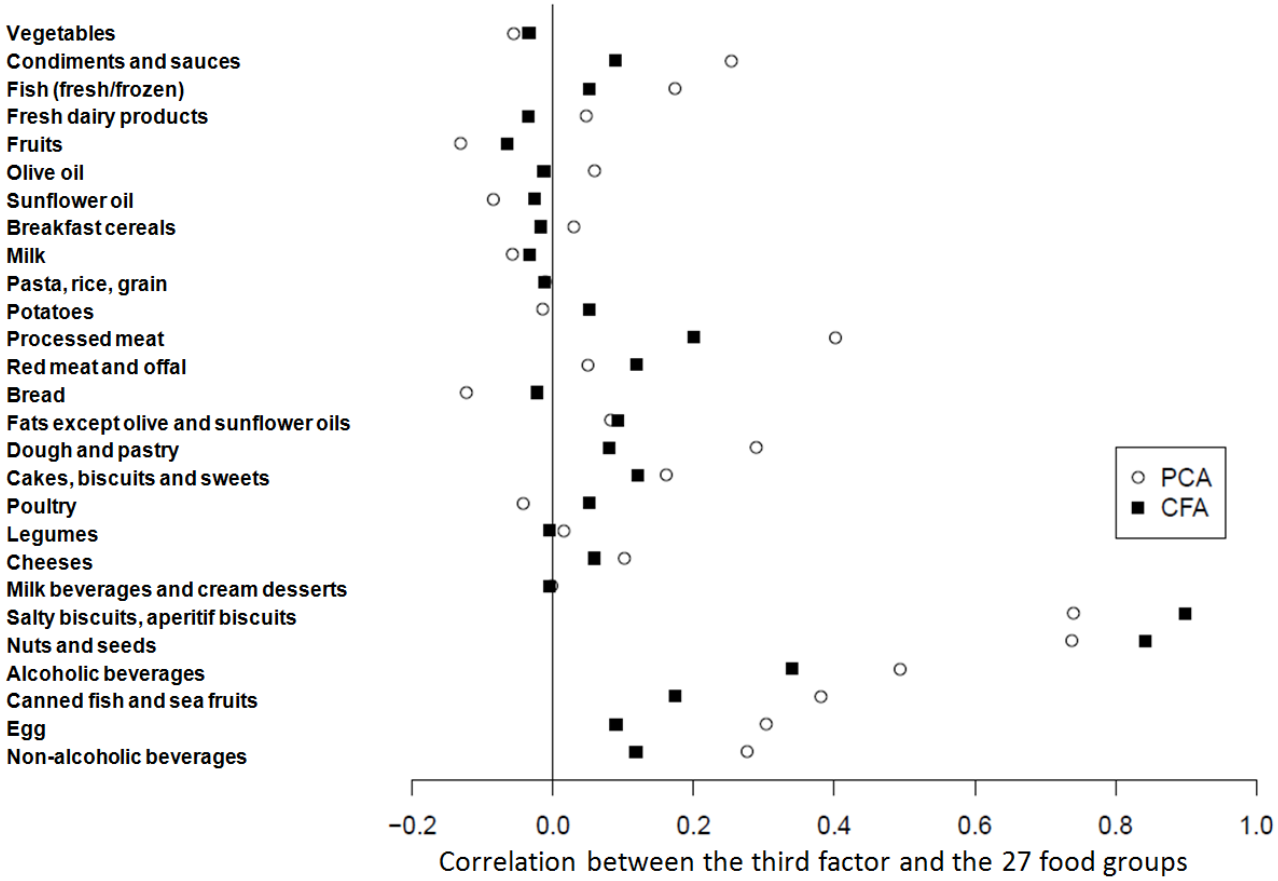
** *p* for trend across quintiles of dietary patterns after adjustment on age. Generalized linear models were used for continuous variables and logistic regression models for categorical variables

† Supplements use was recorded in 1995

Comparison of the third dietary pattern according to PCA and CFA

Factor 3 was characterized by high correlations with the food groups "Salty/aperitif biscuits", "Nuts and seeds", "Alcoholic beverages", "Canned fish and sea fruits" and "Eggs". Lower correlations were observed, for PCA compared to CFA, with the food groups "Salty/aperitif biscuits" and "Nuts and seeds". Higher correlations were observed, for PCA compared to CFA, with the food groups "Alcoholic beverages", "Canned fish and sea fruits" and "Eggs" (see Figure 14). When dietary patterns were independently derived among women retired at baseline and among women not retired at baseline, similar dietary patterns were found for both PCA and CFA (results not shown).

Figure 7. Factor-loading matrix for the third factor identified using both PCA and CFA methods



Whether PCA or CFA was used, women in the highest quintile of Factor 3 were significantly younger than women in the lowest quintile. After adjustment for age, they significantly used more frequently MHT after menopause, had a higher BMI, a higher energy intake, a lower educational level, used less supplements and had less frequently farmer parents as compared to women in the lowest quintile. Women in the highest quintile of Factor 3 identified using PCA had also a significantly higher physical activity level than women in the lowest quintile, whereas the association was only borderline significant using CFA (see Table 21).

No association was found between Factor 3 and adult-onset asthma when CFA was used. When PCA was used, a positive significant association was found between Factor 3 and adult-onset asthma, but the association was no longer observed after adjustment for potential confounders (p for trend=0.15) (see Table 19).

When sensitivity analyses were performed, still no association was found between Factor 3 identified using CFA and adult-onset asthma. When PCA was used, the positive association became borderline significant when restricting the study population to the 28,073 women who did not develop asthma in the first 24 months of follow-up (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.08 [0.86-1.35], 1.22 [0.98-1.51], 1.24 [1.00-1.54] and 1.16 [0.92-1.45], respectively; p for trend=0.10), and significant when restricting to the 20,853 women without supplements use (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.11 [0.86-1.43], 1.30 [1.02-1.66], 1.29 [1.01-1.64] and 1.25 [0.97-1.61], respectively; p for trend=0.04). No association was found after stratification on BMI or on years of education. After stratification on retirement status, a borderline significant positive association was found among the 18,372 women not retired at baseline (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.11 [0.85-1.43], 1.13 [0.88-1.46], 1.30 [1.01-1.66] and 1.21 [0.94-1.56], respectively; p for trend=0.06), whereas no association was observed among the 9,482 women retired at baseline (multivariate RR for 2nd, 3rd, 4th and 5th vs. lowest quintile: 1.02 [0.72-1.46], 1.31 [0.93-1.84], 0.98 [0.67-1.43] and 0.95 [0.64-1.41], respectively; p for trend=0.88).

Table 21. Baseline characteristics of the population according to the third factor identified using both PCA and CFA methods

	PCA					CFA				
	Q1	**Q3**	**Q5**	***p****	***p****	**Q1**	**Q3**	**Q5**	***p****	***p****
Age (years), m(SD)	54.6 (6.9)	53.2 (6.5)	52.4 (6.2)	<.0001	/	53.7 (6.8)	53.5 (6.6)	52.6 (6.3)	<.0001	/
Post menopausal women (%)	65.2	60.0	54.8	<.0001	0.48	61.2	60.9	55.9	<.0001	0.71
Use of HRT (%)	66.1	72.6	77.2	<.0001	<.0001	66.2	72.8	76.1	<.0001	<.0001
BMI (kg/m²), m(SD)	22.5 (3.1)	22.7 (3.1)	23.3 (3.2)	<.0001	<.0001	22.6 (3.3)	22.8 (3.0)	23.2 (3.2)	<.0001	<.0001
BMI (%)										
< 20 kg/m²	19.3	15.8	10.9			19.6	14.9	11.5		
20 to 25 kg/m²	63.4	65.6	65.9	<.0001	<.0001	62.3	66.9	66.3	<.0001	<.0001
≥ 25 kg/m²	17.3	18.6	23.1			18.1	18.2	22.2		
Physical activity (METS/week), m(SD)	48.0 (47.7)	48.1 (42.5)	51.5 (46.4)	<.0001	<.0001	48.7 (46.6)	50.5 (52.1)	49.6 (46.0)	0.32	0.09
Physical activity level (%)										
Low	34.3	33.6	30.7			34.2	31.9	32.1		
Medium	33.9	33.8	33.5	<.0001	<.0001	33.0	34.0	33.8	0.02	0.0003
High	31.8	32.6	35.9			32.8	34.2	34.1		
Total energy intake (kcal/day), m(SD)	2071 (511)	2127 (509)	2529 (566)	<.0001	<.0001	2063 (528)	2160 (519)	2485 (565)	<.0001	<.0001
Years of education (%)										
< 12	14.7	13.0	12.8			14.6	13.5	13.2		
12-14	54.3	56.1	55.4	0.27	0.01	52.3	55.2	56.2	0.004	<.0001
15-16	14.5	16.1	16.6			16.2	15.9	16.2		
≥ 17	16.6	14.8	15.2			17.0	15.4	14.4		
Supplements use (%) †	27.4	26.1	24.7	0.0002	0.01	28.6	25.6	24.0	<.0001	<.0001
Farmer parents (%)	18.6	15.0	11.1	<.0001	<.0001	16.1	15.3	12.7	<.0001	<.0001

Abbreviations: m (SD), mean (standard deviation); Q1, 1st quintile; Q3, 3rd quintile; Q5, 5th quintile.

* *p* for trend across quintiles of dietary patterns. Chi-squared tests were used for categorical variables and t-tests were used for continuous variables

** *p* for trend across quintiles of dietary patterns after adjustment on age. Generalized linear models were used for continuous variables and logistic regression models for categorical variables

† Supplements use was recorded in 1995

DISCUSSION

In this longitudinal study, two methods were used to derive dietary patterns, and to study their associations with new adult-onset asthma. Whether we used PCA or CFA, three similar factors were found and labeled “Prudent-like” pattern, “Western-like” pattern and “Aperitif-like” pattern. Since the method of estimation differs depending on whether PCA or CFA is applied to derive dietary patterns, PCA components are not directly comparable to CFA factors (144–146). Nevertheless in the present study, comparisons between PCA and CFA were made based on the correlations between food groups and dietary patterns rather than the values of the loadings. For each pattern, we reported different correlations between food groups and dietary patterns when using PCA or CFA, leading to different associations between dietary patterns and socio-economic characteristics, and adult-onset asthma.

Labeling factors is arbitrary and is based on an investigator’s interpretation, which can be misleading, as dietary behaviors are specific to the cultural and social context of each country. Food patterns with different labels can be very similar. Conversely, patterns that have the same labels are not always similar (119). In the present study, the “Prudent-like” patterns had a relatively high contribution for the “Sauces and condiments” food groups, which was also found in other European studies (6,305). Dietary habits depend on social aspects as well: the same foods are not consumed according to the socioeconomic level. Therefore, caution is needed when labeling the dietary patterns, especially for the interpretation of the associations found with a health outcome, which may vary between countries (cultural context) and between people (social context).

For the “Prudent-like” pattern, a pattern traditionally loaded by vegetables and fruits, the correlation with the vegetables food group was higher when using CFA than PCA. Beside these differences regarding correlation, the “Prudent-like” patterns derived using both methods also have different characteristics: the one derived using CFA was positively associated with farmer parents, whereas the one derived using PCA was not related to farmer parents. The social context in which a child’s eating pattern develops is important because the local environment serves as a model for the developing child (306). In that context, a farming lifestyle during childhood probably influences later food preferences, due to different food availability in rural areas, and a farming lifestyle was found to be related to a healthier behaviour regarding the intake of fruits and vegetables. Thus, the “Prudent-like” pattern derived using CFA seems to relate more to a “healthy diet” than the one derived using PCA.

Regarding association with adult-onset asthma, an unexpected borderline positive association was found with the “Prudent-like” pattern derived using PCA, as previously reported in the Nurses’ Health Study (9). The positive association disappeared in sensitivity analyses, and in stratified analyses, the association was only observed among women with the highest educational level, which was not consistent with our hypothesis. When CFA was used, no association was reported for the “Prudent-like” pattern, neither in the main analysis nor in sensitivity and stratified analyses.

For the “Western-like” pattern, a pattern traditionally loaded by processed meat and desserts, the correlation with the processed meat food group and the dough and pastry food group was also higher when using CFA than PCA. Regarding the characteristics of the patterns, the “Western-like” pattern derived using CFA was negatively associated with farmer parents, whereas the one derived using PCA was positively associated with farmer parents. Thus, the “Western-like” pattern derived using CFA seems to relate more to an “unhealthy diet” than the one derived using PCA. Regarding association with adult-onset asthma, no association was reported with the “Western-like” pattern derived using PCA, neither in the main analysis nor in sensitivity and stratified analyses, which was consistent with other longitudinal studies (9–11). When CFA was used, a positive association between the "Western-like” pattern and adult-onset asthma was reported. We also reported a stronger association among women who did not complete high school, suggesting that among women with a lower socioeconomic level, the Western diet might have a higher effect on respiratory health, potentially due to a lower quality of foods. However, the fact that this association was attenuated in sensitivity analyses requires caution in the interpretation of our findings.

In the present study, whereas the third pattern identified using PCA is a “Drinker-like” pattern, the third pattern identified using CFA, which has a relatively low correlation with the “Alcoholic beverages” food group, is rather an “Apéritif-like” pattern. When PCA was used, a deleterious effect of the “Drinker-like” pattern on adult-onset asthma was suggested, but only in sensitivity analysis, thus requiring caution interpretation. When CFA was used, no association was reported with the “Apéritif-like” pattern. The only longitudinal study that investigated the association between a “Nuts and wine” pattern and adult-onset asthma reported no association (11).

The assessment of asthma was based on one repeated question; no symptoms, treatment or objective biological data were available, but women’s answers to this question

were found very consistent with asthma medications dispensed to E3N women overtime (294). Diet was assessed using a validated food frequency questionnaire. Reproducibility of the questionnaire was also tested after 1 year in a sample of 119 women and showed a good reproducibility for foods (286). The fact that diet was only assessed once (in 1993) is a limitation of this study, as dietary patterns may change over time. However, longitudinal studies performed in cohorts have shown reasonable tracking of diet in adult life (307). In the present study, we reported similar dietary patterns among retired and non-retired women, showing that among this specific population of older and well-educated women, dietary habits are quite similar before and after retirement from work, which is one of the last transitional life events involving important lifestyle changes (304). It is also reasonable to assume that dietary habits, assessed as dietary patterns, are even less prone to change over time: whereas consumption of specific foods may vary according to age, it is more likely that (un)healthy dietary habits will tend to remain (un)healthy over time. On the other hand, the fact that the associations between dietary patterns and adult-onset asthma were stronger among younger women (i.e. not retired at baseline) suggests that the role of diet in asthma may differ according to windows of exposure, and thus requires caution in the interpretation of our findings. One strength of this study is that E3N women have a high education level and strong involvement in the E3N cohort study (> 80% response rate at each follow up questionnaire). Because of the small prevalence of obesity in E3N women, caution is needed in the interpretation of the role of overweight/obesity in the diet-asthma association. As expected, women lost to follow-up were different from included women: they were older, heavier and less educated. This selection bias is typical in longitudinal epidemiological studies (308,309). Although adjustments for confounders were made, the possibility of residual confounding cannot be ruled out. Whether inverse-probability weighting can be used to account for bias due to selective attrition, and specifically when a source of attrition is mortality, is still a debated topic (308,309), and we decided not to use it in our analyses. Our results are not representative of the oldest women of our population. More studies are needed to verify our findings in different populations.

In summary, the present study supports the alternative use of CFA to PCA for the identification of dietary patterns in epidemiologic studies. While further studies are needed to understand the role of diet in asthma onset, CFA should be considered in the future for the identification of dietary patterns.

2. Obesity and asthma

2.1 Joint effect with physical activity (MSM)

This work has been presented at the Epidemiological study on the genetics and environment of asthma (EGEA) seminar in June 2012.

INTRODUCTION

Obesity is a well known risk factor for asthma in adults, especially in women, but mechanisms that underlie this relationship are still unclear. It may be due to an effect of obesity through lung mechanics, an inflammatory state, or sex hormones (12). It has also been suggested that the effects of obesity on asthma could possibly be explained by lifestyle factors that also have been evolving in the last decades, such as dietary habits, exercise habits or sedentary lifestyle (260). Obesity has been associated with more severe asthma, worse asthma control and more asthma exacerbations (13).

The effect of physical activity on asthma is more controversial: while regular physical activity has been associated with reduced risk of exacerbations in women with asthma (76), there is also the issue of possible reverse causation (i.e. asthma may limit the practice of intense physical activity by causing exacerbations in asthmatics) (74). It is also argued whether physical activity relates more to the evolution than the development of asthma (75–77).

Obesity and physical activity are clearly related to each other (310). It is general knowledge that physical activity has an impact on BMI. However, a high BMI could also have a limiting effect on physical activity, suggesting that physical activity may be a mediator in the causal effect of BMI on asthma. Thus, interrelations between BMI, physical (in)activity and asthma represent a relevant but complex research question, which is poorly studied (311).

Given the time-dependent, bidirectional associations between physical activity and body composition, it is important to determine their relative contributions to current asthma with symptoms. Furthermore, it is of interest to evaluate whether physical activity confounds the relation between obesity and asthma, or if it is an integral step in the causal pathway.

The aim of our study was to consider the joint and independent roles of physical activity and body composition as determinants of current asthma with symptoms, using longitudinal data. Given the time-dependent, bidirectional associations between BMI, physical activity and asthma, standard methods of analysis may be biased. We used marginal structural models to address the issue of time-dependent confounding implicit in the analysis of these data (264).

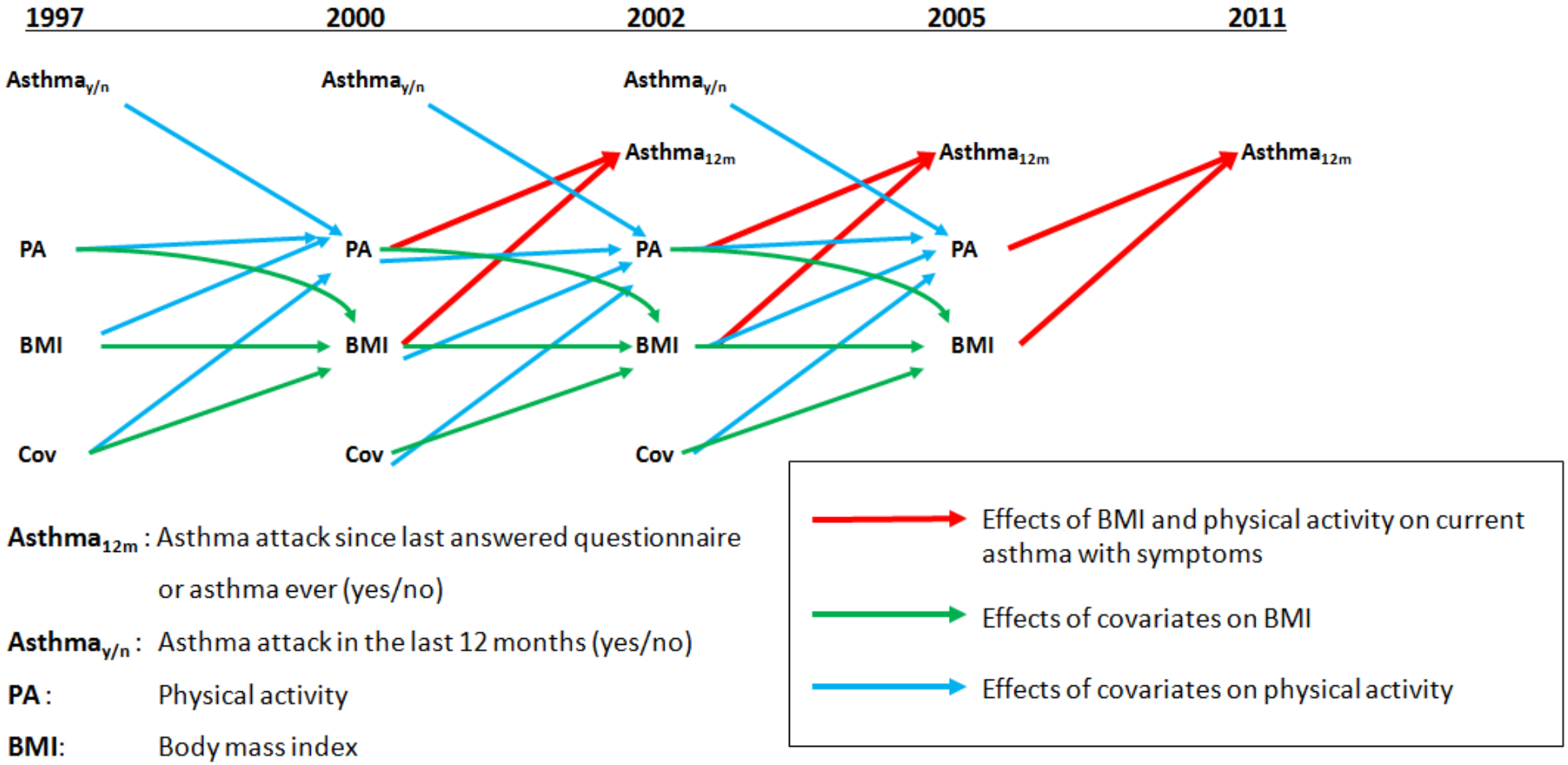
MATERIALS AND METHODS

Study design and periods of interest

The analyses were conducted in the E3N and the Asthma-E3N studies. As we chose to investigate current asthma with symptoms (i.e. asthma attack in the last 12 months), we used data from the 2002 and 2005 questionnaires in the main E3N study, and data from the Asthma-E3N study (the question regarding asthma attacks in the last 12 months was not available in the other questionnaires).

Since we wanted to assess the joint effects of BMI and physical activity at time t on current asthma with symptoms at time t+1, we used data on physical activity and BMI in 2000, 2002 and 2005. These relationships are represented in Figure 15 by red arrows. Green arrows represent the effect of covariates that may affect BMI at time t. We hypothesized that BMI at time t relates to BMI at time t-1 and that physical activity at t-1 affect BMI at time t. In addition, becoming menopausal or quitting smoking at time t-1 may lead to a weight gain at time t. Blue arrows represent the effect of covariates that may affect physical activity at time t. Physical activity at time t relates to physical activity at time t-1. Obesity or asthma at time t-1 may lead to a reduced level of physical activity at time t. In addition, menopause and tobacco status at time t-1 are lifestyle covariates that may relate to physical activity at time t. Thus, 3 periods could be evaluated, each period consisting of 3 time points: if physical activity and BMI are exposures at time t, current asthma with symptoms will be the outcome at time t+1 and covariates at times t-1 affect physical activity and BMI at time t; so the first period is 1997-2002, the second period is 2000-2005 and the last period is 2002-2011.

Figure 8. Time-dependent confounding for the joint roles of physical activity and BMI on current asthma with symptoms



Asthma$_{12m}$: Asthma attack since last answered questionnaire or asthma ever (yes/no)

Asthma$_{y/n}$: Asthma attack in the last 12 months (yes/no)

PA : Physical activity

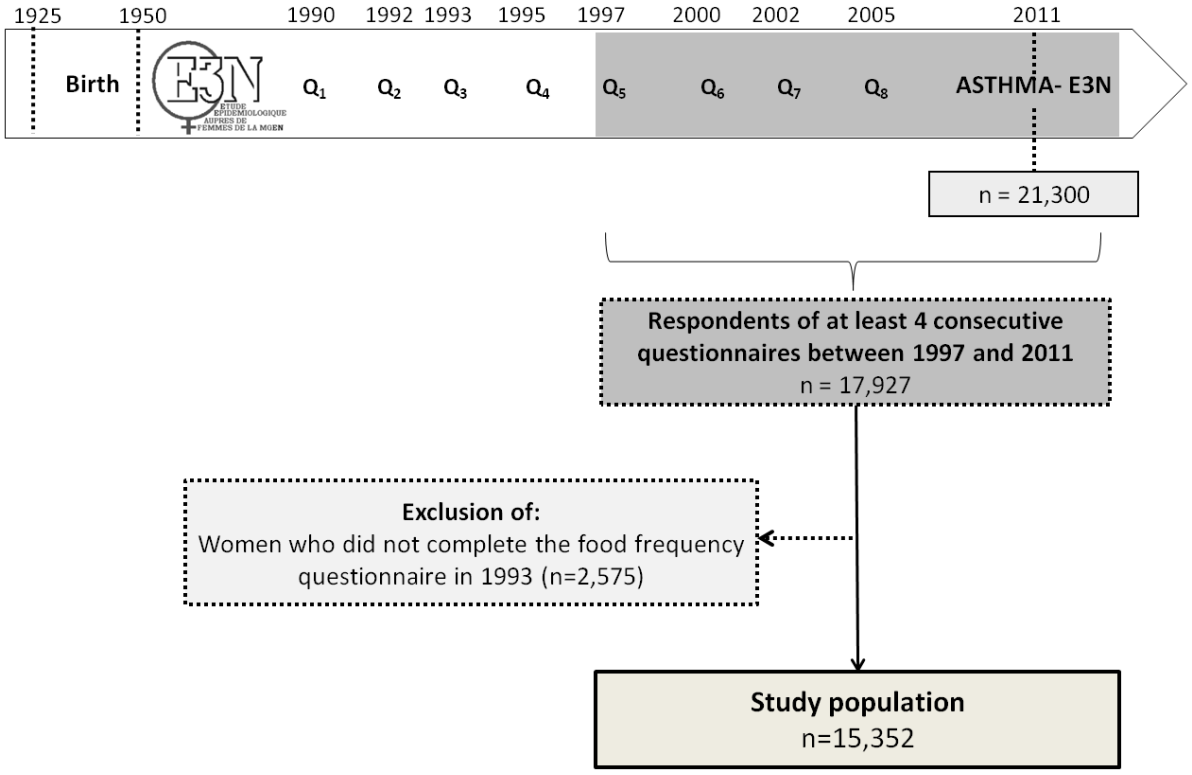
BMI: Body mass index

Cov : Time-varying covariates (menopause, smoking status..)

Study population

Among the 21,300 women who received the Asthma-E3N questionnaire, only women who responded to at least 4 consecutive questionnaires (i.e. either Q5, Q6, Q7 and Q8 or Q6, Q7, Q8 and Asthma-E3N) were included (n=17,927), so that at least 2 periods were evaluated (with only one period evaluated, MSM models would have been pointless). We excluded women who did not complete the food frequency questionnaire in 1993 (n=2,575). In the end, 15,352 women were included (see Figure 16).

Figure 16. Selection of the study population



In comparison with included women, women excluded from the study population were significantly older and thus, had more frequently a postmenopausal status. They used less frequently HRT after menopause, had a lower educational level and were more frequently current smokers. They also had a higher BMI and a lower physical activity level. Excluded women have had ever asthma more frequently, in particular consistent asthma (see Table 22).

Table 22. Comparison of excluded versus included women

	Included (n=15,352)	**Excluded** (n=5,948)	**p**
Age (years), m (SD)	61.2 (6.3)	61.6 (6.4)	0.001
BMI (kg/m²), m (SD)	23.8 (3.8)	24.3 (4.1)	<0.0001
BMI (%)			
< 20 kg/m²	12.2	10.5	
20 to 25 kg/m²	56.8	54.0	<0.0001
25 to 30 kg/m²	24.4	26.3	
≥ 30 kg/m²	6.6	9.2	
Physical activity (METS/week), m (SD)	69.0 (48.0)	66.8 (53.5)	0.007
Years of education (%)			
< 12	10.7	18.2	
12-14	51.2	48.2	<0.0001
15-16	19.0	17.5	
≥ 17	19.2	16.1	
Smoking status (%)			
Non smoker	52.4	51.7	
Past smoker	38.5	35.7	<0.0001
Current smoker	9.1	12.7	
Post menopausal women (%)	96.6	98.1	<0.0001
Use of HRT among post menopausal women (%)	75.3	67.7	<0.0001

m (SD): mean (standard deviation)

Assessment of asthma

Current asthma with symptoms was used as the outcome and asthma ever as a time-dependent covariate. Current asthma with symptoms (asthma (t+1)) was considered in 2002, 2005 and 2011 and defined among women with ever asthma (i.e. women who answered at least once in the previous questionnaires to the question "Have you ever had asthma attacks?"), by the presence of asthma attacks in the last 12 months. Ever asthma (asthma (t-1)) was computed in 1997, 2000, and 2002, based on consistency with previous answers to the asthma question until then, and was categorized in 3 classes: never asthma, "inconsistent" ever asthma (i.e. at least one negative answer to the ever asthma question after a positive one), and "consistent" ever asthma (i.e. no negative answer to the ever asthma question after a positive one).

Assessment of BMI

BMI was obtained from the main questionnaires sent in 1995,1997, 2000, 2002 and 2005.

For BMI used as a time-dependent exposure (BMI (t)), we considered the data in 2000, 2002 and 2005, and classified it in 4 categories (< 20, [20-25[, [25-30[, ≥30 kg/m²), in order to estimate the effect of overweight and obesity on current asthma with symptoms in the final model.

For BMI used as a time-dependent covariate (BMI (t-1)), we considered the data in 1995, 1997, 2000 and 2002 and used as a continuous variable to improve convergence (as BMI (t-1) is highly correlated with BMI (t)). To deal with missing data for time-dependent covariate (overall missingness for BMI: 3% of observations), the mean of BMI at t-1 and t-2 was considered for each period, (i.e. for the first period, we considered the mean of BMI in 1995 and 1997; for the second period, the mean of BMI in 1997 and 2000; and for the third period, the mean of BMI in 2000 and 2002). When one of the BMI variables was missing (i.e. either BMI at t-1 or at t-2), we considered the other variable alone.

Assessment of physical activity

Physical activity was obtained from the main questionnaires sent in 1993, 1997, 2002 and 2005. Since the main E3N questionnaire in 2000 did not include questions on physical activity, we estimated the physical activity in 2000 as the mean of physical activity in 1997 and 2002 (one questionnaire before and one questionnaire after).

For physical activity used as a time-dependent exposure (physical activity (t)), we considered the data in 2000, 2002 and 2005 and total physical activity values expressed in METS/week were converted into tertiles (low, moderate or high physical activity) at each t period.

For physical activity used as a time-dependent covariate (physical activity (t-1)), we considered the data in 1993, 1997, 2000 and 2002, and classified it into tertiles (low, moderate or high physical activity) at each t-1 period. To deal with missing data for time-dependent covariate (overall missingness for physical activity: 2% of observations), we imputed data from the previous questionnaire. Thus, for the first period, if physical activity was missing in 1997, we considered physical activity in 1993; for the second period, if physical activity was missing in 2002 (as availability in 2000 depends on both availability in 1997 and 2002), we considered physical activity in 1997; and for the third period, if physical activity was missing in 2002, we considered physical activity in 1997.

Assessment of time-dependent covariates

Smoking status was considered in 1997, 2000 and 2002, and categorized in 3 classes: non smoker, past smoker and current smoker. Menopausal status was considered in 1997, 2000 and 2002, and categorized in 3 classes, based on age of menopause and information on use of hormone replacement therapy (HRT), which was available in 2005: no menopause, menopause and not taking HRT, menopause and taking HRT.

Assessment of fixed covariates

Age was assessed in 1997 and used as a continuous variable. Educational level was assessed in 1990, and categorized in 4 classes: < high school, high school to 2-level university

diploma, 3-/4-level university diploma, ≥ 5-level university diploma. Since diet was only assessed once in 1993, it was considered as a fixed covariate. As obesity reflects an imbalance between energy provision and energy expenditure (i.e. physical activity), total energy intake may be considered as the most valid confounder in the study of the effect of obesity and physical activity. Thus, it was used as a fixed covariate in our analysis.

Statistical analysis

Application of the MSM requires two steps. The first step aims at creating a pseudo-population by assigning weights to each individual. Standardized weights for physical activity/BMI were stabilized and calculated as follows:

$$SW_{\mathrm{i}}(\mathrm{T}) = \prod_{t \leq T} \frac{P(E_t = e_{it} \mid \bar{E}\,(t-1) = \bar{e}_i\,(t-1),\ V = v_i)}{P(E_t = e_{it} \mid \bar{E}\,(t-1) = \bar{e}_i\,(t-1),\ \bar{L}\,(t-1) = \bar{l}_i(t-1),\ V = v_i)},$$

where $SW_i(T)$ is stabilized weight for subject i, at time T, E represents physical activity/BMI, L represents a vector of time-dependent covariates (smoking status, menopausal status and physical activity for BMI, and smoking status, menopausal status, asthma and BMI for physical activity), and V represents a vector of time-independent (fixed) covariates (age at baseline, total energy intake and educational level).

The weights are proportional to the inverse of the probability that each subject had his own exposure (physical activity or BMI) history at a given time (t-th time period). These probabilities were estimated through "exposure models", that is, multinomial logistic regression models for the probability of exposure at each time t. Thus, for each subject, at each given time, a weight for physical activity and a weight for BMI were estimated. The variables included in the exposure models are presented in Table 23. In order to achieve weight stabilization, the set of baseline covariates V was also included in the weight numerator model (in addition to the weight denominator model). Thus, these variables were not adjusted for through the weights, and were thus added as covariates in the MSM (313).

Table 23. Variables included in exposure models for physical activity and BMI

Exposure model		Included variables
Physical activity (t)	Numerator	Age, time, total energy intake, educational level, physical activity (t-1)
	Denominator	Age, time, total energy intake, educational level, physical activity (t-1), asthma (t-1), BMI (t-1), menopausal status (t-1), smoking status (t-1)
BMI (t)	Numerator	Age, time, total energy intake, educational level, BMI (t-1)
	Denominator	Age, time, total energy intake, educational level, physical activity (t-1), BMI (t-1), menopausal status (t-1), smoking status (t-1)

The second step consists of estimating the joint effect of physical activity and BMI on current asthma with symptoms in the reweighted pseudopopulation. As proposed by Tager el al (273), we used a weighted pooled multinomial logistic model in which the final weight was the product of the weight for physical activity and the weight for BMI.

MSM have been shown to be sensitive to the "positive assumption", which requires that there are a positive number of subjects (at least one) in each exposure category, for all levels of the confounders and at all time-periods. Non-positivity may be structural if, for a given level of a confounder, subjects are by definition all unexposed (or all exposed). This does not occur in our analyses. Non-positivity may also occur at random, especially if the number of covariates included in the exposure model is high, or if some of the categorical covariates have many levels (313).

We performed several sensitivity analyses. The estimated weight distribution may serve as indicator of the "positive assumption" (313). Though no precise numeric criteria have been defined yet, "well-behaved" weights have a mean close to 1 and a "small range" (264). As a sensitivity analysis, we evaluated whether associations observed with the MSM may be driven by a small number of individuals with an extreme weight (intuitively, associations may be biased if a few subjects are assigned a weight disproportionally large or small). For this purpose, we used weight truncation (i.e. we reset the value of weights greater than the 99^{th} percentile to the 99^{th} percentile value and the value of weights lower than the 1^{st} percentile to the 1^{st} percentile value). When weights are truncated, associations observed using the MSM

are expected to be closer to those observed with a standard model, as the time-dependent confounding is less controlled (272,313). Due to the potential overlap between the diagnosis of COPD and asthma, analyses restricted to never smokers (n= 8,062) were also performed.

RESULTS

The characteristics of women are presented in Table 24. The mean age of women in 1997 was 56 years, and almost 40% of them had at least a 3-level university diploma. The prevalence of current asthma with symptoms remained stable between 2002 and 2011, with roughly 6% of women reporting asthma symptoms in the last 12 months. The prevalence of obese women increased from 2000 to 2005, from 6 to 7%. The prevalence of current smokers between 1997 and 2002 remained stable with less than 10% of women.

Using MSM, we found no association between physical activity and current asthma with symptoms: OR (95% CI) were 1.02 (0.91-1.15) and 1.03 (0.91-1.17), respectively for moderate and high physical activity levels versus low level of physical activity (see Figure 17). However, we observed a strong positive and significant association between BMI and current asthma with symptoms with OR (95% CI) = 1.39 (1.22-1.58) for overweight vs. normal BMI and OR (95% CI) = 1.90 (1.56-2.30) for obese vs. normal BMI.

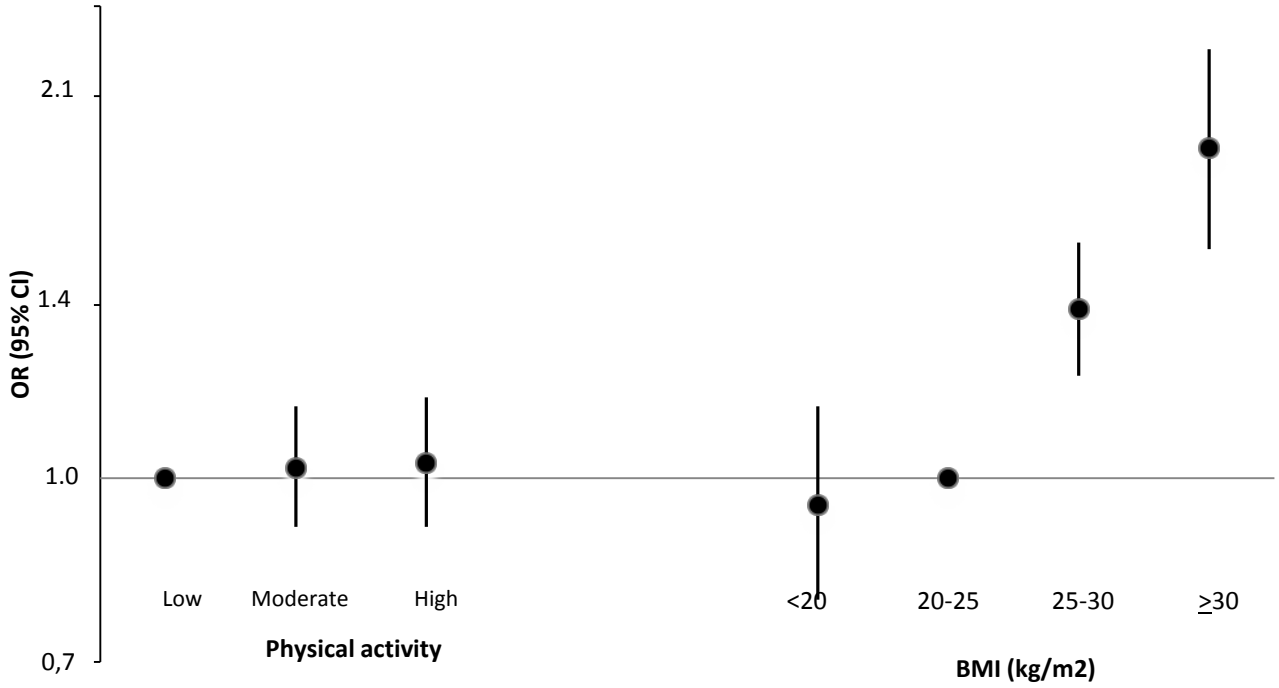
Table 24. Descriptive analysis: subjects' characteristics (n=15,352):

	1990 (Q1)		**1993 (Q3)**		**1997 (Q5)**		**2000 (Q6)**		**2002 (Q7)**		**2005 (Q8)**		**2011 (Asthma E3N)**	
	N missing	m (SD) or %	N missing	m (SD) or %	N missing	m (SD) or %	N missing	m (SD) or %	N missing	m (SD) or %	N missing	m (SD) or %	N missing	m (SD) or %
FIXED COVARIATES														
Age (years)					167	55.9 (6.4)								
Educational level														
< high school	569	10.7												
high school to 2-level university diploma		51.2												
3/4-level university diploma		19.0												
≥ 5-level university diploma		19.2												
Total energy intake (kcal/day)			0	2,226 (557)										
OUTCOME (T+1)														
Current asthma with symptoms									1,112	6.6	1,945	6.5	2,850	6.5
TIME-DEPENDENT EXPOSURES (T)														
Physical activity														
1st tertile							1,004	33.4	499	33.3	309	33.7		
2nd tertile								33.3		33.4		33.0		
3rd tertile								33.3		33.3		33.3		

BMI (kg/m²)								
<20.0			149	12.2	161	12.2	297	12.8
20.0-24.9				58.2		56.8		55.4
25.0-29.9				23.5		24.4		24.8
≥ 30				6.1		6.6		7.0
TIME-DEPENDENT COVARIATE (T-1)								
Physical activity								
1st tertile	19	33.7	571	33.6	66	33.5		
2nd tertile		33.1		33.3		33.4		
3rd tertile		33.2		33.1		33.1		
BMI (kg/m²)	88	23.4 (3.5)	12	23.6 (3.6)	7	23.8 (3.7)		
Ever asthma								
Never	157	79.1	1	77.3	277	71.3		
Ever inconsistent		14.9		17.3		18.1		
Ever consistent		6.0		5.5		10.6		
Smoking status								
Non smoker	174	52.7	2	52.5	117	52.4		
Past smoker		37.4		39.0		38.5		
Current smoker		9.9		8.5		9.1		
Menopausal status								
Non menopausal	303	27.2	136	10.1	136	3.4		
Menopausal without HRT		16.4		20.8		23.9		
Menopausal with HRT		56.4		69.1		72.7		

m (SD): mean (standard deviation). N missing: number of missing data.

Figure 17. Odds Ratios (95% CI) from marginal structural models for the joint effect of BMI and physical activity on current asthma with symptoms in all women (n=15,352)



We also used weight truncation to evaluate whether associations observed with the MSM may be driven by a small number of individuals with an extreme weight. The mean of the weights was 1.00; the range was (0.57; 1.75) for physical activity, (0.50; 1.56) for BMI and (0.49; 1.90) for the total weight; and the 1st and 99th percentiles were (0.81; 1.24) for physical activity, (0.88; 1.14) for BMI and (0.78; 1.27) for the total weight. When extreme weights were truncated, the OR for physical activity and BMI remained very similar (see Table 25). When we restricted our analyses to never smoking women, similar results were also observed (see Table 25).

Table 25. Sensitivity analyses - odds ratios (95% CI) from marginal structural models for the joint effect of BMI and physical activity on current asthma with symptoms after truncation of extreme weights and among non smokers

	MSM after weight truncation*	MSM in non smokers (n=8,062)
Physical activity		
1st tertile	1.00 (ref)	1.00 (ref)
2nd tertile	1.02 (0.91-1.15)	1.00 (0.84-1.19)
3rd tertile	1.03 (0.91-1.17)	0.97 (0.81-1.16)
BMI		
<20.0	0.95 (0.79-1.14)	0.98 (0.76-1.26)
20.0-24.9	1.00 (ref)	1.00 (ref)
25.0-29.9	1.39 (1.22-1.58)	1.38 (1.15-1.65)
≥ 30	1.90 (1.57-2.29)	1.63 (1.21-2.18)

* The value of weights greater than the 99th percentile (i.e. 1.27) was reset to 1.27 and the value of weights lower than the 1st percentile (i.e. 0.78) was reset to 0.78)

DISCUSSION

In this study, we applied marginal structural models to disentangle the time-dependent interrelations between physical activity, obesity and current asthma with symptoms. In this longitudinal analysis, based on causal inference methods, obesity was related causally to current asthma with symptoms, independently of physical activity, while physical activity showed no effect on current asthma with symptoms.

MSMs have been increasingly used in the past decade (267–269,272,273). However, to our knowledge, this is the first study using MSMs to assess the joint roles of physical activity and body composition on asthma. Another study applied MSMs to assess the independent causal effect of physical activity on COPD development and course, adjusting for time-dependent confounding, including obesity (274). This study showed a significant association between regular physical activity and reduced risk of COPD development and hospitalizations, suggesting a protective effect of physical activity, independently of body composition. To our knowledge, only one study assessed the joint effects of physical activity and body composition on a health outcome (i.e. functional limitation in the elderly) and we used the method they proposed to estimate the joint effects (by multiplying weights) (273).

Our results suggest a causal effect of overweight/obesity on current asthma with symptoms, independently of physical activity level. On the other hand, there was no evidence of any independent causal effect of physical activity, suggesting that beneficial effect of physical activity on current asthma with symptoms may be partly mediated by beneficial effects on body composition (273). A recent study assessed the interrelations between obesity, physical fitness, sedentary time and asthma incidence among children using generalized equation analysis and a structural equation model (314), suggesting that low physical fitness levels and high screen time leads to central obesity, which leads to asthma development. Although the study was longitudinal (in terms of associations between nutritional factors and childhood-onset asthma), interrelations between physical fitness level, sedentary time and central obesity were analyzed in a cross-sectional manner. Thus, time-dependent confounding was not taken into account. On the other hand, another recent study assessed the 10-year risk of adult–onset asthma after hypothetical interventions on BMI and physical activity, using the parametric g-formula, which is another method that adjusts for time-dependent confounding (221). This study showed a significant reduction in asthma risk associated with weight loss

intervention and a non-significant reduction associated with intervention on physical activity level, which is consistent with our study.

Even if we used standardized questionnaires to define current asthma with symptoms in our study, our definition is based on self-report only and lung function assessment was not available. However, when we conducted our analyses among never smokers, similar results were obtained, suggesting that there was no overlap between the diagnosis of COPD and asthma. Another limitation to our study is that diet was only assessed once and thus, could not be considered as a time-dependent exposure. However, the existence of an effect of diet on asthma, as opposed to the role of obesity or, to a lesser extent, physical activity, is far from clear. Thus, studying the joint roles of physical activity and overweight/obesity may remain relevant.

We used deterministic (e.g., last observation carried forward) imputation in the case of physical activity missing at 1997 survey. Assuming ignorability holds, this case of missing data was considered completely at random (315) and so our strategy increased efficiency although, if changes in physical activity (not detected by carrying forward) had an effect on asthma, some bias could have been introduced. Other strategies such as multiple imputation would not have provided better results because of the complete lack of the variable at this specific period. Additionally, less than 3% of observations had missing data for physical activity or BMI, which we assumed to be completely at random or at random (315). In the definition of BMI used as a time-dependent covariate, we calculated the mean of the two previous values, which allowed not losing the subjects (increasing efficiency) and would have captured any trend in the time-varying associations with asthma (expected not to result in any bias). Again, other strategies are not expected to provide more valid results.

Although we made adjustments for all the confounders that have previously been reported as related to physical activity, BMI and asthma, the possibility of residual confounding cannot be ruled out, especially for smoking status, given that it is based on self-report and it is prone to many changes over time. The weight distributions (mean close to 1, small range) were not indicative of bias in the exposure models (313). The results we obtained after weight truncation were quite similar to the results obtained without weight truncation, suggesting that there was not a substantial amount of time-dependent confounding in our study, but this could not have been known without the use of this model. MSMs have been developed to estimate causal effects in observational studies, either in the presence or not of

time-dependent confounding. Indeed, the association measures in observational studies cannot usually be interpreted as causal effect measures because the exposed and the unexposed subjects are rarely exchangeable (i.e., exposed and unexposed rarely share the same set of confounder values). Through inverse probability weighting, MSMs allow the creation of a pseudo-population in which exposed and non-exposed subjects are exchangeable (within levels of the available confounders), and thus associations can be interpreted as causal effects (264,274).

Strengths of this study include its longitudinal design, the availability of repeated measurements for outcome, risk factors and covariates, and the use of MSMs which allows adjustment for time-dependent confounding, and thus, making causal inferences with greater confidence. Another strength of this study is the assessment of two exposures that are studied conjointly, which has rarely been used (273).

In conclusion, higher BMI levels are causally related to an increased risk of asthma symptoms in adulthood, and this is independent of physical activity. These results reinforce the widely held conclusion that all efforts to minimize the excess accumulation of fat mass throughout adulthood are a necessary prerequisite for respiratory health in the elderly. More longitudinal studies are needed to confirm the causal role of obesity independently of physical activity on current asthma with symptoms in other population, especially in adolescents and young adults.

2.2 Obesity in interaction with domestic exposure to cleaning sprays

Part of this work led to the publication of an article in the Respiratory Medicine journal (316). *Its results have been presented at the European Respiratory Society congress in Barcelona in September 2013* (317), *at the 2nd French-German school of Pneumology Meeting in September 2013, and at a Respiratory Epidemiology seminar in November 2011.*

INTRODUCTION

Many people are regularly exposed to disinfectant or cleaning agents worldwide and there is growing evidence that healthcare workers and cleaners are commonly and highly exposed to these agents (56–59). Evidence of an adverse effect of cleaning products or disinfectants in asthma mostly comes from studies on occupational risk factors, but a deleterious role of domestic cleaning exposure has also been observed (67,68). This exposure may represent an important public health issue, especially in women (57,68). Asthma in the elderly, still understudied, is a growing public health issue (23), and home cleaning of particular relevance in this context, as it concerns women beyond the age of retirement. In this specific population of elderly women, household help might induce misclassification errors in the evaluation of exposure: one could hypothesize that women with cleaning help answered on behalf of their professional cleaner or felt uneasy to answer that they did not clean their home.

Cleaning and disinfecting products contain numerous chemicals, which may be irritants (bleach, ammonia) or sensitizers (perfumes), and may cause asthma with partly unknown mechanisms. It has been proposed that inhalation of compounds with respiratory irritant properties may induce bronchial epithelial damage and facilitate allergic sensitization by triggering a pro-inflammatory response, neurogenic inflammation, increased lung permeability, and remodelling of the airways epithelium (278). Non-allergic-mediated bronchial inflammation has also been described, and cleaning and disinfectants exposures may lead to non-eosinophilic bronchial inflammation and the onset or aggravation of asthma through non-allergic pathways (279). Furthermore, the possibility of a stronger association between cleaning and disinfectant products with severity in the absence of inhaled steroid treatment (an anti-inflammatory treatment) has been raised (60).

Obesity is a well-known risk factor of asthma (12) and recent studies have shown that obesity in asthma patients was associated with neutrophilic rather than eosinophilic

inflammation (223), especially in women (224). As opposed to asthma in non-obese individuals, which is characterized by T_H2-mediated allergic inflammation, asthma in obese individuals is characterized by a non-allergic mechanism, which might explain the corticosteroid resistance in obese asthma patients (225). Although obesity and the domestic use of cleaning sprays have both been proposed to play a role in asthma through non-allergic and inflammatory pathways, no study has been conducted regarding the effect of the interaction between these two pro-inflammatory risk factors on asthma.

The aims of the present analysis were to study, among elderly women without household help: 1) the association between domestic use of cleaning sprays and current asthma, and 2) the modifying effect of overweight/obesity in this association, by taking into account the use of anti-inflammatory therapy. We hypothesized that among women without ICS, the association between domestic use of cleaning sprays and current asthma is stronger among overweight/obese women.

MATERIALS AND METHODS

Study population

From the 745 women who participated in the Asthma-E3N pilot survey, women with missing data for domestic exposure (n = 24) or asthma (n = 52), or body mass index (n=53) and women with non current asthma (n = 28) were excluded from the analysis. Women with "ever asthma" (according to the main E3N questionnaires) who did not report asthma in the pilot respiratory health questionnaire were also excluded (n = 62) (see Figure 18). The comparison of excluded women because of missing data or inconsistent responses on asthma (n=219) to remaining women (n=526) are presented in Table 26. No significant differences were reported between included and excluded women, except for age, excluded women being older of roughly one year than included women.

Table 26. Comparison of included (n=526) versus excluded (n=219) women

	Included n=526	**Excluded n=219**	**p**
Age (years), mean ± SD	68.2 ± 6.2	69.3 ± 6.9	0.03
BMI (kg/m²), mean ± SD	23.9 ± 3.8	24.1 ± 3.8	0.50
Smoking status (%)			
Never smoker	58.1	55.9	
Past smoker	35.4	34.6	0.39
Current smoker	6.5	9.5	
Educational level (%)			
< High school diploma	9.3	17.1	
High school to 2-level university diploma	55.3	45.0	0.63
3-level or 4-level university diploma	17.2	18.0	
≥ 5-level university diploma	18.2	19.9	
Allergic rhinitis (%)	46.9	48.3	0.73
Dispensed inhaled corticosteroids (%)	24.0	20.6	0.31

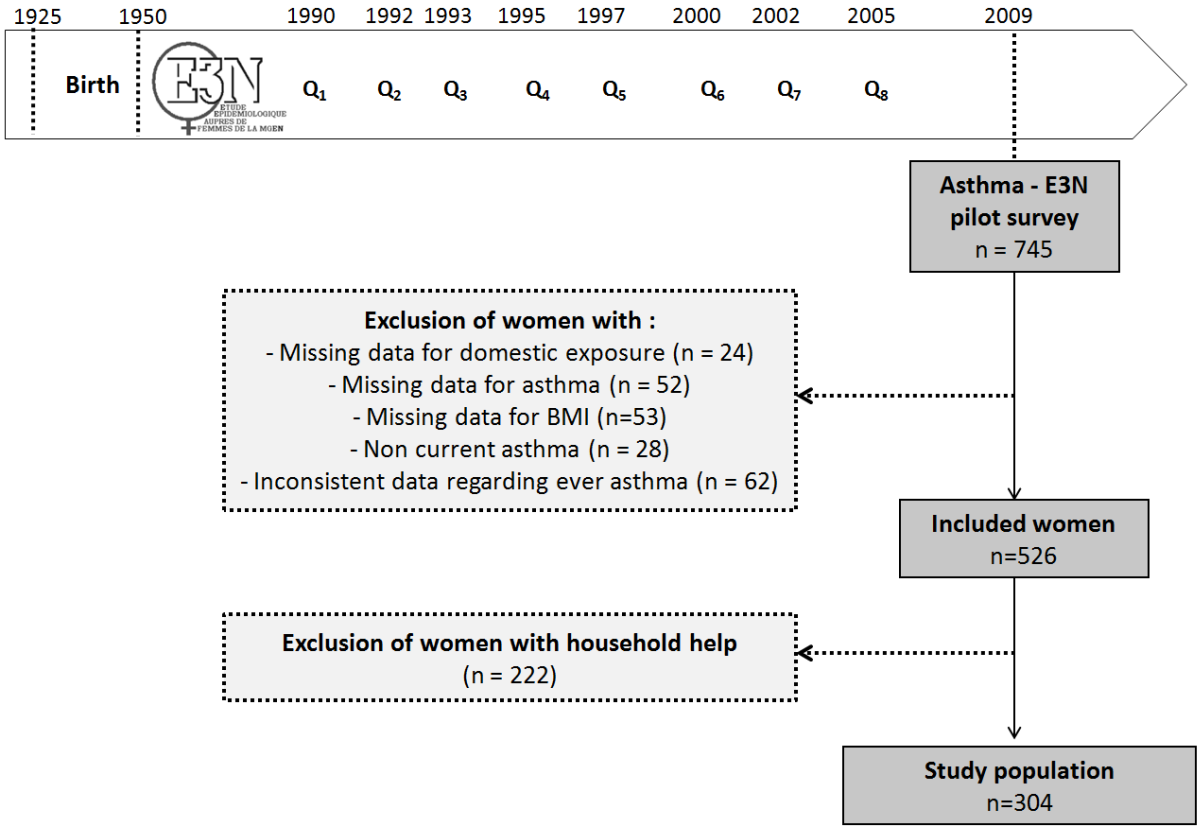
As less misclassification errors are expected among women without household help, we further excluded women with household help (n=222). Comparison of excluded women because of household help (n=222) to women included in the analysis (n=304) is presented in Table 27. Household help increased with educational level and age.

Table 27. Comparison of included (n=304) versus excluded (n=222) women

	Included n=304	**Excluded because of household help n=222**	**p**
Age (years), mean ± SD	66.9 ± 5.7	70.0 ± 6.5	<0.0001
BMI (kg/m²), mean ± SD	23.7 ± 3.7	24.0 ± 4.0	0.38
Smoking status (%)			
Never smoker	61.3	53.7	
Past smoker	32.1	39.9	0.18
Current smoker	6.6	6.4	
Educational level (%)			
< High school diploma	10.9	7.0	
High school to 2-level university diploma	57.3	52.4	0.02
3-level or 4-level university diploma	16.0	18.9	
≥ 5-level university diploma	15.7	21.7	
Weekly home cleaning (%)	81.1	48.1	<0.0001
Weekly use of sprays (%)			
0 spray	76.7	73.2	
1 spray	14.5	17.7	0.52
≥ 2 sprays	8.8	9.1	
Current asthma (%)	41.1	39.2	0.66
Allergic rhinitis (%)	46.1	48.1	0.65
Dispensed inhaled corticosteroids (%)	24.0	23.9	0.97

Therefore, the study population consisted of the 304 women without household help: 125 with current asthma and 179 without asthma history (women who never had asthma) (see Figure 18).

Figure 9. Selection of the study population



Assessment of asthma phenotypes in the specific respiratory health pilot survey

Ever asthma was defined according to the British Medical Research Council (BMRC) definition, by a positive answer to at least one of these two questions “Have you ever had asthma attacks?” and “Have you ever had attacks of breathlessness at rest with wheeze?” (292). Current asthma was further defined among women with ever asthma, by the presence in the last twelve months of asthma attack or asthma treatment or one of five asthma-like symptoms (breathlessness while wheezing, woken up with a feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, woken by attack of shortness of breath). This definition has been used previously in the Epidemiological study on the Genetics and Environment of Asthma (EGEA) study (17,68) and is very close to the one used in the European Community Respiratory Health Survey (ECRHS), in which asthma had to be confirmed by a doctor (18).

Allergic rhinitis, proposed as a good marker of atopy (318), was defined as in the ECRHS survey, by a positive answer to the question: ‘‘Do you have any nasal allergies, including hay fever?’’ (318).

Using the MGEN database, which contains comprehensive information on asthma medications dispensed to all of the E3N women, women with current asthma were classified as having or not inhaled corticosteroids (ICS) canisters dispensed in the 12 months before the exact return date of the pilot respiratory health questionnaire (2008-2009).

Assessment of domestic exposure

Domestic exposure in the past twelve months was estimated by the same questionnaire as the one previously used (67,68). The frequency of various cleaning tasks and products use was provided and classified in four categories: never, less than 1 day/week, ≤ 3 days/week, 4 - 7 days/week. Frequency of nine types of sprays (furniture, glass cleaning, carpets/rugs/curtains, mopping the floor, oven, ironing, air refreshing, degreasing, insecticide/pesticide/anti-dust mite product) was collected. Women who reported the use of at least one type of sprays at least one day per week were considered as exposed for spray use. Women exposed to sprays were classified as either weekly exposed to one spray or weekly exposed to at least two sprays.

Assessment of body mass index

In the main E3N questionnaire sent in 2005, weight and height were recorded and body mass index (BMI) was calculated and classified as <20, 20-24.9, ≥25 kg/m^2. The number of obese women (≥30 kg/m^2) was too small (n=19) to conduct a proper analysis among this category.

Assessment of other variables

Relevant information for educational level (classified as <high school diploma, high school to 2-level university diploma, 3-/4-level university diploma, ≥5-level university diploma) was obtained from the E3N first questionnaire in 1990. The most recent information was used for tobacco consumption (classified as never smoker, past smoker or current smoker).

Statistical analyses

The description of the population according to the asthma status was evaluated using Chi-squared tests for categorical variables and t-tests for continuous variables.

Associations between current asthma and domestic exposure to cleaning sprays were evaluated by univariate and multivariate logistic regression analyses, using women without asthma as reference. All multivariate analyses were adjusted for age (as continuous variable), education level, BMI and smoking status (as categorical variables). Trend analyses were performed using multivariate logistic regression models, considering weekly use of sprays as a continuous variable. Analyses were further conducted by taking into account ICS canisters dispensed among women with current asthma. Analyses were further stratified on allergic rhinitis, in order to evaluate the underlying mechanism (allergic, nonallergic).

To evaluate the potential interaction between BMI and domestic exposure to cleaning products on asthma, analyses were stratified on BMI (in two categories: <25 and ≥25 kg/m^2), and adjusted for age (as continuous variable), education level, and smoking status (as categorical variables). Analyses were further conducted by taking into account ICS canisters dispensed among women with current asthma.

All analyses were conducted using SAS statistical software, version 9.1.

RESULTS

In 2009, the 304 women without household help were aged 59-83 years old (mean age: 67), most of them were never smokers and only 7% current smokers (see Table 28). They had a relatively high educational level (only 11% did not have a high school diploma and 32% had at least a 3 years university level. As expected, women with current asthma were more often overweight/obese (32%) than women without asthma (26%). 51% of women with current asthma had ICS canisters dispensed in the last year.

On average, weekly home cleaning was reported by 81% of the participants. Weekly use of at least one spray was reported by 23% of the participants (14% used 1 spray and 9% used at least 2 sprays), and was significantly more reported by women with current asthma (29% for women with current asthma and 19% for never asthmatics, respectively). The three sprays mostly used were air-refreshing, degreasing and window/mirror sprays. Among women using at least two sprays, 52% used degreasing sprays.

Table 28. Description of the population

	All women n=304	**Never asthma n=179**	**Current asthma n=125**	**p**
Age (years), mean ± SD	66.9 ± 5.7	66.6 ± 5.6	67.2 ± 5.7	0.39
BMI (kg/m²), mean ± SD	23.7 ± 3.7	23.6 ± 3.8	23.9 ± 3.5	0.61
BMI (kg/m²), %				
<20	10.5	10.6	10.4	
[20-25[	60.9	63.1	57.6	0.39
≥ 25	28.6	26.3	32.0	
Smoking status (%)				
Never smoker	61.3	62.7	59.2	
Past smoker	32.1	29.9	35.2	0.57
Current smoker	6.6	7.3	5.6	
Educational level (%)				
< High school diploma	10.9	13.3	7.5	
High school to 2-level university diploma	57.3	57.2	57.5	0. 13
3-level or 4-level university diploma	16.0	15.6	16.7	
≥ 5-level university diploma	15.7	13.9	18.3	
Weekly home cleaning (%)	81.1	79.8	83.1	0.47
Weekly use of sprays (%)				
0 spray	76.7	80.6	70.8	
1 spray	14.5	12.9	16.8	0.04
≥ 2 sprays	8.8	6.5	12.4	
Weekly use of air-refreshing sprays (%)	9.5	9.7	9.2	0.87
Weekly use of degreasing sprays (%)	8.5	4.6	13.9	0.005
Weekly use of window/mirror sprays (%)	8.2	7.3	9.6	0.47
Allergic rhinitis (%)	46.1	24.7	76.9	<0.0001
Dispensed inhaled corticosteroids (%)	24.0	5.0	51.2	<0.0001

Domestic exposure to cleaning sprays and current asthma

The association between weekly use of at least one spray and current asthma was statistically significant (OR [95% CI] = 1.86 [1.04-3.33]). The ORs were 1.29 [0.63-2.66] for weekly use of one spray, and 2.63 [1.03-6.67] for weekly use of at least two sprays (trend, p=0.04). Similarly, for the weekly use of degreasing sprays and current asthma, a significant association was observed (OR [95% CI] = 3.32 [1.34-8.22]).

When restricting the group of women with current asthma to the 61 women without dispensed ICS, the association of current asthma with weekly use of at least one spray increased (OR [95% CI] = 3.11 [1.56-6.17]). No association was found when comparing the

64 women with current asthma and dispensed ICS to the 179 women without asthma history (OR [95% CI] = 0.92 [0.41-2.10]). The formal test for interaction between spray use and ICS canisters dispensed was not statistically significant (p interaction = 0.62).

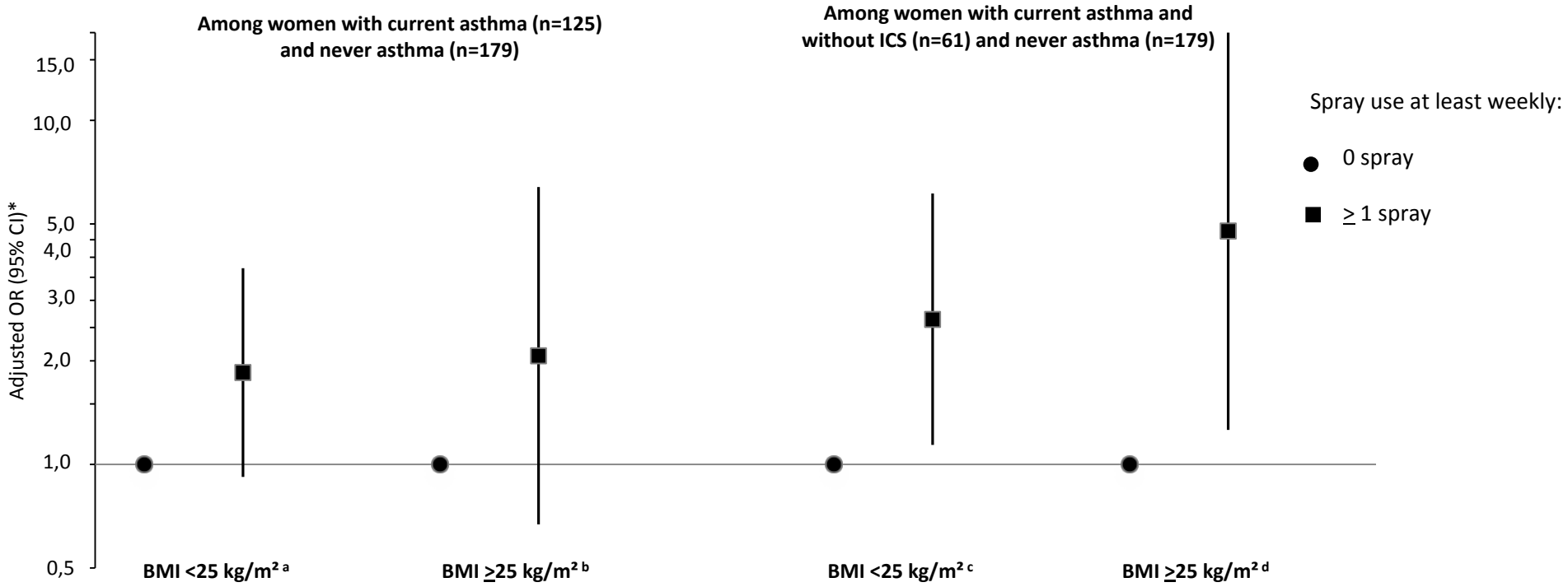
After stratification on allergic rhinitis, the association between weekly use of at least one spray and current asthma largely increased among the 159 women without allergic rhinitis (OR [95% CI] = 7.69 [2.60-22.7]). No association was found among the 136 women with allergic rhinitis (OR [95% CI] = 1.00 [0.39-2.56]). The test for interaction between spray use and allergic rhinitis was statistically borderline significant (p interaction=0.06). No association was found between the weekly use of at least one spray and allergic rhinitis (OR [95% CI] = 1.06 [0.58-1.93]).

Modifying effect of body mass index

When the analysis was stratified according to overweight/obesity, the ORs for the weekly use of at least one spray and current asthma were 1.85 [0.92-3.72] in the 217 women with a BMI < 25 kg/m² and 2.07 [0.67-6.40] in the 87 women with a BMI $\geq$ 25 kg/m^2 (see Figure 19).

After restricting that analysis for the group of women with current asthma to those without ICS canisters dispensed, the OR in the 67 women with a BMI $\geq$ 25 kg/m^2 was almost twice the OR in the 173 women with a BMI < 25 kg/m^2 (ORs: 4.77 [1.26-18.04] and 2.64 [1.14-6.13] respectively; p interaction = 0.54) (see Figure 19).

Figure 10. Weekly spray use and current asthma stratified on BMI



* Odds ratios were for adjusted for age, educational level, and smoking status

[a] Among women with BMI<25 kg/m², current asthma (n=85) versus never asthma (n=132)

[b] Among women with BMI≥25 kg/m², current asthma (n=40) versus never asthma (n=47)

[c] Among women with BMI<25 kg/m², current asthma without dispensed ICS (n=41) versus never asthma (n=132)

[d] Among women with BMI≥25 kg/m², current asthma without dispensed ICS (n=20) versus never asthma (n=47)

DISCUSSION

Positive associations were found between weekly use of at least one spray and current asthma among French elderly women without household help. Mechanisms are not yet known, but the fact that associations were only observed among women without ICS canisters dispensed, suggests an inflammatory role of cleaning sprays. We reported that among women without anti-inflammatory therapy (ICS), the effect of spray use on asthma was nearly twice as high in overweight/obese women than in others, even if the test for interaction between spray use and BMI was not statistically significant. Our results support the hypothesis that cleaning sprays have a deleterious effect in the population at any age and represent a public health problem, and suggest an interaction between two pro-inflammatory risk factors of asthma.

Our results extend in elderly women without household help results regarding the potential deleterious effect of domestic cleaning sprays on asthma observed in younger adults (67,68). In the ECRHS and EGEA surveys, associations of cleaning sprays have been evidenced in young adults, on incidence and asthma activity, respectively. In the present study the same standardized definition as in the EGEA survey was used for current asthma, based on international standardized recommendations (17).

Understanding the types of sprays concerned need further studies, but the associations observed in the present study were mainly explained by the use of degreasing sprays, calling for more studies of such sprays. The deleterious role of products in spray form has been observed in various diseases in the occupational and environmental settings (62–64,319). The use of products in spray form facilitates respiratory exposure (better than those in non-spray form) (65). Allergens and irritants are deposited in large airways by turbulent flow, causing chronic inflammatory changes (69). The size of particles determines how quickly the particle settles, to what extent it follows the movements of the air and the probability of being deposited in a given part of the human respiratory system (70). In a recent experimental scenario simulating human exposure to aerosol, a potential harmful exposure to a household bathroom cleaner/sanitizer spray, after evaporation, with nanoparticles, has been suggested (71). Understanding the role of the size of particles from cleaning sprays, which may differ according to the type of sprays (aerosol, atomizer), need further studies, including information on dose-response relationships.

Previous analyses in the EGEA study have shown associations between the use of sprays and IgE-dependent asthma and non-eosinophilic asthma (68). In the E3N study, no information regarding skin prick tests, levels of IgE or blood eosinophils was available. Allergic rhinitis, which has been proposed as a good marker of atopy (318), was available. Positive associations were found between weekly use of sprays and current asthma only among women without allergic rhinitis, which suggests a non-allergic mechanism. Even if further studies using objective markers are needed, our results are consistent with the hypothesis of an irritant effect of products in spray form.

We tested whether a stronger effect occurred in women without ICS treatment, as hypothesised from results in the EGEA survey (60). Unlike previous studies, we had access to comprehensive dispensed drug database for the whole population. The association of spray use with current asthma was restricted to women without anti-inflammatory therapy. Beyond the hypothesis of an irritant effect of cleaning agents, one hypothesis to explain our results may be an inflammatory role of cleaning agents.

We confirmed our hypothesis that among women without ICS, the association between domestic use of cleaning sprays and current asthma was stronger among overweight/obese women than among non-overweight women, even if this formal test for interaction was not statistically significant. Although the lack of statistical significance is likely due to small sample size, the possibility that this difference is simply the result of additive risks cannot be ruled out. Systemic/airway inflammation is one of the mechanisms which can explain the association of asthma and obesity (12), an association already clearly evidenced in a larger sample from the E3N survey (217). Asthma and obesity are likely to be connected in a multifactorial fashion with modern lifestyles (such as unhealthy diet) or emergent environmental exposures (such as domestic use of sprays), creating new interactions. There are still limited studies on interaction between overweight and environmental factors with asthma, but it is an active topic of research with recent findings demonstrating that overweight increased susceptibility to indoor pollutants among children with asthma (283), and to ambient air pollution among Chinese children (282). A recent study reviewed the literature to identify potential response-modifying factors that should be considered when assessing the association between O_3 exposure and health effects. The authors identified, among other factors, obesity for which they stated there was “suggestive” evidence that it may increase the risk of O_3-related health effects (280).

Even if we used standardized questionnaires to define current asthma in our study, our definition is based on self-report only, which may lead to an over-diagnosis of asthma. The possibility of a (higher) over-diagnosis of asthma in obese patients is debated. While some studies have suggested that asthma may be over-diagnosed in obese patients (320), another study showed a general over-diagnosis of asthma among Canadian adults, regardless of whether or not they were obese (321). Although adjustments for confounders were made, the possibility of residual confounding cannot be ruled out, especially for smoking status, given that it is based on self-report and it is prone to many changes over time. For the present analysis, we acknowledged the cross-sectional design of the study and the self-report of domestic exposure. Beside self-reported exposure, recent studies suggested the use of principal component analysis to synthesize information from numerous variables (68) or a composite score for cleaning sprays or scented products (319). Ongoing research aims at defining objective methods, like home visits using bar codes of various products, which may provide tools to include in epidemiological surveys with home visits or to validate or improve questionnaires used in very large surveys (322,323). Indeed, besides a proper estimate of the actual use of various products, more information is needed regarding the specific products used, and possibly the way they are used. We also faced a power issue in our analyses due to the small sample size. In particular, it was not possible to study either the specific effect of obesity (instead of overweight) as the number of obese women was really small, or the effect of the use of at least two sprays. Nor was it possible to stratify our analysis on allergic rhinitis and overweight at the same time, in order to confirm our hypothesis of an interaction between overweight/obesity and domestic exposure through non-allergic pathways.

Domestic exposures to cleaning products, especially in spray form appear as an emergent pro-inflammatory environmental risk factor for asthma (67,68). Interaction of overweight/obesity in the effect of domestic exposure to sprays on asthma has biological plausibility, as an underlying state of inflammation. Although caution in the interpretation of our findings is necessary in relation to sample size, further studies should clarify the potential modifying role of overweight/obesity on the effect of spray exposure on asthma, in particular in relation to the increasing prevalence of overweight worldwide.

DISCUSSION AND PERSPECTIVES

This thesis has confirmed the usefulness of a new method to assess dietary patterns in nutritional epidemiology, and has extended the role of obesity in asthma by taking into account other nutritional factors (physical activity and diet) and by testing a new hypothesis regarding the modifying effect of obesity in the environmental factors-asthma associations. This last chapter presents, first a summary of main results and their implications regarding public health and methodological aspects related to the assessment of dietary patterns, the main limitations of the performed analyses, and finally the perspectives from the thesis.

1. Main results

Main results of the thesis are presented below first regarding diet, by summarizing methodological and etiological aspects, and then regarding obesity first as a risk factor for asthma, and then as a modifying factor in the association between the domestic use of sprays and asthma.

1.1. Dietary patterns

Besides the fact that the role of diet in asthma development or evolution remains unclear, the assessment of diet represents an active research topic in nutritional epidemiology, with developments of *a priori* and *a posteriori* methods to identify dietary patterns. In our study, we compared two methods to derive dietary patterns, and to study their associations with new adult-onset asthma.

Methodological aspects

We used and compared two methods to derive dietary patterns: PCA, which is the traditionally used *a posteriori* approach, and CFA, which is a half-way method between the *a priori* and *a posteriori* approaches, and has been suggested as a more statistically meaningful method in terms of stability and relevance. Whether we used PCA or CFA, three similar patterns were found: a “Prudent-like” pattern, a “Western-like” pattern and an “Aperitif-like” pattern. However, differences were observed in contributions for some food groups and regarding characteristics of patterns. The “Prudent-like” pattern derived using CFA related

more to a “healthy diet” than the one derived using PCA, both in terms of higher correlations with “healthy” food groups (i.e. vegetables), and in terms of social characteristics. Similarly, the “Western-like” pattern derived using CFA related more to an “unhealthy diet” than the one derived using PCA, both in terms of higher correlations with “unhealthy” food groups (i.e. processed meats, and dough and pastry), and in terms of social characteristics.

Etiological aspects

Up to now, only four longitudinal studies were conducted on dietary patterns and new adult-onset asthma and none of them reported a significant association (8–11). Our longitudinal study, which is the first to use CFA to derive dietary patterns, suggested a deleterious effect of the "Western-like” pattern on adult-onset asthma. A stronger association was observed among women who did not complete high school, suggesting that among women with a lower socioeconomic level, the Western diet might have a higher effect on respiratory health, potentially due to a lower quality of foods. However, the fact that this association was attenuated in sensitivity analyses requires caution in the interpretation of our findings. On the other hand, the fact that the associations between dietary patterns and adult-onset asthma were stronger among younger women suggests that the role of diet in asthma may differ according to windows of exposure.

In summary, the present study supports the alternative use of CFA to PCA for the identification of dietary patterns in epidemiologic studies. While further studies are needed to understand the role of diet in asthma onset, CFA should be considered in the future for the identification of dietary patterns.

1.2. Overweight/obesity

Although obesity is a well known risk factor for asthma in adults, especially in women, several hypotheses have been proposed to explain this relationship, including the hypothesis of an inflammatory mechanism. Besides the mechanisms that could explain the specific effect of obesity on asthma, the association between obesity and asthma may represent an epiphenomenon of more complex interrelations with other nutritional, environmental, behavioral or social factors, that should be addressed as well. In our analyses, obesity was first considered as a risk factor, along with another nutritional factor to assess their joint effects on asthma, and secondly, as a modifying factor in the effect of an

environmental pro-inflammatory factor of asthma, to investigate the hypothesis of an inflammatory role of overweight/obesity in asthma.

Interrelations between obesity, physical activity and asthma

Very few studies investigating the role of obesity in asthma took into account interrelations with other nutritional factors, and most of them had methodological limitations. The role of physical activity in asthma development or evolution remains unclear. Given the time-dependent, bidirectional association between physical activity and body composition, it is important to determine their relative contribution to asthma. Our study is the first using MSMs to assess the time-dependent interrelations between obesity, physical activity and asthma. Our results suggested that obesity may lead to asthma independently of physical activity, and that the beneficial effects on asthma that have previously been reported for physical activity may have been partly mediated by its beneficial effects on body composition. More studies using adapted models to account for time-dependent confounding are needed to confirm these results.

The modifying role of overweight/obesity in the effect of environmental risk factors of asthma

There are still limited studies on interaction between overweight and environmental risk factors of asthma, but it is an active topic of research with recent findings showing that overweight may increase the deleterious effect of susceptibility to ambient air pollution (282) or of indoor pollutants (283) among children. Domestic exposure to cleaning sprays has recently been suggested as an emergent pro-inflammatory environmental risk factor of asthma. Interaction of overweight/obesity in the effect of domestic exposure to sprays on asthma has biological plausibility, as an underlying state of inflammation. Although mechanisms are not yet known, our study showed associations between exposure to cleaning sprays and current asthma only among women without ICS use, suggesting an inflammatory role of cleaning sprays. We further reported that among women without anti-inflammatory therapy (ICS), the effect of spray use on asthma was nearly twice as high in overweight/obese women, supporting the hypothesis of an inflammatory effect of overweight/obesity on asthma. However, as our study was cross-sectional, it is difficult to rule out reverse causation.

1.3. Public health implications

Some results from this thesis might have public health implications that are discussed below, first regarding the global epidemic of obesity, and secondly, regarding the use of cleaning sprays.

Preventing the global epidemic of obesity

In May 2004, the World Health Assembly adopted the WHO Global Strategy on "Diet, Physical Activity and Health", recognizing the opportunity for reducing deaths and diseases worldwide by improving diets and increasing levels of physical activity (324). More recently, the UK National Institute for Health and Care Excellence has provided a draft guidance, advising people to be more physically active, spend less time in front of the television, and reduce their consumption of energy dense foods, takeaways, and sugar sweetened drinks (325). In this context, trying to understand how nutritional factors may interact within each other as determinant of respiratory diseases has an important public health implication regarding the lung health of the population.

Our study assessing the joint roles of obesity and physical activity on asthma, while adjusting for time-dependent confounding, suggested an independent causal effect of obesity on current asthma with symptoms, which goes along with current international guidelines that recommend obese people to lose weight, by following a healthy balanced diet and practicing regular exercise (324,325). Although our results did not suggest an independent protective effect of physical activity on current asthma with symptoms, it is still an effective way to lose weight and thus prevent from obesity and asthma.

Although caution in the interpretation of our findings regarding the modifying role of overweight/obesity on the effect of domestic exposure to household sprays on asthma is necessary in relation to sample size, further studies should clarify the potential modifying role of overweight/obesity on the effect of pro-inflammatory environmental factors of asthma, in particular in relation to the increasing prevalence of overweight worldwide.

Cleaning sprays and asthma: a public health issue over the life course

There is increasing evidence that the use of cleaning products in spray form, both at work and at home increases the risk of asthma (54,58,67,68). The use of cleaning products in

spray form has increased in last decades (61) and many people, and especially women, are exposed worldwide without knowledge on their potential toxicity. Cleaning products and especially fragrance, contained in products in spray form, have been shown to contain a lot of toxic compounds (326). Household cleaning substances are classified as the most frequently involved in all human exposure complaints (327). Our results extend in elderly women without household help results regarding the potential deleterious effect of domestic cleaning sprays observed in adults from two previous surveys (67,68). Furthermore, a deleterious effect was observed between the use of cleaning sprays by parents during pregnancy or early childhood and the risk of wheezing in children, in two European studies (328,329). Together with the literature, results suggest a deleterious effect of cleaning sprays in the population at all stages of life and thus, represent a life course public health problem.

1.4. Methodological implications regarding the use of CFA to assess dietary patterns

In the last years, there has been a growing interest in dietary patterns to evaluate overall diet (5,85,97,119), leading to methodological developments in nutritional epidemiology. Among several exploratory methods, principal component analysis (PCA) is the most frequently used method to derive *a posteriori* dietary patterns (119). PCA is a descriptive method of data reduction where components (dietary patterns) are linear combinations of observed variables (food groups intakes). The alternative use of structural equation modeling (SEM), which allows to test a statistical model specifying dietary patterns as latent variables, has been proposed (131). SEM methods include, among others, confirmatory factor analysis (CFA), which is the SEM equivalent of PCA. CFA is a modeling method that allows specification and testing of a latent variable model where latent variables are dietary patterns and measures are food group intakes assessed via their variance-covariance matrix. Regarding the method of estimation, singular value decomposition is used for PCA, whereas CFA is based on maximum likelihood estimation. PCA can be applied when one knows little or nothing about the data, whereas CFA allows previous knowledge to be taken into account to decide how many patterns will be extracted. One frequent criticism regarding the use of PCA is the low proportion of variance that is usually explained. Although the proportion of variance explained with PCA is inversely related to the number of variables that is used, CFA takes account of more variability than does PCA through residuals that are specified in the statistical model (144–146). Although it was not the classical use of CFA, we thought it would be interesting to compare PCA and CFA in the identification of dietary

patterns and in their associations with a health outcome. We reported similar dietary patterns using PCA or CFA, but different correlations between derived patterns and food groups according to the use of PCA or CFA. The study by Varraso et al was the first to use CFA as a one-step approach, and showed that dietary patterns derived using CFA were more meaningful in terms of relevance and more stable in terms of statistical proprieties (17). Although caution in the interpretation of our results is needed, our results support the use of CFA for the assessment of dietary patterns in nutritional epidemiology.

2. Limitations

Analyses performed during this thesis were performed in the E3N cohort study, and therefore, shared several general limitations listed below.

First, regarding the assessment of asthma in the E3N cohort study, the heterogeneity of questions from one questionnaire to the other represented a limitation, as for example in our MSM analysis, we were only able to assess asthma current asthma with symptoms at three time points. Moreover, even if we used standardized questionnaires to define current asthma in our study, our definition is based on self-report only, which may have led to an overdiagnosis of asthma. The main source of disease misclassification probably is a misdiagnosis with COPD in this population of elderly women; however, the prevalence of ever smokers was quite low in the E3N study (roughly 35%), and analyses were performed among never smokers, when possible, to rule out residual confounding by smoking. Another limitation comes from the fact that no spirometry or bronchial challenge tests have been performed in the E3N population, and thus, we could not assess lung function in our analyses. However, this is very common in epidemiological research on asthma and given the phenotypic heterogeneity of asthma, it is not clear which combination of measures should be used when objective measurements are available.

A major limitation of this thesis was that dietary data were only available at one time point (in 1993) in the E3N study, and thus could not be considered as a time-dependent exposure, along with obesity and physical activity in our MSM analysis. Taking into account the evolution of dietary habits during follow-up would also have been interesting for our study on the effect of dietary patterns in relation to adult-onset asthma. Moreover, the lack of assessment of dietary habits during childhood or early adulthood limits the conclusion that can be drawn from our study. Indeed, since dietary habits track throughout life, when associations are observed between dietary patterns and asthma in adults, it is difficult to

disentangle whether these associations were actually already set during childhood (with adult dietary patterns reflecting childhood dietary patterns), or whether these associations were really determined during adulthood. This is an important limitation in terms of public health since it is impossible to conclude whether or not changing dietary habits during adulthood will be beneficial for the prevention of asthma. We also acknowledge that there is likely misclassification in the FFQ-assessed intake of diet. The heterogeneity of the questions on physical activity was another limitation, since we were forced to consider levels of physical activity in tertiles instead of continuous variables.

Analyses were adjusted for several potential confounders using, when possible, time-dependent variables. Regarding statistic and our models, we acknowledge possible effect size of the sample, and even if we controlled for several potential and known confounders, our results might still be explained by some left-over confounding as well as by other healthy lifestyle. Even if our cohort consisted of well-educated elderly women (i.e. a relatively homogenous group regarding educational level), the use of educational level as a proxy of socio-economic status may have provided too small contrast and thus, residual differences in socioeconomic status may have contributed to the observed results. We also recognize that our results obtained among this very specific population are not necessarily generalizable to the whole population, as differences in health awareness, socio-economic status, and smoking behavior might differ significantly from the general population to our study population. Inherent to the choice of study population (only women), gender-specific effects could not be assessed. However, the specificity of the E3N population also provides less heterogeneity within our study population, which may increase the probability to observe true associations in our analyses.

3. Perspectives

Several perspectives might be raised to pursue the work begun during the thesis. Some of them are presented below. First, we present analyses that could be conducted using repeated assessment of diet, then we present analyses that could be conducted using data from the Asthma-E3N study, and lastly, we present analyses that could be conducted to assess the modifying role of obesity on other determinants of asthma.

3.1. Analyses to conduct using repeated assessment of diet

Within the E3N study, several perspectives might be presented. Although dietary data were only available in 1993, a second food frequency questionnaire was sent to E3N women in 2008: data cleaning is still under process but these dietary data will soon be available. Once available, it will be interesting to repeat our MSM analysis with diet considered as a time-dependent exposure, along with obesity and physical activity, to study the joint effects of the three nutritional factors (i.e. diet, physical activity and obesity) on asthma. It would also be interesting to investigate their joint effects on asthma incidence, when data will be available (data cleaning is currently under process for the assessment of asthma, and more particularly for age of onset, in the Asthma-E3N study).

Once dietary data collected in 2005 are available, it would be interesting to repeat our study on the effects of dietary patterns in relation to adult-onset asthma, taking into account the evolution of dietary habits during follow-up. It would also be interesting to use more detailed data on asthma from the Asthma-E3N study, which would also enable a longer follow-up. Besides, our study on dietary patterns and asthma was essentially methodological and thus, does not allow making any nutritional recommendation. It would therefore be interesting to repeat CFA by including *a priori* hypotheses in the patterns construction, in order to take into account nutritional recommendations. It would also be interesting to use other methods, such as RRR, to assess dietary patterns, and compare them with PCA and CFA. On the other hand, using the DII to assess diet would also allow investigation of the hypothesis of an inflammatory mechanism to explain the role of diet in asthma. In fact, it would be interesting to study the potential modifying pro-inflammatory role of obesity in the association between the DII and adult-onset asthma, to study it further.

3.2. Analyses to conduct in the Asthma-E3N study

As domestic exposure to cleaning products was assessed in the Asthma-E3N study, it would be interesting to replicate our study on the association between domestic exposure to cleaning sprays and asthma, and the potential modifying role of obesity, to verify our hypotheses in a larger population. It would then be possible to study the effect of obesity, which was not possible in the pilot study as the number of obese women was too small, and to verify our hypothesis that obesity may play a role in asthma through non-allergic and inflammatory pathways. A Master's student (Julien Gallois), that I co-supervised with Nicole

Le Moual between February and July 2014, has already worked on the domestic exposure questionnaire. When the most recent assessment of BMI (2011) will be available (data cleaning is currently under process), we will be able to study the interaction with overweight/obesity in the Asthma-E3N study. Beside self-reported exposure, recent studies have suggested the use of principal component analysis to synthesize information from numerous variables (68), or a composite score for cleaning sprays or scented products (319). It would also be interesting to use CFA to assess "domestic cleaning patterns" and investigate their effects on current asthma. Furthermore, ongoing research aims at defining objective methods, like home visits using bar codes of various products, to validate or improve assessment of domestic exposure to cleaning products in epidemiological studies (322,323). These methods are currently being developed in our research team. Indeed, besides a proper estimate of the actual use of cleaning products, it would be interesting to get more information on the specific products used, and possibly the way they are used.

As detailed information on respiratory health has been assessed in the Asthma-E3N study, it would be interesting to take into account asthma control, asthma severity, current asthma (in the last 12 months), or an asthma symptom score in all our analyses. Regarding asthma control which has been assessed using the Asthma Control Test (297), it would be interesting to investigate the hypothesis of worse asthma control in obese asthmatics than in non-obese asthmatics, as well as the hypothesis of corticosteroid resistance among obese asthmatics. All this detailed information on respiratory health available in the Asthma-E3N study also provides an opportunity to conduct cluster analyses in order to identify asthma phenotypes. Taking into account detailed information on the onset and the course of asthma would also be interesting, as it would allow distinction between childhood-onset asthma and adulthood-onset asthma in our analyses, especially when studying asthma activity at a specific time point.

3.3. Analyses to conduct on the modifying role of obesity on other factors of asthma

Regarding the hypothesis of an inflammatory mechanism to explain the effect of obesity on asthma, it would be interesting to investigate the potential modifying role of obesity on the effect of other pro-inflammatory factors of asthma, such as air pollution, which has been assessed in the E3N study in the context of the European FP7-ESCAPE project (European Study of Cohorts for Air Pollution Effects, Principal Investigator: Bert Brunekreef), or tobacco exposure which has been assessed at each questionnaire in the E3N and Asthma-E3N

studies. Furthermore, as the interrelations between BMI, tobacco exposure and asthma are complex and prone to reverse causation, it would be more adequate to use MSMs to adjust for time-dependent confounding when investigating the potential modifying role of obesity on the effect of tobacco exposure on asthma.

Finally, it might be very interesting to investigate how social factors are involved in the nutritional factors/asthma association. A challenge when analyzing the association between environmental and/or lifestyle determinants, socio-economic variables and health, is the complex nature of the potential interrelationships among these variables. For socio-economic variables, a source of methodological complexity comes from the fact that these variables can be taken into account either at individual level or at area level. Those two variables per se are linked between each other but also, for asthma, to the probability of being exposed to other environmental factors such as domestic exposure to cleaning sprays or ICS use, and also to nutritional factors through lifestyle behaviors. Within the E3N study, social variables at the individual level are available (educational level achieved; and an occupation-based indicator built from the occupational coding, using the two last occupations that women have held on, recorded in Asthma-E3N). As all the residential addresses of Asthma-E3N participants are already geo-referenced, several deprivation indexes are currently being constructed (thesis of Sofia Temam in our research team). It would be very interesting to disentangle the causal effects of social and nutritional factors in asthma, using appropriate statistical tools, such as MSM.

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APPENDICES

Appendix 1. Pictograms proposed by Sørensen *et al*. to evaluate body silhouette at different stages of life, in men and women (206).