Universiteit Utrecht

University Medical Center Utrecht

Diet and COPD:

How have recent epidemiological studies added to the current knowledge on this association?

Justine Sinsai

May 2011

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This thesis is the written assessment of the MSc-Epidemiology programme by Justine Sinsai (3096297) at Utrecht University, supervised by Dr. H.A. Smit, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht.

I. Introduction

Although smoking has long been known as an important risk factor for Chronic Obstructive Pulmonary Disease (COPD), research over the last two decades has indicated the importance of dietary factors. Despite advances in the management and prevention, COPD remains a major public health problem in the world. COPD is characterized by an irreversible decline in lung function with a chronic increase in respiratory symptoms [1]. Disease state has previously been described based on post-bronchodilator forced expiratory volume in one second (FEV1) and its ratio to the forced vital capacity (FVC) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standards [1]. In 2004, the World Health Organization (WHO) estimated that up to 64 million worldwide suffered from COPD [2]. The global burden of COPD has been increasing along with increases in the impact of non-communicable diseases. The WHO estimates show that by the year 2030, COPD will be the third leading causes of death worldwide [3].

Tobacco smoking has long been known as a risk factor for COPD, however other environmental and lifestyle factors are becoming of importance. Diet has been shown to be one of the cornerstones in chronic disease prevention [4]. Generally, the importance of dietary intake of fruits and vegetables has been recognized globally. Supporting this, several previously published cross-sectional and longitudinal studies have illustrated an association between diet and COPD. In epidemiological studies, increasing evidence on various dietary nutrients and foods, and their beneficial and adverse effects on lung function and COPD has been reported. In an extensive review of epidemiological evidence, Tricon and colleagues [5] investigated and summarized the previous findings on nutrients and food intake and their associations with indicators of asthma and COPD. The majority of studies have confirmed a beneficial association of several dietary factors, including antioxidants Vitamins C, E and beta-carotene, on lung function and COPD [6].

Over the last two decades, epidemiological research has indicated the importance of dietary habits and COPD. However, causality of this association remains uncertain. There are several key issues that still need further clarification to establish the nature of the diet-COPD association and to what extent this association is a causal one. Primarily, it is crucial to identify the role of smoking habits on this association and whether residual confounding has been eradicated. Previously, this has proven difficult since it is often complex to neutralise the

effect of smoking status on this diet-COPD relationship [7]. Additionally, the temporal relationship between diet and COPD needs to be further investigated. Given the nature of observational and cross-sectional studies, it is often difficult to infer causality. These uncertainties have previously been highlighted in the Tricon *et al.* review [5]. For these reasons, the current paper is aimed at evaluating the extent to which more recent studies, ensuing this review, have addressed the aforementioned uncertainties, and to what extent causality between diet and COPD can be established.

II. The Evidence

A. Previous epidemiological evidence

Over the last decades, a substantial number of epidemiological studies have provided evidence on possible associations between diet and lung function and/or COPD. Observational studies have repeatedly shown the beneficial effects of antioxidant vitamins C and E and beta-carotene on lung function and COPD [5]. Majority of these studies have either indicated protective effects of these nutrients on oxidative lung damage, which results from oxidative stress due to tobacco smoke and other environmental pollutants. Given the narrow implications of assessing nutrients in the development of nutritional guidelines, more studies have assessed the role of dietary intake of foods including fruits, vegetables and fish. Recent conclusions on the beneficial role of fruit and vegetable intake on lung function have been associated to their antioxidant properties, particularly the presence of vitamin C. Generally, these beneficial effects have been consistently reported in observational studies [8-10], but longitudinal studies are often scarce and may report conflicting findings [11-13]. Moreover, there has been evidence on the beneficial association of fish intake on lung function and COPD, though findings have generally been incoherent [10, 12-15]. In their review, Tricon and colleagues summarised these findings extensively [5]. An examination of more recent studies will unveil the extent to which the previously highlighted uncertainties in diet-COPD studies have been addressed and how these add to current knowledge on the subject matter.

B. Recent epidemiological evidence

Although a vast number of studies have explored the associations of dietary nutrients and foods on COPD, no studies have established whether this relationship is causal in nature. More recently, only 7 studies have investigated associations between diet and COPD (*see*

Table 1). Noticeably, there has been a shift from assessing individual nutrient or food intake towards assessments on dietary patterns and their implications on lung function and COPD. Four of these studies have investigated the relationship between dietary patterns and COPD both through cross-sectional and longitudinal study designs [16-19]. Generally, these studies have demonstrated that a 'prudent' or 'cosmopolitan' pattern, generally consisting of a combination of 'healthy' foods such as fruits, vegetables and whole grain products, is negatively associated with the risk of COPD. In contrast, a more 'western' or 'traditional' pattern, consisting of refined products, cured and red meats amongst other 'unhealthy' foods, was associated with an increased COPD risk [16-19]. However, this beneficial association of a 'healthy diet' pattern and COPD should be interpreted with caution, since these observations cannot be attributed solely to the presence of foods rich in antioxidants, which previously have demonstrated beneficial effects [8-10]. Furthermore, the more 'unhealthy' patterns were positively associated with an increased risk of COPD [16-19]. Perhaps, these detrimental effects could be attributed to the presence of (cured) meats in the dietary pattern for which interesting observations have recently been reported [20, 21]. In their studies, Jiang and colleagues observed that cured meat consumption was associated with reduced lung function and an increased risk of COPD. Another study assessed total dietary fibre intake from cereal, fruits and vegetables, and found an overall negative association with COPD. This supports previous evidence on the protective role of fruits and vegetables on COPD. However, these conclusions should be considered with caution since assessments of independent effects of these foods did not yield the same effect, except in the case of cereal [22]. Essentially, these studies further highlight the importance of taking into consideration the combined effect of foods on observed effects.

III. Issues related to the analysis of the diet-COPD relationship

A. Assessment of dietary factors and COPD

Since the Tricon et al. review [5], studies have added knowledge to the current evidence on the diet and COPD association. A broader look at recent studies generally reflects the importance of a 'healthy' diet including foods such as fruits, vegetables and wholemeal products. Nevertheless, interpretation of evidence should be done carefully, especially when non-standardised methods are used to label food intake or to classify COPD, which in turn may bias evidence on the diet-COPD association. Study design, with regards to food intake and COPD assessments may inflate estimates of observed effects if done incorrectly. In recent

studies, healthier food patterns, 'prudent' or 'cosmopolitan', and unhealthier food patterns, 'western' or 'traditional', have been used to label dietary patterns [16-19]. These dietary patterns generally varied in composition since they included different food combinations which were subjectively determined. Additionally, these studies have continued using food frequency questionnaires in grouping food items subjectively, an aspect that may affect the robust nature of measurement [cited in18]. Additionally, limitations in study methodology for assessing COPD may bias observed effects in epidemiological studies. In recent prospective studies, inconsistent COPD classifications, using self-reported and non-standardised methods have been reported [17, 21, 22]. Additionally, given that spirometry is the golden standard diagnostic tool for COPD, using self-reported methods might influence COPD prevalence especially due to its overlap with asthma indicators. Though their approaches are generally comprehensible, the lack of standardised assessment methods may generally inflate estimates of observed effects.

B. Individual food intake vs. food patterns

In general, these recent studies explore new dimensions of assessing diet and COPD associations in terms of combined food effects rather than assessments of individual nutrients and foods. For instance, in a recent study [22], combined dietary fibre from cereal, fruits and vegetables, was negatively associated with COPD, whereas an assessment of independent food effects did not yield the same conclusion, except in the case of dietary fibre from cereal. This reflects the importance of underlining combined effect of food components when assessing the relationships between diet and COPD. Limitations to studying dietary patterns, rather than individual nutrients or foods, arise when beneficial effect are observed yet cannot be attributed to the presence of specific food components in dietary patterns. Interactions of food combinations are difficult to study due to the complexity of their contents and interactions between and within a given dietary patterns As a result, interpretation of combined food effects should be made with caution, since knowledge on within- and between-food components, their interactions and their effects on COPD are scarce. This causes difficulty in studying definitive health effects of diet on COPD.

Nevertheless, recent studies have been useful in adding to the current knowledge, especially with respect to assessing a wider combination of food components which has several implications for public health, particularly for food policy. However, the extent to which information on dietary patterns can be interpreted and generalized can be challenging.

Generally, dietary patterns are embedded in different geographical, social and ethnic spheres, which make them difficult to study. Nevertheless, studies assessing dietary patterns and COPD have useful implications for public health, since foods are generally eaten in combinations rather than individually. Previous studies assessing individual nutrients/foods have been of critical importance in our understanding of the biological and metabolic mechanisms involved. Food patterns, on the other hand, are more relevant in depicting the overall importance of diet on COPD. This is important especially for suggesting useful nutritional strategies, since individuals can easily manipulate their dietary preferences directly through their food choices. The challenge now is to identify how specific foods and their components work wholly to produce observed effects on COPD. Moreover, further insight on the within and between individual differences, especially in terms of (non)smoking status should be further explored.

C. The role of smoking

There is a need to address the issue of confounding due to smoking which was previously emphasised [5, 7]. Although more recent cross-sectional and longitudinal studies have focused on dietary patterns of food intake and COPD, little is still known about the modification of this association by smoking. Tobacco smoking has been of major importance when assessing the protective effect of diet on respiratory disease, since it is a known risk factor for COPD. Generally, studies have adjusted for smoking and some for multiple smoking parameters, in order to limit their confounding effects. Nevertheless, studies to date, that assess the association between diet and COPD have failed to evaluate evidence from smokers versus non-smokers. Non-smokers have not been studied extensively studied and as a result, the issue of smoking has not been fully addressed. Universally, evidence from cross-sectional and longitudinal studies has been determined after adjusting for multiple potential confounders, including smoking. In general, adjustments for potential confounding factors have not changed study findings suggesting that the observed associations are unlikely to be explained by these potential confounders [16, 17, 20, 21]. In a prospective study on dietary patterns and COPD, Varasso and colleagues observed beneficial associations of diet on COPD, which remained consistent both in smokers and non-smokers, although associations were significantly less in non-smokers [17]. Additionally, one study demonstrated an overall lack of association in non-smokers in comparison to smokers and this observed effect was attributed to the generally small prevalence of COPD in non-smokers group [21]. Essentially,

invariable associations were still observed when adjustments for multiple potential confounders were made. This suggests that there was no apparent modification by smoking.

This raises the issue of residual confounding by smoking and effect modification by other unmeasured confounders which may not be completely eradicated. Assessing the role of smoking on this association is key and proves to be a rather complex issue. Generally, smokers are known to have elevated levels of oxidants and inflammatory agents, suggesting that a shift to antioxidant rich diets, which have shown to have a protective effect on lung function [6], will naturally show beneficial effects. Additionally, smokers tend to eat unhealthily [17] an aspect that may strengthen the observed beneficial effects of a 'healthy' diet such as the 'prudent' pattern on lung function and COPD [16,17]. Generally, there is difficulty in assessing the issue of residual confounding by smoking, since the effects of smoking are often difficult to isolate or neutralise in epidemiological research. Additionally, there is difficulty in assessing the exposure time of developing COPD, which may be exacerbated in smokers in comparison to non-smokers. In addition to modification by smoking, other lifestyle factors may confound this association and as a result, it is challenging to infer the true causal nature of this association.

D. Temporal relationship

Previously, Tricon et al. [5] have highlighted the importance of addressing the temporal nature of the diet-COPD relationship in the interpretation of causality. Though recent longitudinal evidence provide insight on the diet and COPD association [16, 17, 21, 22], data do not provide sufficient evidence on a temporal relationship between diet and COPD. Despite the growing number of longitudinal studies assessing this association, very little is still known about the induction time for a dietary effect. Evidence on a temporal effect of dietary factors and their involvement in the development and course of COPD is scarce. Moreover, the development and course of COPD is most likely exacerbated in smokers in comparison to non-smokers, since smoking is a known risk factor. These critical issues have been are seldom investigated and for these reasons, causation in the diet-COPD relationship is difficult to ascertain.

Additionally, it has previously been suggested that, tracking lung development and decline from childhood may elucidate on the development of COPD in adult life. Early disruptions in lung growth and function, by childhood respiratory diseases, may predispose individuals to

chronic deficits in lung function in their adult life [23]. Similarly, perhaps tracking dietary intake during childhood years and assessing lung function parameters may give insight on the temporality of the association. Could the presence of respiratory diseases during childhood, such as asthma, cause a change in dietary habits, which would later have implications on lung function in adult life? Given this scenario, reverse causation seems unlikely, since it is difficult to comprehend how children with respiratory diseases, such as asthma, would consume 'unhealthier' diets. Evidently, the degree of certainty on a temporal relationship is generally lacking. Further research is needed on childhood diet and respiratory diseases and its implications on the development of COPD in adult life. In essence, there is a need for more sophisticated longitudinal research on the temporal effect of diet on COPD.

Difficulty lies in designing appropriate studies that can investigate these issues definitively. Vast epidemiological knowledge has accumulated over the decades, especially through observational studies. However, interventional studies are often considered more appropriate when inferring causality. Due to ethical constraints, especially in assessments of involving smoking, designing appropriate studies can be challenging. Despite statistically controlling for smoking in cross-sectional and longitudinal studies, residual confounding and modification by other lifestyle factors may still modify this diet-COPD relationship. Nevertheless, longitudinal studies continue to provide evidence on the involvement of dietary factors and the course of COPD. For these reasons, priority lies in designing appropriate studies that assess the diet-COPD relationship both longitudinally and in non-smokers, in order to ascertain the true nature of this diet-COPD association.

IV. Conclusions

Previously, the importance of a diet-COPD relationship has been recognised in epidemiological research. However, several uncertainties, including residual confounding by smoking and assessment of a temporal diet-COPD relationship, have previously been highlighted [5]. In the recent 5 years, there has been a shift to dietary pattern assessments and their implications on lung function and COPD. These recent studies have added knowledge to the current evidence on diet and COPD, particularly in their explorations of dietary patterns and combined food effects, as opposed to assessments of individual foods and nutrients. Additionally, evidence has suggested that a 'healthy' diet such as the 'prudent' diet may have

beneficial implications on COPD [16, 17, 19]. These conclusions are in light with the globally recognised importance of healthy eating, and in essence, have important implications on public health. However, no studies to date have investigated the temporality of this association and to what extent smoking modifies this association. As a result, the interpretation of current evidence is not sufficient to establish causality in the association between diet and COPD. The current challenge is to prospectively identify the role of smoking on this relationship by comparing smokers and non-smokers. Moreover, future studies are needed to elucidate on the impact of diet on the development and course of COPD. This will allow us to definitively establish causality, and in essence will have important implications for further public health research.

V. References

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VI. Appendix

Table 1: *Recent studies on Diet and COPD outcomes*

Source	Study characteristics	Dietary intake assessment	Outcomes	Adjusted confounders	Results
Jiang *et al*. (2007)	Cross-sectional study; Third National Health and Nutrition Examination Survey (NHANES III); 7,352 participants, ≥45years	Cured meat consumption (total consumption of bacon, sausage, luncheon meats); Never, 1-2times/mo, 3-4times/mo, 5-13times/mo, ≥14times/mo (FFQ)	Lung function: FEV1, FVC COPD: FEV1/FVC≤0.7 and FEV1 <80% predicted	Age ,sex, smoking status, pack years of smoking and multiple additional confounders	Cured meat consumption is inversely associated with FEV1 and FEV1/FVC but not with FVC and; increased risk for developing COPD OR for COPD (high versus low category of cured meat consumption): 1.78(1.29-2.47); OR for mild, moderate and severe COPD: 1.11, 1.46, 2.41 respectively
Varraso *et al*. (2007)	Prospective study; Health Professionals Follow-up Study (1986-1998); 42,917 men, 40-75years	Dietary patterns: Prudent pattern (fruits, vegetables, fish, whole grains); Western pattern(refined grains, cured and red meats, desserts and sweets, French fries) (FFQ)	COPD risk	Age, smoking, pack-years, pack-years², race/ethnicity, physician visits, US region, BMI, physical activity, multivitamin use, energy intake	Prudent pattern: negatively associated with newly diagnosed COPD (highest versus lowest quintile, RR=0.50(0.35-0.98); Western pattern: positively associated with newly diagnosed COPD (highest versus lowest quintile, RR=4.56(1.95-10.69)
Varrasso *et al*. (2007)	Prospective study; Nurses' Health Study (1984-2000); 72,043 women, 30-55years	Dietary patterns: Prudent diet (fruits, vegetables, fish, whole-grain products); Western diet (refined grains, cured and red meats, desserts, French fries Frequency of consumption: Almost never' to '≥6times/d' (FFQ)	COPD risk	Age, smoking status, pack-years, pack-years², exposure to second hand tobacco smoke, BMI, physical activity, energy intake, and other potential confounders	Prudent: negative association (highest versus lowest quintile, RR=0.75 (0.58-0.98); Western: positive association (highest versus lowest quintile, RR=1.31(0.94-1.82)
Jiang *et al*. (2008)	Prospective study; Nurses' Health Study(1984 – 2000); 71,531 women, 38-63years	Cured meat consumption: Never or almost never, 1-3servings/mo, 1serving/wk, 2-3servings/wk, ≥4servings/wk	COPD risk	Age, smoking status, pack-years,, and other multiple confounders	Frequent cured meat consumption positively associated with COPD risk: RR: (Never or almost never, 1-3servings/mo, 1serving/wk, 2-3servings/wk, ≥4servings/wk): 1.0, 1.14 (0.78- 1.66), 1.15 (0.79- 1.69), 1.40

		(FFQ)			(0.96- 2.05), and 1.51 (1.00-2.27) respectively.
McKeever *et al.* (2010)	Cross- sectional study; MORGEN-EPIC Study; 12,648 adults, 20-59years	Dietary patterns: Traditional diet (higher intake of red meat, processed meat, boiled vegetables, added fat, coffee, beer, potato); Cosmopolitan diet (vegetables, fish, chicken, wine); Refined foods (FFQ)	Lung function: FEV1, longitudinal change in FEV1 (5yrs); symptoms of COPD, asthma, wheeze	Age, sex, smoking status, pack-years of smoking, BMI, educational level, town of examination	Traditional diet: lower FEV1, higher prevalence of COPD; Cosmopolitan diet: higher FEV1, increased wheeze & asthma; Refined foods: associated with accelerated decline in FEV1 over 5years
Shaheen *et al.* (2010)	Cross-sectional study; Hertfordshire Cohort Study (HCS); 1,551 males, 1,391 females, mean age: 66years	Dietary patterns: Prudent diet (fruit, vegetables, oily fish, wholemeal cereals); Traditional diet (vegetables, processed meat, offal, fish, red meat, puddings) (FFQ)	Lung function:FEV1, FVC; COPD	Age, height, smoking status, pack-years smoked, alcohol consumption, energy intake and other potential confounders	Prudent pattern positively associated with FEV1 and FVC. Effect modification by sex: in males positive association with prudent pattern; higher FEV1/FVC and lower prevalence of COPD (OR highest versus lowest quintile 0.46(0.26-0.81). Beneficial effects in males strongest in current smokers
Varraso *et al.* (2010)	Prospective study; Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) (1984-2000); 111,580 men and women, NHS(30-55years), HPFS(40-75years)	Dietary fibre intake from cereal, fruits and vegetables: total fibre; cereal fibre; fruit fibre; vegetable fibre (FFQ)	COPD risk	Age, sex, smoking, energy intake, BMI, US region, physician visits, physical activity, diabetes, intake of omega-3 and cured meat	Total dietary fibre negatively associated with risk of newly diagnosed COPD (highest versus lowest risk, RR-0.67 (0.50-0.90)) Only cereal fibre associated with newly diagnosed COPD independently (highest vs. lowest quintile, RR=0.77 (0.59-0.99))
Abbreviations: 95%CI – confidence interval, RR – relative risk, OR – odds ratio					