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Commentary

Diet and COPD: Are we what we eat?

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Chronic obstructive pulmonary disease (COPD) is a global epidemic that requires urgent attention and action. In the United States, COPD is the 2nd leading causing disability and worldwide, it is the 6th leading cause of death [1]. The Global Burden of Disease (GBD) group projects that by 2040 COPD will become the 4th leading cause of mortality largely owing to continued increases in its prevalence and successful treatment (or prevention) of other common competing causes of morbidity and mortality such as cancer and cardiovascular diseases [2]. Although rates of cigarette smoking, the leading risk factor for COPD, have decreased dramatically in most industrialized countries over the past two decades, paradoxically the COPD prevalence has increased by nearly 50% since 2007 [3] and is expected to increase by another 50% over the next two decades [2]. Why?

While it is well known that anthropometric measures such as low body mass index (BMI) increase the risk of COPD, dietary factors related to obesity (or cachexia) have not been adequately explored [4]. In this issue of *EClinicalMedicine* Varraso and colleagues [5] ascertained the dietary patterns of 116,429 female registered nurses, between the ages of 25–44 years, who participated in the Nurses' Health Study II (NHSII) [5]. The study began in 1989 and completed the last follow-up in 2017 accumulating over 2.2 million person-years of follow-up time during this interval. The investigators found that regular intake ($\geq$1 serving/week) of processed meat increased the risk of incident COPD by 140%. Adjustments for age and smoking, the two most important risk factors for COPD, reduced the excess risk by half to 70%. What was most striking was the synergy of regular intake of processed meat with cigarette smoking and unhealthy diet in amplifying the risk of incident COPD. Individuals who had all 3 risk factors (regular intake of processed meat, cigarette smoking, and unhealthy diet) had a 7.8 fold increase in the risk of COPD; whereas those with only 2 of these 3 risk factors experienced a 1.9 fold higher risk and those with only one risk factor had a 28% increase in the risk. These data are consistent with a "multiple hit" hypothesis of COPD, which suggests that COPD only occurs in the presence of 2 or more major risk factors (e.g. advanced age and cigarette smoking) [4].

There were many strengths to this study including its large sample size, the long follow-up time with very few drop-outs and a relatively narrow distribution of socioeconomic status (SES) (as all were registered nurses), another well-established risk factor for COPD, which reduced the "noise" of the findings. There were also some limitations. As with all observational studies, there may have been unmeasured (e.g. air pollution) or inadequately measured factors (e.g. daily smoking amount, depth of inhalation, content of cigarettes) that could have distorted the results. However, it was reassuring that inclusion of many covariates including smoking, age, BMI and others did not explain away the strong association between regular intake of processed meat and the risk of COPD. Further, the clear monotonic dose–response between number of risk factors and incidence of COPD (Fig. 1 of Varraso's paper [5]) enhances the confidence that the findings were real and not spurious.

The findings of Varraso's study are important for several reasons. Most of the major established risk factors are non-modifiable (e.g. age and genes) or very difficult to quickly modify (e.g. SES class). Dietary factors, on the other hand, are readily mutable. The present study suggests that individuals at risk for COPD (or who have COPD) should avoid (or significantly reduce) their intake of processed meats and replace it with "heathier" food items such as whole grains, polyunsaturated fatty acids, nuts, and long chain omega-3 fats. A previous study by the same group suggests that COPD patients and at risk individuals should also avoid refined grains and sugar sweetened drinks in their daily diet [6]. What are the proposed biological mechanisms for these recommendations?

While the answers to this important question were beyond the purview of the present, it is now well-established that processed meat contains high concentrations of nitrites, advanced glycation end-products (AGEs), and other contents, which promote oxidative stress and inflammation in the host. Nitrites do this by generating strong reactive nitrogen species such as peroxynitrites; while AGEs promote inflammation by engaging pattern recognition receptors and activating nuclear factor kappa b (NF-kB), which controls transcription of pro-inflammatory cytokines, such as interleukin (IL) 1, IL-6, tumor necrosis factor (TNF) and others [7]. Lungs are particularly vulnerable to the effects of oxidant stress and inflammation because they are constantly exposed to microbes and environmental toxins

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that stimulate the host immune system. Specific to AGEs, the lungs are particularly susceptible to their effects as lungs have the highest expression for their receptor, the receptor for AGE (RAGE) [8], which activates their pro-inflammatory and pro-oxidant pathways. Polymorphisms in the gene encoding for RAGE have been strongly linked with risk of COPD in genome-wide association studies (GWASs) [9].

Clinical and public health implications of the present study are clear: processed meat and an "unhealthy" diet in general are bad for the lungs and predispose individuals to chronic lung disease such as COPD, probably because they are pro-oxidant and pro-inflammatory. Those living in poor neighborhoods with low disposal income, who are vulnerable to COPD, have on average a higher consumption of processed meat and eat unhealthy diets than those in higher SES. Worldwide, the average per capita consumption of meat and processed meat in particular is rising exponentially, especially in middle-income countries, which are now adopting a more "Western" diet [10]. The strongest epidemiological evidence for the adverse impact of this trend is observed in the escalating incidence of colorectal cancer. The findings of Varraso's study suggest that we can add COPD to this list of adverse effects of unhealthy diet. The good news is that (unhealthy) diet is modifiable and we should encourage our patients to eat less processed meat and sweets and more grains and fruit.

Authors' contribution

DDS conceived the paper and wrote it.

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Declaration of competing interest

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