Journal of *Respiration*

MDPI

Article

Association between Obstructive Lung Disease and Cardiovascular Disease: Results from the Vermont Diabetes Information System

Maria E. Ramos-Nino [1,2,*], Charles D. MacLean [3] and Benjamin Littenberg [3]

[1] Department of Microbiology, Immunology, and Pharmacology, St. George's University, St. George's, Grenada
[2] Department of Pathology and Laboratory Medicine, University of Vermont, Burlington, VT 05401, USA
[3] Department of Medicine, University of Vermont, Burlington, VT 05401, USA; charles.maclean@uvm.edu (C.D.M.); Benjamin.Littenberg@uvm.edu (B.L.)
* Correspondence: mramosni@sgu.edu

Abstract: The association between obstructive lung disease and cardiovascular disease (CVD) has been suggested previously, but few studies have looked at this association in a diabetic cohort, a population highly susceptible to both comorbidities. A total of 1003 subjects in community practice settings were interviewed at home at the time of enrolment into the Vermont Diabetes Information System, a clinical decision support program. Patients self-reported their personal and clinical characteristics, including any obstructive lung disease. Laboratory data were obtained directly from the clinical laboratory. We performed a cross-sectional analysis of the interviewed subjects to assess a possible association between obstructive lung disease and CVD. In a multivariate logistic regression model, obstructive lung disease was significantly associated with CVD, even after correcting for potential confounders, including gender, obesity, low income, cigarette smoking, alcohol problems, and high comorbidity (odds ratio = 1.96; 95% confidence interval 1.37–2.81; $p < 0.01$). All components of CVD, including coronary artery disease (CAD), congestive heart failure (CHF), peripheral vascular disease (PVD), and cerebrovascular accidents (CVA), were also significantly associated with obstructive lung disease. These data suggest an association between obstructive lung disease and CVD in patients with diabetes. Future studies are needed to identify the mechanism supporting this association

Keywords: asthma; COPD; cardiovascular disease; diabetes

Citation: Ramos-Nino, M.E.; MacLean, C.D.; Littenberg, B. Association between Obstructive Lung Disease and Cardiovascular Disease: Results from the Vermont Diabetes Information System. *J. Respir.* **2021**, *1*, 165–172. https://doi.org/10.3390/jor1030016

Academic Editor: Cesar A. Moran

Received: 15 May 2021
Accepted: 18 June 2021
Published: 23 June 2021

1. Introduction

The burden of chronic respiratory diseases is increasing worldwide and, among these, the obstructive lung diseases asthma and chronic obstructive pulmonary disease (COPD) are among the main causes of mortality and morbidity [1]. The prevalence of COPD increases with age, as does the prevalence of comorbid conditions, while asthma is the most common chronic disease in children in Western countries, and it can be diagnosed at any age [2].

Obstructive lung disease has been shown to have an association with many comorbidities [2–5], especially cardiovascular disease (CVD). A more robust association is found in patients with COPD and CVD [6–11] than patients with asthma and CVD [12–16]. The mechanisms involved in the association between obstructive lung disease and cardiac disease are complex, but may be related to systemic inflammation, chronic infections, shared risk factors (such as smoking), or other undefined factors [17]. However, the impact of these mechanisms is difficult to ascertain [18]. In the current cross-sectional study, we determined the association between obstructive lung disease and the prevalence of associated CVD using information obtained from the Vermont Diabetes Information System (VDIS) study.

2. Materials and Methods

This study is part of a larger project, the VDIS, a study of 7412 adults with diabetes in primary care practices [19]. The subjects comprised all diabetic adults in 64 practices in Vermont and adjacent New York. A field survey was completed at study baseline with a subsample of subjects. Patient names were randomly sorted and patients were contacted by telephone until a sample of approximately 15% of patients from each practice agreed to participate in the field survey to give a sample of 1007 at the time of analysis. Four patients were dropped from the analysis due to incomplete information, leaving a final sample of 1003.

Subjects completed a questionnaire at home, and then were visited by a trained research assistant who reviewed the questionnaire responses, assisted the subject with any missing or unacceptable responses, reviewed the subject's medications, and measured their height and weight using a portable stadiometer and scale. Race, education, income, marital status, functional status, smoking, alcohol consumption, and comorbid conditions were obtained by questionnaire. To determine comorbidity, we used a modification of the Self-Administered Comorbidity Questionnaire [20], in which we asked each patient to indicate whether they had had the following conditions: heart attack, heart failure, peripheral arterial disease, stroke, dementia, rheumatic disease, peptic ulcer, cirrhosis, paralysis, renal insufficiency, diabetic vascular complications, AIDS/HIV, and depression. The primary outcome variable, presence of obstructive lung disease, was the patient's response to the question "Do you have asthma, emphysema, or chronic bronchitis?" The primary predictor variable, presence of CVD, was determined by the patient's responses to the following questions: (A) "Have you had a heart attack?" (coronary artery disease (CAD)); (B) "Have you had heart failure? (You may have been short of breath and your doctor may have told you that you had fluid in your lungs or that your heart was not pumping)" (congestive heart failure (CHF)); (C) "Have you had blockages in the arteries in your legs? (May have been referred to as claudication)" (peripheral vascular disease (PVD)); and (D) "Have you had a stroke, cerebral vascular accident, blood clot, bleeding in the brain, or transient ischemic attack (TIA)?" (cerebrovascular accident (CVA)).

Most laboratory data were obtained from the patients' local clinical laboratories, which all used the same Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications high-performance liquid chromatography (HPLC) method for the determination of glycosylated hemoglobin (A1C). Less than 1% of A1C tests were performed using the Bayer DCA 2000 immunoassay point of care instrument, which compares favorably with the HPLC method [21].

The research protocol was approved by the Committee on Human Research of the University of Vermont. The interviewed subjects provided written informed consent. The full study protocol and variables, and the medication profiles of the subjects have been previously reported [19,22].

Statistical Approach

We used logistic regression to assess the univariate relationship of obstructive lung disease as the outcome variable with CVD as the predictor. We then adjusted for possible confounding by social and clinical factors. Potential confounders tested were gender (male/female), age (years), race (white/other), body mass index (BMI) (kg/m^2), glycosylated hemoglobin level (A1C; %), insulin use (yes/no), self-reported history of alcohol problems (yes/no), cigarettes (per day), low annual income (<USD 30,000 per year), duration of diabetes in years, and high comorbidity (>2), not including chronic lung obstructive diseases and cardiovascular diseases. To reduce the number of variables in the final model, we excluded potential confounders that were associated with the outcome in univariate analyses with $P > 0.15$. Such a weak association implies that the variable is unlikely to be a confounder. We also performed separate multivariate analyses on the different components of CVD, including CAD, CHF, PVD, and CVA. We used Stata/SE v.16 (StataCorp, College Station, TX, USA) for all analyses.

3. Results

The characteristics of the study population are described in Table 1. The study population was representative of adults with diabetes in primary care practices in northern New England, USA. Because many of the subjects were over retirement age or suffered disabilities from chronic conditions, their income was lower than that of healthy younger Americans. The prevalence of obstructive lung disease was 203 (20.2%). A total of 310 (30.9%) of the subjects reported CVD (Table 1).

Table 1. Baseline characteristics of 1003 adults with diabetes.

Characteristic	N (%) or Mean (SD)
Age, years	64.8 (12.0)
Female gender	547 (54.5%)
White race	973 (97.3%)
Income, median USD/year	15,000–29,999
Income below <USD 30,000	548 (59.1%)
Body mass index (BMI) kg/m^2	33.8 (7.4)
Obese (BMI $\geq$ 30 kg/m^2)	666 (67.3%)
Cigarettes per day	2.8 (7.8)
Alcohol problem	78 (7.9%)
Duration of diabetes, years	10.2 (10.3)
Glycosylated hemoglobin A1C	7.1 (1.3)
Insulin use	186 (18.5%)
Obstructive lung disease prevalence	203 (20.2%)
Cardiovascular disease, all types	310 (30.9%)
Coronary artery disease	193 (19.2%)
Congestive heart failure	172 (17.2%)
Peripheral vascular disease	88 (8.8%)
Cerebrovascular accident	118 (11.8%)
High comorbidity (>2)	91 (9.0%)

SD, standard deviation; N, number of subjects with the characteristic.

Table 2 presents univariate associations between obstructive lung disease and the other study variables that had the potential of being significantly associated with obstructive lung disease prevalence.

Next, potential confounding variables associated with obstructive lung disease with $P \leq 0.15$ were included in a logistic regression model using obstructive lung disease as the outcome. These included gender (male), obesity (kg/m^2), alcohol problems, cigarettes per day, low annual income (<USD 30,000/year), and high comorbidity (>2). This model showed that the odds of having obstructive lung disease among those with CVD were nearly twice as high as among those without CVD (OR = 1.96; 95% confidence interval = 1.37, 2.81; $P < 0.01$). Other variables that were positively and significantly associated with obstructive lung disease included obesity, low annual income, and cigarettes per day. Male gender was protective (Table 3).

Table 2. Univariate associations between obstructive lung disease and other patient characteristics.

Characteristic	Obstructive Lung Disease Patients	Non-Obstructive Lung Disease Patients	OR	*P*
	% or Mean (SD)	% or Mean (SD)		
Number of subjects	203	800		
Age, years	64.3 (11.4)	64.9 (12.1)	1.00	0.54
Male	33.5%	48.6%	0.53	<0.01
White race	96.1%	97.6%	0.60	0.23
Low annual income	75.7%	54.8%	2.57	<0.01
Obese (BMI > 30 kg/m^2)	77%	64.8%	1.82	<0.01
Cigarettes per day	4.5 (10.2)	2.3 (7.0)	1.03	<0.01
Alcohol problem	12.1%	6.8%	1.88	0.02
Duration of diabetes, years	11.1 (10.6)	10.0 (10.3)	1.01	0.20
A1C, mg	7.2 (1.3)	7.1 (1.3)	1.03	0.67
Insulin use	27.2%	22.8%	1.27	0.19
Cardiovascular disease, all types	43.4%	27.8%	1.99	<0.01
Coronary artery disease	27.6%	17.1%	1.84	<0.01
Congestive heart failure	28.6%	14.3%	2.41	<0.01
Peripheral vascular disease	12.3%	7.9%	1.64	0.05
Cerebrovascular accident	18.7%	10.0%	2.07	<0.01
High comorbidity (>2)	16.3%	6.8%	2.68	<0.01

Each cell contains either % or mean (standard deviation).

Table 3. Multivariate logistic regression: obstructive lung disease vs. CVD and potential confounders (N = 903).

Characteristic	OR	*P*	95% CI
Cardiovascular disease, all types	1.96	<0.01	1.37–2.81
Gender (male)	0.48	<0.01	0.33–0.70
Obesity	1.81	<0.01	1.21–2.71
Low annual income	2.08	<0.01	1.40–3.08
Cigarettes per day	1.03	0.01	1.01–1.05
Alcohol problem	1.71	0.07	0.96–3.04
High Comorbidity	1.70	0.05	1.01–2.86

To determine the contribution of each component of CVD, namely CAD, CHF, PVD, and CVA, to the association with obstructive lung disease, we performed individual multiple regressions (Table 4).

Table 4. Multivariate logistic regression of dependent variable, obstructive lung disease, vs. CAD, CHF, PVD, and CVA.

Characteristic	OR	*P*	95% CI
Coronary artery disease	1.67	0.01	1.12–2.51
Gender (male)	0.49	<0.01	0.34–0.72
Obesity	1.76	0.01	1.18–2.63
Low income	2.17	<0.01	1.47–3.22
Cigarettes per day	1.02	0.01	1.00–1.04
Alcohol problem	1.61	0.10	0.91–2.86
High comorbidity	1.84	0.02	1.10–3.09
Congestive heart failure	2.06	<0.01	1.35–3.13
Gender (male)	0.49	<0.01	0.34–0.71
Obesity	1.77	0.01	1.18–2.65

Table 4. *Cont.*

Characteristic	OR	*P*	95% CI
Low income	2.09	<0.01	1.41–3.09
Cigarettes per day	1.03	0.01	1.01–1.05
Alcohol problem	1.50	0.17	0.84–2.68
High comorbidity	1.83	0.02	1.09–3.08
Peripheral vascular disease	1.77	0.04	1.01–3.09
Gender (male)	0.51	<0.01	0.35–0.73
Obesity	1.82	<0.01	1.22–2.73
Low income	2.23	<0.01	1.51–3.30
Cigarettes per day	1.02	0.02	1.00–1.04
Alcohol problem	1.65	0.09	0.93–2.93
High comorbidity	1.86	0.02	1.11–3.12
Cerebrovascular accident	1.88	0.01	1.17–3.01
Gender (male)	0.52	<0.01	0.36–0.76
Obesity	1.80	<0.01	1.20–2.68
Low income	2.24	<0.01	1.51–3.30
Cigarettes per day	1.03	0.01	1.01–1.05
Alcohol problem	1.52	0.16	0.85–2.70
High comorbidity	1.72	0.04	1.02–2.90

4. Discussion

Comorbid conditions are commonly associated with obstructive lung disease and increase the risk of hospitalization, increase the levels of polypharmacy, and are associated with higher mortality [23]. In the literature, estimates of the prevalence of individual comorbidities associated with obstructive lung disease vary substantially depending on the patient population evaluated, the methods for patient evaluation used, and the definitions of diseases [24]. In a retrospective observational study from the Truven Health MarketScan Commercial Claims and Encounters and the MarketScan Medicare Supplemental Databases, it was found that among 183,681 patients with COPD, the most common comorbidities were CVD (34.8%), diabetes (22.8%), asthma (14.7%), and anemia (14.2%) [25].

Similar to our study, the association between obstructive lung disease and an increased risk of CVD has been described in both asthma and COPD [26–30]. Studies on asthma and its associations with CVD suggest this association is dependent on the age of asthma onset and allergies [16,31–33]. The concomitant occurrence of COPD and CVD suggests that COPD could be a driving force of CVD or vice versa, but it could also reflect the shared risk factors, such as cigarette smoking and obesity [34].

The prevalence of CVD in our diabetic population (31%) is similar to those found in other studies [35]. The prevalence of obstructive lung disease in our diabetic cohort was 20.2%, but results in other studies varied between 2 and 37% [36]. The association between obstructive lung disease and CVD in the diabetic population has been less studied, although asthma and COPD have been individually and independently associated with an increased risk of type 2 diabetes in women [37]. Here, we showed that CVD and obstructive lung disease were significantly associated in this diabetic cohort. Furthermore, this association was also true for the components of CVD, including CAD, PVD, and CVA, with the strongest association found between obstructive lung disease and CHF.

The multivariate regression logistic model also showed a negative association between gender (male) and obstructive lung disease. Women are 37% more likely to have COPD than men [38]. Furthermore, there is a higher prevalence of asthma in boys than girls before puberty, but a higher prevalence in women than men in adulthood [39]. The association between gender and obstructive lung disease may be further confounded by CVD. The mean age in this cohort was 64.8 years of age, and menopause is a risk factor for CVD because estrogen withdrawal has a detrimental effect on cardiovascular function and metabolism [40]. Furthermore, the model shows a positive association that was significant

with potentially confounding variables that have similar results in other studies, including obesity [41–43], low income [44], cigarette smoking [45], and high comorbidities [2,46].

This study has several limitations, including the self-reporting of obstructive lung disease, lack of confirmation of obstructive lung disease and CVD diagnoses, inability to distinguish between asthma and COPD patients, and lack of information on the time relation between the onset of obstructive lung disease and CVD. As in any cross-sectional study, unmeasured confounders could be responsible for the apparent associations found. Generalizability beyond those patients represented in nonacademic primary care practices in the US may be limited.

5. Conclusions

These findings suggest a possible association between obstructive lung disease and CVD and all its components (CAD, CHF, PVD, and CVA) in diabetes. More research is needed to identify the mechanisms at work.

Author Contributions: Conceptualization, M.E.R.-N.; methodology, M.E.R.-N.; formal analysis, M.E.R.-N.; investigation, C.D.M. and B.L.; resources, C.D.M. and B.L.; data curation, C.D.M. and B.L.; writing—original draft preparation, M.E.R.-N.; writing—review and editing, C.D.M. and B.L.; project administration, C.D.M. and B.L.; funding acquisition, B.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by NIH grants RO1 DK61167, K24 DK068380 (BL).

Institutional Review Board Statement: The research protocol was approved by the Committee on Human Research of the University of Vermont. The interviewed subjects provided written informed consent. The full study protocol and variables and the medication profiles of the subjects have been previously reported [19,22].

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data used is reported in this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ehteshami-Afshar, S.; Fitzgerald, J.M.; Doyle-Waters, M.M.; Sadatsafavi, M. The global economic burden of asthma and chronic obstructive pulmonary disease. *Int. J. Tuberc. Lung Dis.* **2016**, *20*, 11–23. [CrossRef]
2. Soriano, J.B.; Visick, G.T.; Müllerová, H.; Payvandi, N.; Hansell, A. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* **2005**, *128*, 2099–2107. [CrossRef] [PubMed]
3. Cazzola, M.; Calzetta, L.; Bettoncelli, G.; Cricelli, C.; Romeo, F.; Matera, M.G.; Rogliani, P. Cardiovascular disease in asthma and COPD: A population-based retrospective cross-sectional study. *Respir. Med.* **2012**, *106*, 249–256. [CrossRef] [PubMed]
4. Gershon, A.S.; Wang, C.; Guan, J.; To, T. Burden of comorbidity in individuals with asthma. *Thorax* **2010**, *65*, 612–618. [CrossRef] [PubMed]
5. Fabbri, L.M.; Luppi, F.; Beghe, B.; Rabe, K.F. Complex chronic comorbidities of COPD. *Eur. Respir. J.* **2008**, *31*, 204–212. [CrossRef]
6. Cazzola, M.; Bettoncelli, G.; Sessa, E.; Cricelli, C.; Biscione, G. Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration* **2010**, *80*, 112–119. [CrossRef]
7. Feary, J.R.; Rodrigues, L.C.; Smith, C.J.; Hubbard, R.B.; Gibson, J. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: A comprehensive analysis using data from primary care. *Thorax* **2010**, *65*, 956–962. [CrossRef]
8. Rabe, K.F.; Hurst, J.R.; Suissa, S. Cardiovascular disease and COPD: Dangerous liaisons? *Eur. Respir. Rev.* **2018**, *27*, 180057. [CrossRef]
9. Rutten, F.H.; Cramer, M.-J.M.; Lammers, J.-W.J.; Grobbee, D.E.; Hoes, A.W. Heart failure and chronic obstructive pulmonary disease: An ignored combination? *Eur. J. Heart Fail.* **2006**, *8*, 706–711. [CrossRef] [PubMed]
10. Nacul, L.; Soljak, M.; Samarasundera, E.; Hopkinson, N.; Lacerda, E.; Indulkar, T.; Flowers, J.; Walford, H.; Majeed, A. COPD in England: A comparison of expected, model-based prevalence and observed prevalence from general practice data. *J. Public Health* **2010**, *33*, 108–116. [CrossRef] [PubMed]
11. Morgan, A.D.; Zakeri, R.; Quint, J.K. Defining the relationship between COPD and CVD: What are the implications for clinical practice? *Ther. Adv. Respir. Dis.* **2018**, *12*. [CrossRef]

12. Xu, M.; Xu, J.; Yang, X. Asthma and risk of cardiovascular disease or all-cause mortality: A meta-analysis. *Ann. Saudi Med.* **2017**, *37*, 99–105. [CrossRef] [PubMed]
13. Enright, P.L.; Ward, B.J.; Tracy, R.P.; Lasser, E.C. Asthma and its association with cardiovascular disease in the elderly. *J. Asthma* **1996**, *33*, 45–53. [CrossRef]
14. Schanen, J.G.; Iribarren, C.; Shahar, E.; Punjabi, N.M.; Rich, S.S.; Sorlie, P.D.; Folsom, A.R. Asthma and incident cardiovascular disease: The Atherosclerosis Risk in Communities Study. *Thorax* **2005**, *60*, 633–638. [CrossRef] [PubMed]
15. Appleton, S.L.; Ruffin, R.E.; Wilson, D.H.; Taylor, A.W.; Adams, R.J. Asthma is associated with cardiovascular disease in a representative population sample. *Obes. Res. Clin. Pract.* **2008**, *2*, 91–99. [CrossRef]
16. Onufrak, S.J.; Abramson, J.L.; Austin, H.D.; Holguin, F.; McClellan, W.M.; Vaccarino, L.V. Relation of adult-onset asthma to coronary heart disease and stroke. *Am. J. Cardiol.* **2008**, *101*, 1247–1252. [CrossRef] [PubMed]
17. André, S.; Conde, B.; Fragoso, E.; Boléo-Tomé, J.P.; Areias, V.; Cardoso, J. COPD and cardiovascular disease. *Pulmonology* **2019**, *25*, 168–176. [CrossRef]
18. Thomsen, M.; Ingebrigtsen, T.S.; Marott, J.L.; Dahl, M.; Lange, P.; Vestbo, J.; Nordestgaard, B.G. Inflammatory Biomarkers and Exacerbations in Chronic Obstructive Pulmonary Disease. *JAMA J. Am. Med. Assoc.* **2013**, *309*, 2353–2361. [CrossRef]
19. MacLean, C.D.; Littenberg, B.; Gagnon, M.; Reardon, M.; Turner, P.D.; Jordan, C. The Vermont Diabetes Information System (VDIS): Study design and subject recruitment for a cluster randomized trial of a decision support system in a regional sample of primary care practices. *Clin. Trials* **2004**, *1*, 532–544. [CrossRef]
20. Sangha, O.; Stucki, G.; Liang, M.H.; Fossel, A.H.; Katz, J.N. The self-administered comorbidity questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis Rheum.* **2003**, *49*, 156–163. [CrossRef] [PubMed]
21. Tamborlane, W.V.; Kollman, C.; Steffes, M.W.; Ruedy, K.J.; Dongyuan, X.; Beck, R.W.; Chase, P.; Fox, L.A.; Wilson, D.M.; et al.; The Diabetes Research in Children Network (DirecNet) Study Group. Comparison of fingerstick hemoglobin A1c levels assayed by DCA 2000 with the DCCT/EDIC central laboratory assay: Results of a Diabetes Research in Children Network (DirecNet) Study. *Pediatr. Diabetes* **2005**, *6*, 13–16. [CrossRef] [PubMed]
22. MacLean, C.D.; Littenberg, B.; Kennedy, A.G. Limitations of diabetes pharmacotherapy: Results from the Vermont diabetes information system study. *BMC Fam. Pract.* **2006**, *7*, 50–56. [CrossRef] [PubMed]
23. Chetty, U.; McLean, G.; Morrison, D.; Agur, K.; Guthrie, B.; Mercer, S.W. Chronic obstructive pulmonary disease and comorbidities: A large cross-sectional study in primary care. *Br. J. Gen. Pract.* **2017**, *67*, e321–e328. [CrossRef]
24. Franssen, F.M.E.; Rochester, C.L. Comorbidities in Patients with COPD and Pulmonary Rehabilitation: Do They Matter? *Eur. Respir. Rev.* **2014**, *23*, 131–141. Available online: http://ow.ly/qy5MK (accessed on 19 April 2021). [CrossRef] [PubMed]
25. Mannino, D.M.; Higuchi, K.; Yu, T.-C.; Zhou, H.; Li, Y.; Tian, H.; Suh, K. Economic burden of COPD in the presence of comorbidities. *Chest* **2015**, *148*, 138–150. [CrossRef]
26. Ingebrigtsen, T.S.; Marott, J.L.; Vestbo, J.; Nordestgaard, B.G.; Lange, P. Coronary heart disease and heart failure in asthma, COPD and asthma-COPD overlap. *BMJ Open Respir. Res.* **2020**, *7*, e000470. [CrossRef]
27. Boulet, L.-P. Influence of comorbid conditions on asthma. *Eur. Respir. J.* **2009**, *33*, 897–906. [CrossRef]
28. Su, X.; Ren, Y.; Li, M.; Zhao, X.; Kong, L.; Kang, J. Prevalence of comorbidities in asthma and nonasthma patients. *Medicine* **2016**, *95*, e3459. [CrossRef]
29. Müllerova, H.; Agusti, A.; Erqou, S.; Mapel, D.W. Cardiovascular comorbidity in COPD: Systematic literature review. *Chest* **2013**, *144*, 1163–1178. [CrossRef]
30. Chen, W.; Thomas, J.; Sadatsafavi, M.; FitzGerald, J.M. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Lancet Respir. Med.* **2015**, *3*, 631–639. [CrossRef]
31. Tattersall, M.C.; Barnet, J.H.; Korcarz, C.; Hagen, E.W.; Peppard, P.E.; Stein, J.H. Late-onset asthma predicts cardiovascular disease events: The wisconsin sleep cohort. *J. Am. Heart Assoc.* **2016**, *5*, e003448. [CrossRef] [PubMed]
32. Wang, L.; Gao, S.; Yu, M.; Sheng, Z.; Tan, W. Association of asthma with coronary heart disease: A meta analysis of 11 trials. *PLoS ONE* **2017**, *12*, e0179335. [CrossRef] [PubMed]
33. Knoflach, M.; Kiechl, S.; Mayr, A.; Willeit, J.; Poewe, W.; Wick, G. Allergic Rhinitis, Asthma, and Atherosclerosis in the Bruneck and ARMY Studies. *Arch. Intern. Med.* **2005**, *165*, 2521–2526. [CrossRef] [PubMed]
34. Vivodtzev, I.; Maltais, F. Cardiovascular Risk in COPD: Searching for a Culprit. *Chest* **2020**, *157*, 753–754. [CrossRef]
35. McGurnaghan, S.; Blackbourn, L.A.K.; Mocevic, E.; Panton, U.H.; McCrimmon, R.J.; Sattar, N.; Wild, S.; Colhoun, H.M. Cardiovascular Disease Prevalence and Risk Factor Prevalence in Type 2 Diabetes: A Contemporary Analysis. *Diabet. Med.* **2018**, *36*, 718–725. Available online: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.13825 (accessed on 19 April 2021). [CrossRef]
36. Rogliani, P.; Lucà, G.; Lauro, D. Chronic obstructive pulmonary disease and diabetes. *COPD Res. Pract.* **2015**, *1*, 454. [CrossRef]
37. Song, Y.; Klevak, A.; Manson, J.E.; Buring, J.E.; Liu, S. Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the Women's Health Study. *Diabetes Res. Clin. Pract.* **2010**, *90*, 365–371. [CrossRef]
38. Lung Health Institute | Is COPD in Women More Common than in Men? Available online: https://lunginstitute.com/blog/is-copd-in-women-more-common-than-in-men/ (accessed on 1 May 2021).
39. Postma, D.S. Gender Differences in Asthma Development and Progression. *Gend. Med.* **2007**, *4* (Suppl. 2), S133–S146. Available online: https://pubmed.ncbi.nlm.nih.gov/18156099/ (accessed on 1 May 2021). [CrossRef]

40. Rosano, G.M.C.; Vitale, C.; Marazzi, G.; Volterrani, M. Menopause and Cardiovascular Disease: The Evidence. *Climacteric* **2007**, *10*, 19–24. Available online: https://pubmed.ncbi.nlm.nih.gov/17364594/ (accessed on 11 May 2021). [CrossRef] [PubMed]
41. Ramos-Nino, M.E.; MacLean, C.D.; Littenberg, B. Association between prevalence of obstructive lung disease and obesity: Results from The Vermont Diabetes Information System. *Asthma Res. Pract.* **2021**, *7*, 1–6. Available online: https://asthmarp.biomedcentral.com/articles/10.1186/s40733-021-00073-1 (accessed on 11 May 2021). [CrossRef]
42. Franssen, F.M.E.; O'Donnell, D.E.; Goossens, G.H.; Blaak, E.E.; Schols, A.M.W.J. Obesity and the Lung: 5 • Obesity and COPD. *Thorax* **2008**, *63*, 1110–1117. Available online: http://thorax.bmj.com/ (accessed on 11 May 2021). [CrossRef]
43. Poulain, M.; Doucet, M.; Major, G.C.; Drapeau, V.; Sériès, F.; Boulet, L.P.; Tremblay, A.; Maltais, F. The Effect of Obesity on Chronic Respiratory Diseases: Pathophysiology and Therapeutic Strategies. *CMAJ* **2006**, *174*, 1293–1299. Available online: https://www.cmaj.ca/content/174/9/1293 (accessed on 11 May 2021). [CrossRef]
44. Kanervisto, M.; Vasankari, T.; Laitinen, T.; Heliövaara, M.; Jousilahti, P.; Saarelainen, S. Low socioeconomic status is associated with chronic obstructive airway diseases. *Respir. Med.* **2011**, *105*, 1140–1146. [CrossRef] [PubMed]
45. Hylkema, M.N.; Sterk, P.J.; De Boer, W.I.; Postma, D.S. Tobacco Use in Relation to COPD and Asthma. *Eur. Respir. J.* **2007**, *29*, 438–445. Available online: www.erj.ersjournals.com/misc/ (accessed on 13 May 2021). [CrossRef]
46. Maselli, D.J.; Hanania, N.A. Asthma COPD Overlap: Impact of Associated Comorbidities. *Pulm. Pharmacol. Ther.* **2018**, *52*, 27–31. Available online: https://pubmed.ncbi.nlm.nih.gov/30172866/ (accessed on 13 May 2021). [CrossRef]