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Metabolic profiles among COPD and controls in the CanCOLD population-based cohort

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Abstract

A high prevalence of intermediate cardiometabolic risk factors and obesity in chronic obstructive pulmonary disease (COPD) has suggested the existence of pathophysiological links between hypertriglyceridemia, insulin resistance, visceral adiposity, and hypoxia or impaired pulmonary function. However, whether COPD contributes independently to the development of these cardiometabolic risk factors remains unclear. Our objective was to compare ectopic fat and metabolic profiles among representative individuals with COPD and control subjects and to evaluate whether the presence of COPD alters the metabolic risk profile. Study participants were randomly selected from the general population and prospectively classified as non-COPD controls and COPD, according to the Global Initiative for Chronic Obstructive Lung Disease classification. The metabolic phenotype, which consisted of visceral adipose tissue area, metabolic markers including homeostasis model assessment of insulin resistance (HOMA-IR), and blood lipid profile, was obtained in 144 subjects with COPD and 119 non-COPD controls. The metabolic phenotype was similar in COPD and controls. The odds ratios for having pathologic values for HOMA-IR, lipids and visceral adipose tissue area were similar in individuals with COPD and control subjects in multivariate analyses that took into account age, sex, body mass index, tobacco status and current medications. In a population-based cohort, no difference was found in the metabolic phenotype, including visceral adipose tissue accumulation, between COPD and controls. Discrepancies between the present and previous studies as to whether or not COPD is a risk factor for metabolic abnormalities could be related to differences in COPD phenotype or disease severity of the study populations.

Introduction

Cardiometabolic diseases are at the forefront of comorbidities in the Chronic Obstructive Pulmonary Disease (COPD) population [1]. It has been reported that individuals with COPD have a 2- to 5-time higher risk of cardiovascular disease compared with controls, independently of shared risk factors such as age and smoking [2,3]. Understanding the nature of the link between COPD and co-existing metabolic conditions/comorbidities may provide personalized treatment strategies and identify new mechanistic pathways to be targeted.

The relationship between COPD and its comorbidities is complex and studies having reported a high prevalence of metabolic syndrome and obesity in patients with COPD [4–7] have suggested the existence of pathophysiological links between hypertriglyceridemia and hypoxia [8,9], obesity and hypoxia [10–12], or visceral adiposity and pulmonary function [13–16]. Various phenotypes of COPD have emerged, some of which being defined by the adiposity and metabolic profile of the patients [17–20]. In a previous investigation [21], we found that the degree of visceral adiposity with its associated hypertension and diabetes correlated with the severity of COPD [Global initiative for Obstructive Lung Disease (GOLD) grade]. Several potential confounders (tobacco exposure, dietary habits, sedentarity) may, however, complicate the establishment of a link between COPD and metabolic abnormalities.

In the present investigation based on the above-mentioned cohort, we aimed to further explore whether COPD is linked to established metabolic variables (insulin resistance [22–26], lipid control [27] and visceral adiposity [28,29]) in a well-phenotyped cohort representative of the general population. We hypothesized that if there is causal and self-sustaining links between COPD and metabolic abnormalities, then differences in metabolic risk factors should emerge between individuals with COPD and control subjects. The present study was embedded in the Canadian Cohort Obstructive Lung Disease Study (CanCOLD), a prospective longitudinal study of COPD with random population sampling [30].

Methods

Participants

The study was approved by the local ethics committee (Comité d'éthique du centre de recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec, IRB N° 20690, Study N° 2012–1359). CanCOLD (ClinicalTrials.gov: NCT00920348) steering and scientific committees approved the sub-study protocol. All study participants signed written consent before inclusion.

Participants in two CanCOLD study centres (Montreal and Quebec City, Quebec, Canada) were recruited between February 2012 and December 2015 for this sub-study. CanCOLD is a longitudinal cohort study based on the characterization of COPD among a random sample of the population in 9 Canadian cities [30]. Subjects had to be 40 years or older to participate in the CanCOLD study. Further details concerning the CanCOLD study design and eligibility criteria have been previously described [30]. Study participants underwent the standard Can-COLD assessment procedures, which provide information about patients' characteristics (age, gender, smoking history), medical history and current medications, body weight and height, and pulmonary function. Although no sleep studies were done in CanCOLD, the presence of sleep apnea was documented based on the use of continuous airway positive pressure (CPAP) and on standardized questionnaires, including the Pittsburg Sleep Quality Index [31]. Additional pre-specified measures were done including measurements of waist and hip circumferences, blood sampling to determine glucose and lipid profiles, and a computed tomography (CT) abdominal scan at 4th/5th lumbar vertebrae level (L4-L5) to quantify body fat distribution

[21]. Participants were divided according to the pulmonary function testing results as follows: 1) control subjects with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) > 80% predicted value and FEV_1/forced vital capacity (FVC) ratio > 0.7; 2) patients with COPD with a post-bronchodilator FEV_1/FVC ratio < 0.7 were further classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) airflow limitation classification scheme into GOLD 1, with an $FEV_1 \geq$ 80% predicted, and GOLD 2+ with an $FEV_1 <$ 80% predicted. All COPD subjects were invited to be enrolled in the final CanCOLD cohort, whereas some of the healthy subjects were enrolled to serve as controls with a control/COPD ratio of 1 to 1 [30]. Patients with a pulmonary restrictive profile were excluded from the analysis.

Procedures

Body fat distribution and visceral adipose tissue assessment. L4-L5 CT scan images were analyzed without knowledge of the clinical status of the subjects. Abdominal fat distribution was assessed using the specialized software Tomovision SliceOMatic (v4.3 Rev-6f, Montreal, Quebec, Canada). The detailed method used for image analysis has been previously reported [32, 33]. The middle of the muscle wall surrounding the abdominal cavity was delineated to determine the visceral adipose tissue (VAT) area. Abdominal adipose tissue areas were computed using an attenuation range of –190 to –30 Hounsfield units (HU). Body fat distribution parameters were obtained with methodology commonly applied in our Core Lab, with high levels of intra and inter-observer agreement [32].

Blood sample and biochemical analysis. Blood samples were collected in the morning, after a 12-hour fast to determine levels of glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. All analyses were carried-out in plasma or whole blood using automated techniques (Roche Diagnostics). Glucose, total cholesterol (TC), HDL-cholesterol, LDL-cholesterol, and triglycerides were measured by enzymatic *in vitro* tests. Insulin was determined using electrochemiluminescence immunoassay (ECLIA). Insulin resistance was assessed using the homeostatic model assessment for insulin resistance (HOMA-IR), calculated using the following formula: insulinemia × glucose/22.5 (glucose units mmol/L) [34].

Data analysis

Continuous data are presented as median and interquartile range (IQR) or mean and 95% confidence interval in case of normal distribution, and categorical data as frequency and percentage. Continuous variables were analysed using a Mann-Whitney test and categorical data and proportions were analysed using the Fisher exact tests. Metabolic phenotypes were compared between COPD and controls by using four complementary strategies: 1) univariate comparisons of adiposity and metabolic parameters (triglycerides, total/HDL cholesterol ratio, and HOMA-IR) between COPD subjects, GOLD 1 subjects, GOLD 2+ subjects and controls (Mann-Whitney test); 2) univariate linear regression with coefficient of determination (R^2) and analysis of covariance (ANCOVA) to study the relationships between metabolic parameters (triglycerides, total/HDL cholesterol ratio, HOMA-IR) and indices of adiposity (body mass index (BMI), waist-to-hip ratio and VAT area) according to COPD status; 3) multivariate linear regression models to detect possible interactions between the COPD status and the various metabolic parameters studied. A logarithmic transformation (Ln) was performed on each non-log-linear variable of interest. These models took into consideration (variable entry) all potential confounders available, including age, sex, smoking status, BMI, waist-to-hip ratio, corticosteroid treatment, hypolipidemic and hypoglycemic agents. Final models were selected with backwards elimination, with COPD status as a forced variable and keeping only the

significant variables at $p < 0.05$; and 4) multivariate logistic regressions to estimate the odds ratio of having hypertriglyceridemia (triglyceride >1.5 mmol/L), increased total /HDL cholesterol ratio>4 [35], and insulin resistance (HOMA-IR>3) [22–26] in the presence of COPD (all COPD and COPD GOLD2+ only) compared to non-COPD controls. These models were adjusted for potential confounders (age, sex, smoking status, BMI, corticosteroid treatment and ongoing pharmacological treatment related to the parameter studied, namely hypolipidemic drugs or hypoglycemic drugs). The odds ratio of having visceral obesity (L4-L5 VAT cross-sectional area >75th percentile of the whole population by sex) in the presence of COPD (all COPD and COPD GOLD2+ only) in comparison to non-COPD controls was analysed by multivariate logistic regression including age, smoking status and inhaled corticosteroid treatment as known confounding factors. In these multivariate logistic regressions, continuous variables were entered as quartiles. Missing data were not replaced. All statistical analyses were performed using IBM SPSS v.23 software (IBM statistics, USA) and GraphPad Prism v6.05 (GraphPad Software, USA).

Results

This CanCOLD sub-study included 263 participants having a median age of 65 [59–71] years and of whom two thirds were males. Based on pulmonary lung function, subjects were divided into control subjects with normal lung function (n = 119), and individuals with COPD (n = 144, 70 GOLD 1 and 74 GOLD 2+). No missing data in variables of interest have to be reported. There was no statistically significant between-group difference for age, sex, BMI, waist-to-hip ratio, and use of hypolipidemic and oral hypoglycemic agents (**Table 1**).

Metabolic profiles according to COPD status are provided in **Fig 1**. There was no significant difference between groups in triglyceride levels (**Fig 1A**), total/HDL cholesterol ratio (**Fig 1B**), and insulin resistance (HOMA-IR) (**Fig 1C**). The median VAT levels in control subjects (146.4 cm^2 [106.2–222.6]) was not different compared to COPD subjects (155.7 cm^2 [108.9–233.9], $p = 0.59$), and to GOLD 1 or GOLD 2+ COPD (**Fig 1D**). No significant difference was observed between COPD and controls in univariate analysis stratified by BMI for any metabolic parameter (**S1 Fig**).

Triglycerides, total/HDL cholesterol ratio and HOMA-IR were positively associated with the three indices of adiposity (BMI, waist-to-hip ratio and VAT area) in individuals with COPD and controls. (**Fig 2**, all regression lines with a p<0.05). However, the slopes of the regression lines were similar for both groups (p>0.05 for all comparisons) suggesting that the relationships between metabolic markers and adiposity were not modified in the presence of COPD.

In linear multivariate analyses, the COPD status was not significantly associated with triglyceride levels, total/HDL cholesterol, insulin resistance (HOMA-IR) or VAT area (**Table 2**). A higher BMI was associated with an increase in triglycerides, total/HDL cholesterol, and HOMA-IR levels, and current smokers with one third of additional VAT. No significant interaction was observed between the COPD status and any characteristic tested.

Lastly, a triglyceride level above 1.5 mmol/L, a total/HDL cholesterol ratio above 4 or a HOMA-IR above 3 were respectively observed in 54 (37.5%), 36 (25%) and 58 (40.3%) of COPD patients and in 37 (31.1%), 33 (27.7%) and 54 (45.4%) of control subjects. In multivariate analysis, the COPD status (or COPD 2+) was not associated with triglyceride >1.5 mmol/L, total/HDL cholesterol ratio >4, HOMA-IR>3, or VAT area>75th percentile. Only the COPD 2+ status was associated with a VAT area>75th percentile (OR = 2.27, CI95% 1.00; 5.15, p = 0.05). Complete regression models are available in supplementary S1–S8 Tables.

Table 1. Baseline characteristics by group.

	Control subjects (n = 119)	COPD (n = 144)	P value
Age, years	65 [59–71]	65 [59–71]	0.88
Male, n (%)	73 (61.3)	93 (64.6)	0.61
BMI, kg/m^2	26.5 [23.5–29.7]	26.6 [23.7–29.4]	0.96
Waist-to-hip ratio, mean (95% CI)	0.93 (0.92–0.94)	0.94 (0.93–0.95)	0.14
Waist circumference, cm	96 [87.8–103]	98 [89–106]	0.20
Current smokers, n (%)	12 (10.1)	39 (27.1)	<0.001
Former smokers, n (%)	70 (58.8)	74 (51.4)	0.26
Never smokers, n (%)	37 (31.1)	31 (21.5)	0.09
Pack/year	11 [0–28]	27 [0–50]	<0.001
Comorbidities			
Hypertension, n (%)	32 (26.9)	53 (36.8)	0.11
Diabetes, n (%)	10 (8.4)	14 (9.7)	0.83
Dyslipidemia, n (%)	31 (26.1)	41 (28.5)	0.68
Coronary artery disease, n (%)	6 (5.0)	14 (9.7)	0.17
Stroke, n (%)	1 (0.8)	9 (6.3)	0.02
Sleep apnea, n (%)	4 (3.4)	9 (6.3)	0.39
Pulmonary Function, post BD			
FEV$_1$, L	2.88 [2.37–3.48]	2.14 [1.55–2.99]	<0.001
FEV$_1$, % predicted	101 [92–110]	79 [65–93]	<0.001
FVC, L	3.79 [3.09–4.52]	3.63 [2.75–4.69]	0.48
FVC, % predicted	120 [112–132]	118 [103–135]	0.21
FEV$_1$/FVC, %	76.8 [73.4–79.9]	62.3 [55.7–66.5]	<0.001
PEF, mean L/sec (95% CI)	7.42 (6.98–7.86)	7.42 (7.02–7.82)	<0.001
FEF 25–75, L/sec	1.60 [0.96–2.41]	1.58 [0.95–2.41]	<0.001
GOLD 1, n (%)	-	70 (48.6)	-
GOLD 2, n (%)	-	61 (42.4)	-
GOLD 3–4, n (%)	-	13 (9.0)	-
GOLD A, n (%)	-	91 (63.2)	-
GOLD B, n (%)	-	40 (27.8)	-
GOLD C, n (%)	-	3 (2.1)	-
GOLD D, n (%)	-	10 (6.9)	-
Medications at baseline			
Short-acting BD, n (%)	2 (1.7)	24 (16.6)	<0.001
Long-acting BD, n (%)	1 (0.8)	1 (0.7)	1
Inhaled CS, n (%)	3 (0.3)	33 (22.9)	<0.001
Statins, n (%)	28 (23.5)	38 (26.4)	0.67
Other hypolipidemic drugs, n (%)	4 (3.3)	3 (2.1)	0.70
Insulin, n (%)	1 (0.8)	0 (0)	0.45
Oral hypoglycemic agents, n (%)	9 (7.6)	10 (6.9)	1

Values are median [IQR] if not stated otherwise. COPD: chronic obstructive pulmonary disease; BMI: body mass index; CI: confidence interval; BD: bronchodilator; FEV$_1$: forced expiratory volume in 1 second; FVC: forced vital capacity; BD: bronchodilator; CS: corticosteroids; GOLD: global Initiative for obstructive lung disease classification.

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Discussion

In a population-based cohort consisting of individuals with mild to moderate COPD and control subjects, we found metabolic profiles (lipid profile, HOMA-IR, and VAT accumulation)
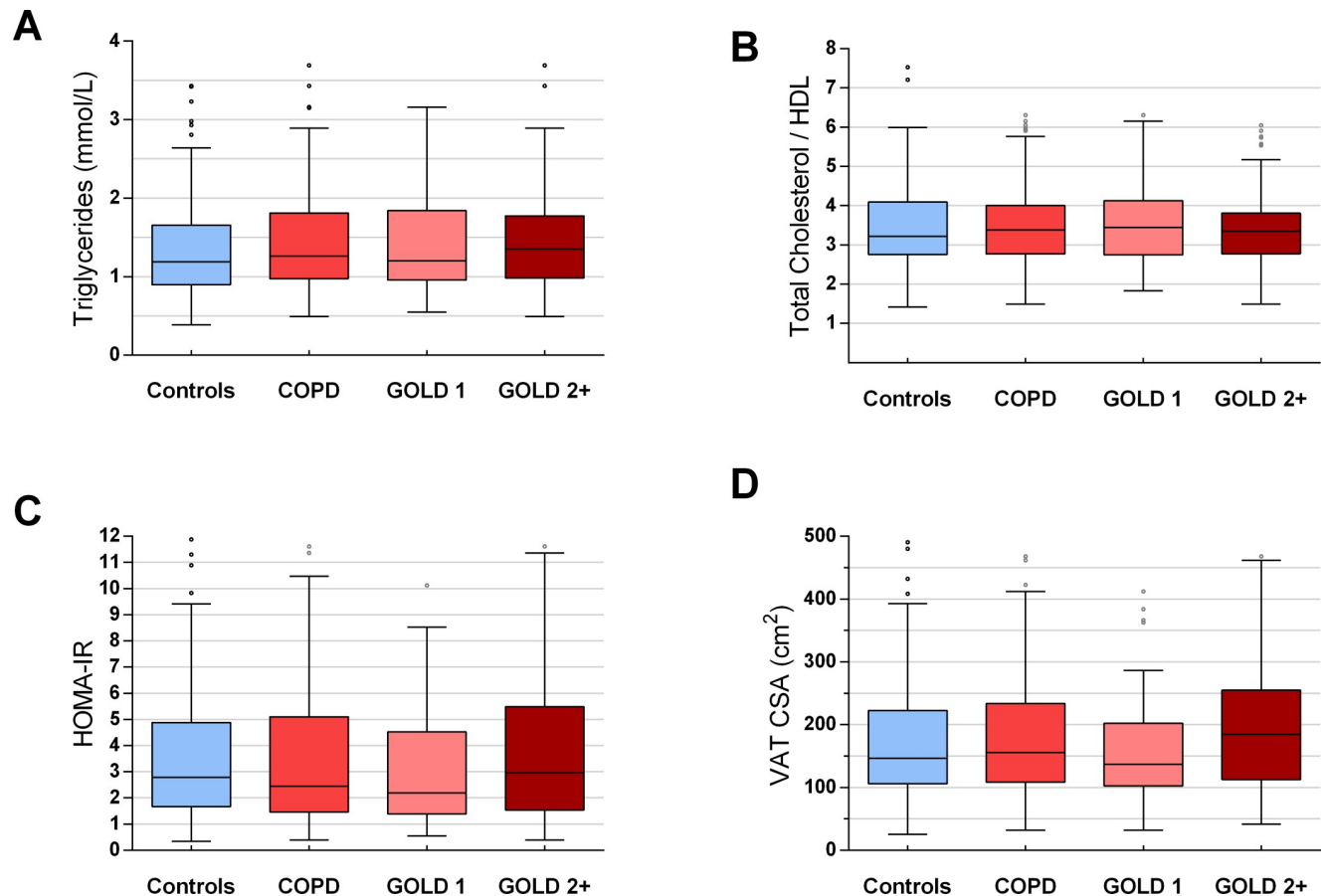
Fig 1. Metabolic parameters according COPD status. COPD: chronic obstructive pulmonary disease; HDL: high density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; VAT CSA: visceral adipose tissue cross-sectional area on L4-L5. $p > 0.05$ for all between-group comparisons.

that were not influenced by the presence of COPD. The well-established relationships between triglycerides, total/HDL cholesterol ratio, and HOMA-IR to indices of adiposity [36,37], which were confirmed here, were not modified in the presence of COPD. Univariate and multivariate analyses showed an absence of association between COPD and metabolic disorders or visceral adiposity. Therefore, based on this thorough statistical approach, we conclude that COPD does not emerge as an independent risk factor for metabolic disorders and visceral adiposity in a cohort that can be considered representative of the entire population.

Numerous studies have explored possible physiopathological links between COPD, asthma or sleep apnea and cardiometabolic components [38]. In those respiratory diseases, several bidirectional mechanisms have been proposed to enhance the risk of hypertriglyceridemia, adipose tissue accumulation and insulin resistance, including hypoxia [8–12] and hypercapnia [39]. Activation of lipolysis in adipose tissue in the presence of hypoxia led to the "adipose tissue hypoxia" concept [11]. Adipose tissue would then appear to play a central role in the development of chronic inflammation, macrophage infiltration, and would also be responsible for increasing circulating free fatty acids [8,10,11]. In addition, fat-induced systemic inflammation involving adipokines [38,40–42], insulin and its receptor, has been implicated in lung injury and airway responsiveness [38,43,44], causing a deleterious pathophysiological loop.
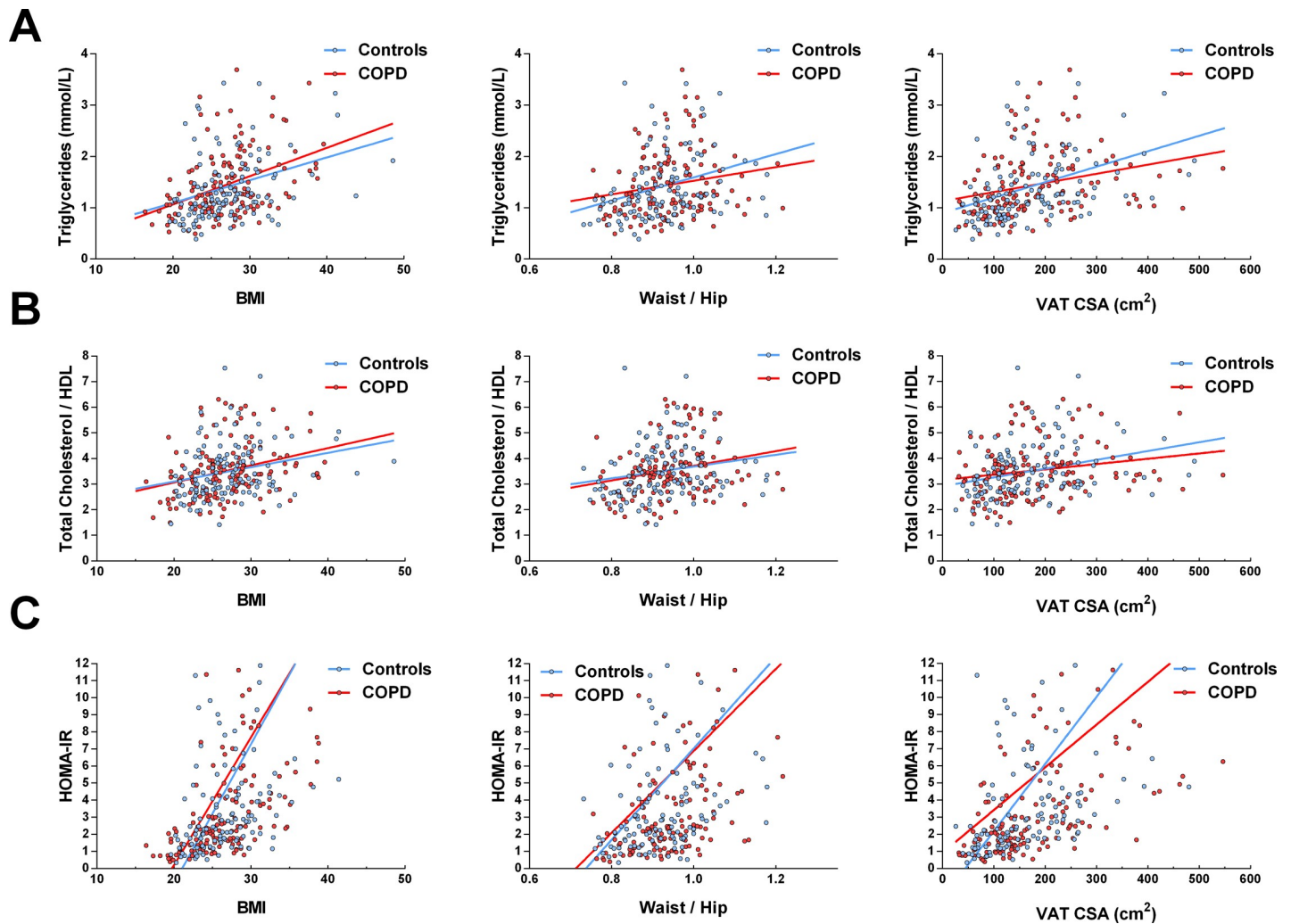
Fig 2. Relationships between metabolic parameters and BMI, waist-to-hip ratio and VAT CSA in individuals with COPD and controls. COPD: chronic obstructive pulmonary disease; BMI: body mass index; HDL: high density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; VAT CSA: visceral adipose tissue cross-sectionnal area on L4-L5. All coefficients of determination (R^2) are<0.3; All regression line slopes were significantly different from 0 ($p<0.05$); however, none of the regression lines couples (COPD vs. controls) were significantly different ($p>0.05$ for all comparisons).

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In light of the above potential pathophysiological links between chronic respiratory diseases and cardiometabolic risk factors, it was deemed legitimate to propose that COPD may contribute to the development of metabolic abnormalities. In one of the most large-scale studies in the field, Leone et al. [13] found an association between lung function impairment and "classical" components of the metabolic syndrome. This result was obtained in a heterogeneous population (obstructive and restrictive ventilatory defects), and a sub-analysis restricted to individuals with an obstructive ventilatory defect failed to find an association between glucose or lipid levels and lung function impairment, in line with our present results as well as previous ones [45,46].

The phenotypic heterogeneity of COPD patients and many confounding factors must be considered when comparing the interaction between COPD and metabolic variables across studies. The prevalence of obesity in COPD is highly variable between studies and countries [47]. Some populations showed higher prevalence of obesity [48] with an over-representation

Table 2. Multivariate linear regression models.

	Effect (%) [#]	p-value
Triglycerides		
COPD	+5.5	0.262
Age (years)	**-0.6**	**0.029**
BMI Kg/m^2	**+3.8**	**<0.001**
Total/HDL cholesterol		
COPD	+1.2	0.721
Sex (men)	**+10.3**	**0.005**
BMI Kg/m^2	**+2.3**	**<0.001**
Hypolipidemic (yes)	**-18.0**	**<0.001**
HOMA-IR		
COPD	-1.8	0.858
Sex (men)	**+27.0**	**0.020**
BMI Kg/m^2	**+12.0**	**<0.001**
VAT CSA		
COPD	+1.1	0.866
Age (years)	**+1.0**	**0.007**
Sex (men)	**+14.7**	**0.047**
Current smoker (yes)	**-32.6**	**<0.001**
Pack-years (n)	**+0.7**	**<0.001**

Significant p-values are shown in bold.

#: effect on variable in %, per increase in variable. COPD: chronic obstructive pulmonary disease; BMI: body mass index; HDL: High Density Lipoprotein; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; VAT CSA: Visceral Adipose Tissue Cross-sectionnal Area. Only significant factors and COPD are kept in the model by a backward selection.

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in patients with moderate airflow limitation [49,50], whereas in the worldwide population-based BOLD study [47], obesity was less frequent in COPD than in non-COPD. The importance of BMI as a confounding factor in the observed link between COPD and metabolic parameters is clearly illustrated in our data (**S1 Fig**, **Table 2**). In multivariate analyses, BMI was the factor with the strongest association with the metabolic parameters studied. In the same way, treatment with inhaled corticosteroids (present in only 23% of our COPD subjects) could also confound the relationship between COPD, metabolism and adipose tissue accumulation. Inhaled corticosteroids have been related to a 3-fold increase in the likelihood of having a VAT > 75th percentile (**S7 Table**). Based on these considerations, it becomes obvious that differences in population phenotypes across studies could at least partially account for inconsistent conclusions about COPD being a risk factor for altered metabolic status [5]. In this regard, data obtained from clinical cohorts are unlikely to be generalizable to the populational level where the majority of patients has only mild to moderate COPD.

Our study has some limitations. First, given the relatively small sample size, a lack of statistical power could be proposed to explain the absence of differences in endpoints between COPD subjects and controls. However, the similitude in the distribution of metabolic variables and obesity in the two groups studied makes this explanation unlikely. Second, the relatively small size of our otherwise well phenotyped sample could have led to a lesser representative image of the population than did the entire CanCOLD cohort. Despite this, the distribution of study participants' characteristics in this sub-study was very similar to that of the entire cohort [51], with a majority of subjects with GOLD 1 and few GOLD 3 and 4 COPD. Furthermore,

only 30% of individuals with COPD in this sub-study were previously diagnosed with the disease, another similitude with other population-based cohorts [52], providing further reassurance regarding how representative the present cohort is of the general population. That said, despite all the care devoted to building a cohort of individuals representative of the general population, some biases may still be present. For example, the most fragile or diseased subjects would probably be less inclined to participate in a clinical study. Third, focusing on a representative and occidental population of COPD, our findings do not necessarily apply to individuals with severe COPD or to those exhibiting particular phenotypes (inflammatory, underweight or obese, with preponderant vascular comorbidities). Finally, physical activity, an important confounder for cardiovascular risk, was not included in the analysis; also, sleep apnea, another potential contributor, was underdiagnosed by far in this cohort when considering the reported prevalence.

Conclusions

In our cohort randomly drawn from the general population in which individuals with COPD mostly had mild-to-moderate airflow limitation, no difference in the distribution of metabolic parameters appeared compared to control subjects. As such, COPD did not emerge as a specific risk factor for metabolic disorders or visceral adiposity. Although a strong mechanistic rationale can be developed for the existence of physiopathological links between chronic respiratory diseases and dyslipidemia, insulin resistance or visceral adiposity, their existence is likely restricted to specific phenotypes or to the most severely affected patients who are not widely represented in the general population.

Supporting information

S1 Table. Multivariate logistic regression on triglycerides > 1.5 mmol/L.
(DOCX)

S2 Table. Multivariate logistic regression on triglycerides > 1.5 mmol/L, COPD 2+ only.
(DOCX)

S3 Table. Multivariate logistic regression on TC/HDL > 4.
(DOCX)

S4 Table. Multivariate logistic regression on TC/HDL > 4, COPD 2+ only.
(DOCX)

S5 Table. Multivariate logistic regression on HOMA-IR > 3.
(DOCX)

S6 Table. Multivariate logistic regression on HOMA-IR > 3, COPD 2+ only.
(DOCX)

S7 Table. Multivariate logistic regression on visceral adipose tissue cross-sectional area (VAT CSA) > 75th percentile by sex of the total population.
(DOCX)

S8 Table. Multivariate logistic regression on visceral adipose tissue cross-sectional area (VAT CSA) > 75th percentile by sex of the total population, COPD 2+ only.
(DOCX)

S1 Fig. Univariate analysis stratified by BMI for all metabolic parameters. COPD: chronic obstructive pulmonary disease; BMI: body mass index; HDL: high density lipoprotein; HOMA-IR:

homeostasis model assessment of insulin resistance; VAT CSA: visceral adipose tissue cross-sectionnal Area on L4-L5. p>0.05 for all between-group (COPD vs. controls) comparisons.
(TIF)

S1 Dataset. Anonymised data.
(XLSX)

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