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Associations between spirometric impairments and microvascular complications in type 2 diabetes: a cross-sectional study

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ABSTRACT

Objective Evidence shows that the conventional cardiometabolic risk factors do not fully explain the burden of microvascular complications in type 2 diabetes (T2D). One potential factor is the impact of pulmonary dysfunction on systemic microvascular injury. We assessed the associations between spirometric impairments and systemic microvascular complications in T2D.

Design Cross-sectional study.

Setting National Diabetes Management and Research Centre in Ghana.

Participants The study included 464 Ghanaians aged ≥35 years with established diagnosis of T2D without primary myocardial disease or previous/current heart failure. Participants were excluded if they had primary lung disease including asthma or chronic obstructive pulmonary disease.

Primary and secondary outcome measures The associations of spirometric measures (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio) with microvascular complications (nephropathy (albumin-creatinine ratio ≥30 mg/g), neuropathy (vibration perception threshold ≥25 V and/or Diabetic Neuropathy Symptom score >1) and retinopathy (based on retinal photography)) were assessed using multivariable logistic regression models with adjustments for age, sex, diabetes duration, glycated haemoglobin concentration, suboptimal blood pressure control, smoking pack years and body mass index.

Results In age and sex-adjusted models, lower Z-score FEV_1 was associated with higher odds of nephropathy (OR 1.55, 95% CI 1.19–2.02, p=0.001) and neuropathy (1.27 (1.01–1.65), 0.038) but not retinopathy (1.22 (0.87–1.70), 0.246). Similar observations were made for the associations of lower Z-score FVC with nephropathy (1.54 (1.19–2.01), 0.001), neuropathy (1.25 (1.01–1.54), 0.037) and retinopathy (1.19 (0.85–1.68), 0.318). In the fully adjusted model, the associations remained significant for only lower Z-score FEV_1 with nephropathy (1.43 (1.09–1.87), 0.011) and neuropathy (1.34 (1.04–1.73), 0.024) and for lower Z-score FVC with nephropathy (1.45 (1.11–1.91), 0.007) and neuropathy (1.32 (1.03–1.69), 0.029). Lower Z-score FEV_1/FVC ratio was not significantly associated with microvascular complications in age and sex and fully adjusted models.

Conclusion Our study shows positive but varying strengths of associations between pulmonary dysfunction and microvascular complications in different circulations. Future studies could explore the mechanisms linking pulmonary dysfunction to microvascular complications in T2D.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study assessed complementary measures of microvascular complication in three microcirculatory beds (neural, renal and retinal microcirculation).
- ⇒ Individuals with primary lung diseases including asthma and chronic obstructive pulmonary disease were excluded from the study to eliminate the potential impact of systemic manifestations of primary lung disease.
- ⇒ A directed acyclic graph was used in selecting the potential confounders since the traditional methods of adjusting for potential confounders can introduce conditional associations and bias rather than minimise it. In the multivariable logistic regression models, a wide range of pulmonary, cardiovascular and diabetes-related risk factors were adjusted for.
- ⇒ The cross-sectional design limits the assessment of causation.
- ⇒ The study did not assess microvascular complications of the coronary and cerebral microcirculation due to the current technical challenges associated with microvascular functional testing in these circulations.

INTRODUCTION

Diabetes is a global public health burden, currently affecting over 10.5% of the world's adult population.[1] Type 2 diabetes (T2D), characterised by hyperglycaemia from progressive loss of adequate beta-cell insulin secretion frequently on the background of insulin resistance, accounts for 90%–95% of all diabetes.[2 3] A characteristic complication of T2D is microvascular disease including retinopathy, neuropathy and nephropathy, which are important causes of blindness, end-stage renal failure and lower-limb amputations, respectively.[4]

The mechanistic basis of microvascular complications in T2D has been extensively studied. Based on work done by our team among sub-Saharan Africans,[5–7] and those of other researchers in other populations,[4 8 9] the conventional risk factors do not sufficiently explain the burden of microvascular complications in T2D. One potential factor is the impact of pulmonary dysfunction on systemic microvascular injury. The potential role of pulmonary dysfunction based on measures including spirometric impairment in predicting adverse cardiovascular events has an epidemiological basis. For example in the Framingham heart study, forced vital capacity (FVC) was shown to be inversely associated with 10-year cardiovascular-event risk, irrespective of metabolic syndrome or abdominal obesity, in the general population without obstructive lung disease.[10] In a larger international community-based cohort study, the forced expiratory volume in 1 s (FEV_1) was shown to be an independent and generalisable predictor of cardiovascular disease, even across the clinically normal range.[11] The relationship between reduced spirometric measures and cardiovascular disease risk is robust.[11] For example, the population-attributable risk for incident cardiovascular disease from low FEV_1 is second only to the risk from hypertension.[11]

While the reduction in FEV_1 and FVC has been reported in T2D,[12] their clinical implications including associations with microvascular complications, and how these associations might vary across different microcirculatory beds are unclear. The few existing reports in the general population[13] and individuals with diabetes[14 15] have focused on the association between pulmonary dysfunction and albuminuria alone. While albuminuria is a marker of renal microvascular dysfunction, it may also reflect generalised endothelial dysfunction.[16] In assessing the relationship between pulmonary dysfunction and microvascular complications, it is therefore important to assess multiple/complementary measures of microvascular complications (instead of albuminuria alone) as this may better characterise the relationship. Using a sample of adults with T2D, we tested the hypothesis that pulmonary dysfunction assessed by a reduction in the FEV_1, FVC and FEV_1/FVC ratio is associated with microvascular complications in individuals with T2D.

METHODS

Study design

This was a cross-sectional study at a National Diabetes Management and Research Centre at the Korle Bu Teaching Hospital in Accra, Ghana. Between 2019 and 2022, a total of 500 adult Ghanaians with established diagnosis of T2D and who did not have primary heart disease (primary myocardial disease) and/or previous/current heart failure were recruited for pulmonary, cardiac and vascular functional assessment. The patients were systematically sampled from patients who reported for clinic visits. The sample frame consisted of all the diabetes record books registered at the laboratory test sample collection point of the clinic. Using a sampling interval k=3, a number of folders were chosen each weekday by selecting every third folder that met the eligibility criteria. The first diabetes record book was selected at random. The diagnosis of T2D was based on fasting plasma glucose ≥7.0 mmol/L and/or 2-hour plasma glucose ≥11.1 mmol/L and/or on hypoglycaemic agents who reported the start of their diabetes age >30 years, and whose diabetes initially did not require insulin for management. The current analyses included 464 participants aged ≥35 years with technically acceptable spirometry data and with no history of primary lung disease including asthma or chronic obstructive pulmonary disease (COPD) (figure 1). The exclusion of primary lung disease was based on self-report and/or clinical diagnosis code/documentation in the medical records.

Measurements

A structured questionnaire was used to record the sociodemographic, lifestyle and health-related behaviours of the study participants. Smoking status was self-reported and classified into non-smokers, ex-smokers and current smokers. Educational level was used as a proxy for socioeconomic status and was classified as lower (never or elementary and lower) and higher level. The duration of diabetes was obtained from the patient's medical records. Anthropometric and blood pressure (BP) measurements were obtained by physical examination. Weight was measured in light clothing and without shoes with SECA-877 scales. Height was measured without shoes with a SECA-217 stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Obesity was defined as a BMI ≥30 kg/m^2. BP was measured three times using the Omron BP Monitor HEM-907XL device, with appropriate-sized cuffs after at least 5 min of rest while seated. The mean of the last two BP measurements was used for the analyses. Hypertension was based on a clinical diagnosis code/documentation in the medical records, evidenced by documented elevated BP (≥140/90 mm Hg) at the time of diagnosis, and the use of antihypertensive therapy. Suboptimal BP control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg.[17] These cut-off values are consistent with the American Diabetes Association's recommendation (2018 update) for individuals with diabetes with higher cardiovascular risk.[18]

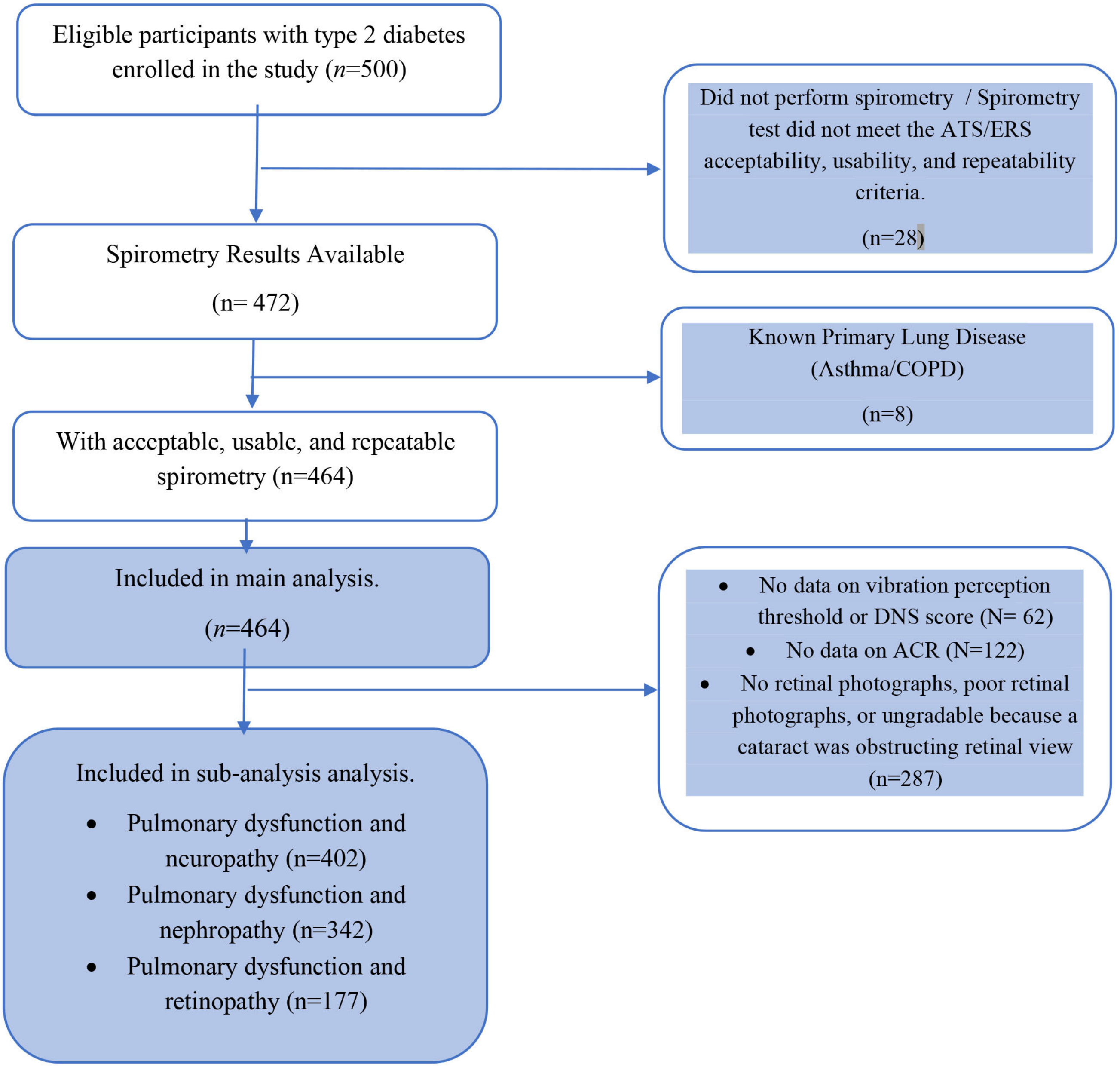

Figure 1 Flowchart showing the selection of study participants. ACR, urine albumin-to-creatinine ratio; ATS/ERS, American Thoracic Society/European Respiratory Society; COPD, chronic obstructive pulmonary disease; DNS, Diabetic Neuropathy Symptom.

Pulmonary function testing

Pre-bronchodilator spirometry was conducted by trained physicians/technicians using the Vitalograph Pneumotrac Portable Screening Pneumotachograph (Morgan Scientific) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[19] Measured and calculated indices included the FEV$_1$, FVC and the FEV$_1$/FVC ratio. The predicted values of the FEV$_1$, FVC and FEV$_1$/FVC were determined for each participant using the Global Lung Function Initiative 2012 equations.[20] Abnormal results for spirometric indices were determined by comparison to their lower limits of normal (LLN).[20] The values of FEV$_1$/FVC and FVC were used to categorise pulmonary function patterns as normal, obstructive, restrictive, or mixed obstructive and restrictive based on ATS/ERS guidelines.[21] Due to heterogeneity in individuals with impaired spirometry, we analysed FEV$_1$, FVC and FEV$_1$/FVC as a continuous variable via Z-score. Reductions in FEV$_1$, FVC and FEV$_1$/FVC are known to predict mortality and/or adverse cardiovascular events.[11 22–25]

Microvascular functional assessment

Symptoms of diabetic neuropathy were scored with the Diabetic Neuropathy Symptom (DNS) score.[26] The vibration perception threshold (VPT) was assessed using the Horwell Neurothesiometer (Scientific Laboratory Supplies, Nottingham) according to the manufacturer's guidelines. Neuropathy was diagnosed if the VPT was ≥25 V[27] and/or a DNS score ≥1.[26] The ZEISS 500 Fundus

Camera (ZEISS Inc. JENA) was used for retinal photography after dilatation, and retinal images were analysed and graded by a certified ophthalmologist according to the Early Treatment Diabetic Retinopathy Study criteria.[28] Direct analyses of urinary albumin (immunochemical turbidimetric method) and creatinine concentration (kinetic spectrophotometric method) were performed on an early morning urine sample (Roche Diagnostics). Nephropathy was based on albuminuria, defined as the urinary albumin-creatinine ratio ≥30 mg/g (category ≥A2)) according to the 2012 Kidney Disease: Improving Global Outcomes guidelines.[29]

Statistical analysis

Data were analysed using the IBM SPSS V.25 for Windows. Differences in sociodemographic/clinical characteristics between individuals with normal and abnormal spirometry were assessed by the χ^2 test or Fisher's exact test for categorical variables, t-test for continuous variables, or the Mann-Whitney U test for variables not normally distributed. Multivariate logistic regression analyses were used to examine the associations between decreasing Z-score FEV_1, FVC and FEV_1/FVC ratio (independent variable) and measures of microvascular complication (dependent variable), with adjustment for potential covariates. ORs and their corresponding 95% CI were estimated. The minimal sufficient adjustment sets for estimating the direct effect of impaired spirometry on microvascular complications were determined by a directed acyclic graph (DAG) (available at dagitty.net/mHbo6GZ). Based on the DAG, the minimal sufficient adjustment sets were age, sex, diabetes duration, glycated haemoglobin (HbA1c) concentration, suboptimal BP control, smoking pack years and BMI. Two models were used to examine the data. Model 1 was age-sex adjusted. Model 2 was adjusted for age, sex, diabetes duration, HbA1c concentration, suboptimal BP control, smoking pack years and BMI. Since an increasing duration of diabetes could result in pulmonary and microvascular complications, we performed a sensitivity analysis where diabetes duration was not adjusted for in the fully adjusted model. A statistical test of significance was set at a p value <0.05.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research. The results of this study will be disseminated to the public through publication in this journal.

RESULTS

General characteristics

Table 1 summarises the baseline characteristics of the study population. Nearly a third (31.3%) of the study population had impaired spirometry. Compared with individuals with normal spirometry, individuals with impaired spirometry were more frequently females and had a higher mean BMI, diabetes duration, and HbA1c levels. While the proportion of individuals with hypertension was higher in individuals with impaired spirometry compared with those with normal spirometry, the mean diastolic BP, systolic BP, and heart rate, as well as the proportion of individuals with suboptimal BP control were similar in the two groups. The mean eGFR, total cholesterol concentration, LDL-cholesterol concentration, and triglyceride concentrations were similar between the two groups. The proportion of previous and current smokers in the study population was low (1.9%) and did not differ between the two groups. The mean age, the proportion of individuals with higher education, and the proportion of individuals on statin or insulin therapy did not differ between the two groups.

Prevalence of microvascular complications

Overall, the prevalence of nephropathy, neuropathy and retinopathy were 25.4%, 31.1% and 28.8%, respectively. Figure 2 compares the prevalence of microvascular complications stratified by FEV_1, FVC and FEV_1/FVC categories. Compared with individuals with normal values, individuals with FEV_1, FVC and FEV_1/FVC values less than the LLN tended to have a higher frequency of microvascular complications. Of the indicators of pulmonary function, abnormal FEV_1 was associated with the highest prevalence of microvascular complications with a 90% higher prevalence of nephropathy, a 33% higher prevalence of neuropathy and a 40% higher prevalence of retinopathy compared with those with FEV_1 <LLN. Compared with individuals with normal FVC, the prevalence of nephropathy, neuropathy and retinopathy in individuals with FVC <LLN were higher by 34%, 16% and 16%, respectively. The prevalence of nephropathy, neuropathy and retinopathy was higher by 26%, 18% and 16%, respectively in individuals with FEV_1/FVC ratio <LLN compared with individuals with normal FEV_1/FVC ratio. Except for the difference between the prevalence of nephropathy in individuals with normal FEV_1 and reduced FEV_1 (p<0.001), the observed differences in all the other associations were not statistically significant (p>0.05).

Mean spirometric indices in individuals with and without microvascular complication

Table 2 compares the mean Z-score FEV_1, FVC and FEV_1/FVC ratio in individuals with and without microvascular complication. Compared with individuals without nephropathy, individuals with nephropathy had lower mean Z-score FEV_1 (−1.43 vs −0.98, p<0.001) and lower Z-score FVC (−1.36 vs −0.88, p<0.001), but similar Z-score FEV_1/FVC ratio (−0.38 vs −0.27, p=0.400). Compared with individuals without neuropathy, individuals with neuropathy had lower mean Z-score FVC (−1.26 vs −1.03, p=0.048), but similar lower Z-score FEV_1 (−1.31 vs −1.10,p=0.062) and Z-score FEV_1/FVC ratio (−0.27 vs −0.22, p=0.706). The differences between Z-score FEV_1/FVC ratios between individuals with or without nephropathy, neuropathy and retinopathy were not statistically

Table 1 Baseline characteristics of the study participants

	All participants	Normal spirometry	Impaired spirometry*	P value
N	464	319	145	
Age (years)	55.09 (±10.45)	54.79 (±10.86)	55.76 (±9.49)	0.330
Sex (%)				<0.001
Female	314 (67.7%)	193 (60.5%)	121 (83.4%)	
Male	150 (32.3%)	126 (39.5%)	24 (16.6%)	
Education (%)				0.412
Below secondary education	196 (56.6%)	125 (55.1%)	71 (59.7%)	
Secondary/tertiary education	150 (43.4%)	102 (44.9%)	48 (40.3%)	
Smoking status				0.892
Never smoker	455 (98.1%)	313 (98.1%)	142 (97.9%)	
Current/previous smoker	9 (1.9%)	6 (1.9%)	3 (2.1%)	
Smoking pack years†	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.889
Diabetes duration (years)	10.00 (±7.36)	9.11 (±7.20)	12.21 (±7.30)	<0.001
Insulin use (%)	139 (30.0%)	92 (28.8%)	47 (32.4%)	0.436
Statin use (%)	192 (41.4%)	124 (38.9%)	68 (46.9%)	0.104
Obesity (%)	169 (36.4%)	107 (33.5%)	62 (42.8%)	0.056
BMI, kg/m^2	29.13 (±6.00)	28.71 (±5.56)	30.04 (±6.78)	0.040
Hypertension (%)	199 (42.9%)	123 (38.6%)	76 (52.4%)	0.005
Systolic BP, mm Hg	135.26 (±15.67)	134.62 (±15.04)	136.65 (±16.93)	0.196
Diastolic BP, mm Hg	79.14 (±8.23)	78.95 (±8.23)	79.55 (±8.23)	0.468
Heart rate, bpm	79.36 (±10.72)	79.34 (±10.73)	79.40 (±10.75)	0.952
Suboptimal BP control (%)	323 (69.6%)	214 (67.1%)	109 (75.2%)	0.079
Biochemical measures				
HbA1c, %	7.98 (±1.77)	7.85 (±1.79)	8.23 (±1.71)	0.046
Total cholesterol, mmol/L	4.86 (±1.27)	4.80 (±1.28)	4.97 (±1.26)	0.271
Triglyceride, mmol/L	1.22 (±0.50)	1.23 (±0.53)	1.22 (±0.45)	0.813
HDL-cholesterol, mmol/L	1.34 (±0.35)	1.33 (±0.35)	1.35 (±0.35)	0.671
LDL-cholesterol, mmol/L	2.95 (±1.15)	2.90 (±1.15)	3.04 (±1.16)	0.299
eGFR, mL/min/1.73m^2	97.43 (±22.39)	97.43 (±22.21)	97.44 (±22.84)	0.997

Suboptimal BP control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg.

*Impaired spirometry defined as the presence of pulmonary restriction and/or airway obstruction.

†Data presented as median (IQR).

BMI, body mass index; BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; $FEF_{25-75\%}$, forced expiratory flow at 25% point to the 75% point of forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV1/FVC, ratio of FEV_1 to FVC; FVC, forced vital capacity; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

significant. Similar results were obtained when the mean FEV_1 and FVC percentage predicted, and FEV_1/FVC ratio were compared in individuals with and without nephropathy, neuropathy and retinopathy.

Association between spirometric indices and microvascular complication

The associations of lower Z-score FEV_1, FVC and FEV_1/FVC ratio with nephropathy, neuropathy and retinopathy are summarised in table 3. In age-sex adjusted models, lower Z-score FEV_1 was associated with higher odds of nephropathy (OR 1.55, 95% CI 1.19–2.02, p=0.001), and neuropathy (1.27 (1.01–1.65), 0.038) but not retinopathy (1.22 (0.87–1.70), 0.246). Similar observations were made for the associations of lower Z-score FVC with nephropathy (1.54 (1.19–2.01), 0.001), neuropathy (1.25 (1.01–1.54), 0.037) and retinopathy (1.19 (0.85–1.68), 0.318). The associations between lower Z-score FEV_1/FVC ratio and nephropathy (1.14 (0.90–1.44), 0.266), neuropathy (1.05 (0.87–1.27), 0.604) and retinopathy (1.08 (0.79–1.48), 0.611) were not statistically significant after age-sex

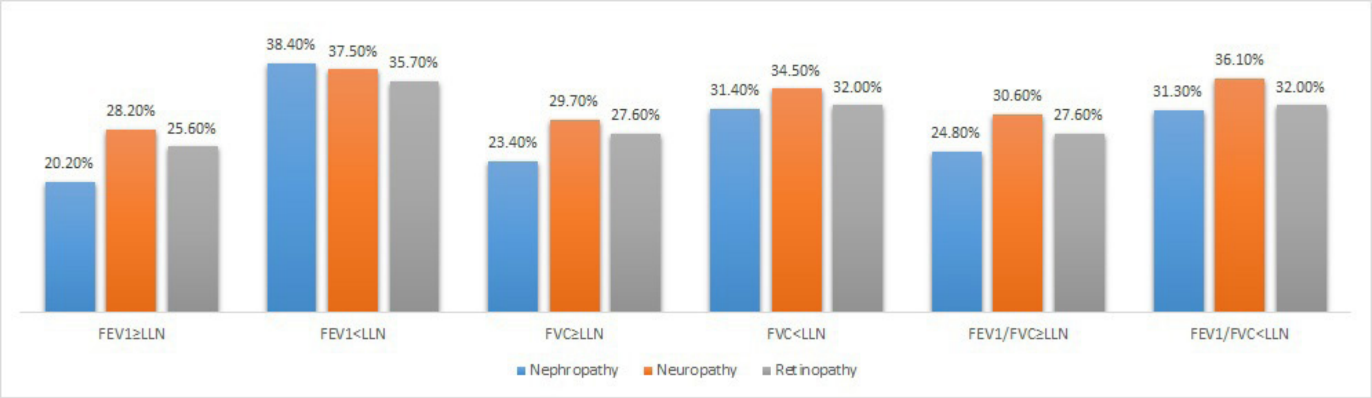

Figure 2 Prevalence of microvascular complications by FEV_1, FVC and FEV_1/FVC categories. FEV1/FVC <LLN is suggestive of airway obstruction. FVC <LLN is suggestive of pulmonary restriction. FEV_1, forced expiratory volume in 1 s; FEV_1/FVC, ratio of FEV_1 to FVC; FVC, forced vital capacity; LLN, lower limit of normal.

adjustment. In the fully adjusted model, the associations remained significant for only lower Z-score FEV_1 with nephropathy (1.43 (1.09–1.87), 0.011) and neuropathy (1.34 (1.04–1.73), 0.024) and for lower Z-score FVC with nephropathy (1.45 (1.11–1.91), 0.007) and neuropathy (1.32 (1.03–1.69), 0.029). Similar results were obtained when the duration of diabetes was not included in the fully adjusted model (online supplemental table 1).

DISCUSSIONS

Key findings

In this study among adults with T2D, we observed positive but varying strengths of associations of reduced spirometric indices with measures of microvascular complications in different circulations. Lower Z-score FEV_1 was significantly associated with higher odds of nephropathy and neuropathy but not retinopathy. Like FEV_1, lower Z-score FVC was significantly associated with higher odds of nephropathy and neuropathy but not retinopathy. The associations of lower FEV_1/FVC ratio with nephropathy, neuropathy and retinopathy were not statistically significant. After adjusting for a wide range of pulmonary and vascular risk factors, lower Z-score FEV_1 and FVC remained significantly associated with nephropathy and neuropathy.

Discussion of key findings

Large population-based studies suggest that impaired lung function based on spirometry might share similar developmental pathways with or increase the risk of cardiometabolic disease.[11 30] The current study contributes to this field of research by characterising the cross-sectional associations between spirometric impairment and microvascular complications in T2D.

The first microvascular measure we evaluated was nephropathy, a marker of renal microvascular injury. Our results show that lower Z-score FEV_1 and FVC, but not lower FEV_1/FVC ratio were positively associated with higher odds of nephropathy. Studies characterising the relationship between pulmonary and renal microvascular complications are limited. Among T2D Chinese patients with preserved renal function (based on eGFR >60 mL/min/1.73m^2), low FEV_1 and low FVC were independently associated with albuminuria.[14] The current study among individuals with T2D with or without impairment in eGFR agrees with this previous finding. Conceivably, such associations could reflect the impact of primary lung disease with systemic manifestations (eg, COPD) on renal function. For example, existing evidence shows that overt or concealed renal dysfunction is independently associated with COPD.[31] Therefore, excluding the impact of primary lung disease is required to link diabetes-related pulmonary dysfunction with renal microvascular complications. The current study achieved this by excluding individuals with primary lung disease including asthma and COPD.

With albuminuria considered to reflect both generalised endothelial dysfunction and damage in the renal microcirculation,[16] it might not be right to conclude that low FEV_1 or FVC is associated with microvascular complication if the outcome measure is only albuminuria. Concurrent assessment of microvascular complications in other circulations could more robustly characterise the relationship between spirometric impairments and microvascular complications. Like nephropathy, we observed that lower Z-scores FEV_1 and FVC were positively associated with neuropathy, after adjustments for a wide range of cardiometabolic risk factors. Our study, which is the first to report this, suggests that a reduction in FEV_1 or FVC is associated with dysfunction in the neural microcirculation. Our results are consistent with findings in individuals with COPD where the magnitude of nerve action potential was found to correlate positively with FEV_1% predicted.[32]

The final microvascular measure assessed in this study was retinopathy, which reflects microvascular injury in the retina. In this study, the association of lower Z-score FEV_1 or FVC with retinopathy was not statistically significant. Like neuropathy, studies assessing the associations between pulmonary dysfunction and retinopathy in T2D are limited. In the Multi-Ethnic Study of Atherosclerosis

Table 2 Mean spirometric indices stratified by microvascular function status

	Nephropathy			Neuropathy			Retinopathy		
	No (=255)	**Yes (=87)**	**P value**	**No (N=277)**	**Yes (N=125)**	**P value**	**No (N=126)**	**Yes (N=51)**	**P value**
Z-score									
Z-score FEV_1	0.98 (±1.02)	1.43 (±0.92)	<0.001	1.10 (±0.97)	1.31 (±1.11)	0.062	1.03 (±1.04)	1.30 (±1.09)	0.133
Z-score FVC	0.88 (±1.05)	1.36 (±0.87)	<0.001	1.03 (±1.06)	1.26 (±1.08)	0.048	0.97 (±1.06)	1.22 (±1.02)	0.148
Z-score FEV_1/FVC	0.27 (±1.08)	0.38 (±1.01)	0.400	0.22 (±1.14)	0.27 (±1.14)	0.706	0.24 (±0.93)	0.30 (±1.32)	0.732
Percentage predicted									
FEV_1 pp	84.73 (±16.34)	76.89 (±15.22)	<0.001	82.22 (±16.40)	78.78 (±18.21)	0.061	83.51 (±16.91)	79.38 (±17.47)	0.146
FVC pp	86.80 (±16.04)	79.04 (±13.11)	<0.001	84.13 (±16.88)	80.62 (±16.50)	0.053	85.17 (±16.15)	81.57 (±15.02)	0.173
FEV_1/FVC ratio (%)	78.18 (±7.30)	77.34 (±7.11)	0.354	78.16 (±8.71)	77.61 (±8.13)	0.552	78.34 (±6.28)	77.51 (±9.77)	0.504

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; pp, percentage predicted.

Table 3 Associations of spirometric indices with microvascular complications

	OR (95% CI), p value					
	Nephropathy (N=342)		**Neuropathy (N=402)**		**Retinopathy (N=177)**	
	Age-sex adjusted	**Fully adjusted**	**Age-sex adjusted**	**Fully adjusted**	**Age-sex adjusted**	**Fully adjusted**
Lower Z-score FEV_1	1.55 (1.19–2.02), 0.001	1.43 (1.09–1.87), 0.011	1.27 (1.01–1.65), 0.038	1.34 (1.04–1.73), 0.024	1.22 (0.87–1.70), 0.246	0.98 (0.68–1.42), 0.923
Lower Z-score FVC	1.54 (1.19–2.01), 0.001	1.45 (1.11–1.91), 0.007	1.25 (1.01–1.54), 0.037	1.32 (1.03–1.69), 0.029	1.19 (0.85–1.68), 0.318	0.96 (0.66–1.40), 0.821
Lower Z-score FEV_1/FVC ratio	1.14 (0.90–1.44), 0.266	1.10 (0.86–1.39), 0.458	1.05 (0.87–1.27), 0.604	1.04 (0.83–1.30), 0.741	1.08 (0.79–1.48), 0.611	1.02 (0.73–1.43), 0.889

Fully adjusted model was adjusted for age, sex, diabetes duration, glycated haemoglobin concentration, suboptimal blood pressure (BP) control, smoking pack years and body mass index. Suboptimal BP control was defined per the 2017 American College of Cardiology/American Heart Association guidelines criteria and European Society of Cardiology/European Society of Hypertension guidelines (for individuals with hypertension and diabetes) as systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg.

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

(MESA) involving 3397 adults without clinical cardiovascular disease, retinal venular calibre, an early marker of microvascular changes, was associated with low FEV_1.[33] The current study did not find any significant association between lower FEV_1 and retinopathy. While the study populations in the current and MESA studies are relevantly different, the lack of a statistically significant association between lower Z-score FEV_1(or FVC) and retinopathy in the current study may be attributable, in part, to the reduced number of individuals included in the retinopathy subanalyses. Alternatively, it could be argued that the different strengths of associations could reflect different levels of progression of microvascular dysfunction in the kidney, nerves and eye, in the setting of pulmonary dysfunction. It could also reflect different sensitivities of different microcirculatory beds to pulmonary dysfunction. A previous report has shown that the prognostic potency of the individual vascular risk factors for atherogenesis varies in the different vascular beds.[34]

The mechanistic basis of the associations between reduced FEV_1 or FVC and systemic microvascular complications is not known. It may be argued that such an association could reflect the impact of smoking on the pulmonary and vascular systems. However, the proportion of smokers in the current study was remarkably low, and we adjusted for smoking pack years in the analyses. While smoking was self-reported in this study which could have introduced bias, this does not seem likely, because the low prevalence of smoking reported in this study reflects the low smoking rates in Ghana.[35] Alternatively, such an association may reflect the impact of other common risk factors for diabetes-related complications like poor glycaemic control, increased duration of diabetes, and obesity. However, the associations remained significant after adjusting for these conventional risk factors. Such an association in T2D could reflect the existence of COPD, a pulmonary disease with multisystem manifestations. In this study, we excluded patients with COPD. It is also possible that such an association could reflect the impact of T2D on both the pulmonary and microvascular systems. While this study design cannot completely exclude this, the association remained significant after adjusting for diabetes-related factors including glycaemic control and duration of diabetes. It is conceivable—in theory—that there might be a common susceptibility for pulmonary and microvascular complications in the setting of T2D. While rare conditions like Goodpasture's Syndrome (anti-GBM disease) and antineutrophil cytoplasmic antibody have been reported in the existing literature in the general population, no study has reported such common susceptibility in T2D. While this cross-sectional design cannot assess causation, we speculate that a reduction in FEV_1 or FVC might be an indicator of inherent susceptibility to developing microvascular complications in the setting of T2D. It may also be the case that reduced FEV_1 or FVC might be causally related to systemic microvascular complications via intermediary processes including the role of hypoxia in dysregulated vascular degeneration,[36] as well as enhanced systemic oxidative stress and inflammatory pathways,[37 38] resulting in adverse multiorgan dysfunction including the microcirculation. This may be more relevant in T2D where the risk of microvascular injury is high.[4] Future longitudinal studies could explore the mechanisms linking pulmonary dysfunction to microvascular complications in T2D.

Regardless of whether the association between impaired pulmonary function and systemic microvascular complications is causal or not, the findings from this study may have clinical utility. For example, individuals with impaired pulmonary function may benefit from more frequent evaluation of microvascular complications for early detection. Existing guidelines including that of the American Diabetes Association guidelines recommend a minimum of annual screening for microvascular complications in individuals with T2D.[39] Given the findings from this study and the known predictive role of pulmonary functional measures like FEV_1 on cardiovascular disease, pulmonary function could be a discriminant for more or less frequent screening for microvascular complications in T2D. FEV_1 is easy to measure and a very reproducible physiological variable.[40 41] Alternatively, individuals with microvascular complications may benefit from more frequent evaluation of pulmonary dysfunction, for early detection of decline in pulmonary function. This is clinically relevant given the evidence that in the general population, low FEV_1 or decline in FEV_1 is associated with mortality including sudden cardiac death,[22 25 42–45] independent of cardiac function.[25 42] If there is a causal relationship, the recommendation remains valuable whether pulmonary dysfunction is an etiologic or exacerbating factor for microvascular complication. Future longitudinal studies are required to assess these potential clinical utilities. These longitudinal studies may also assess therapeutic benefits including the effect of treatment of impaired pulmonary function on microvascular complications. Future studies are also required to further elucidate a potential causal role for glycaemic control on pulmonary function in T2D and the effects of lifestyle measures and antidiabetic medication on the progression of pulmonary dysfunction in susceptible patients.

Strengths and limitations

The strengths of our study include the exclusion of individuals with primary lung diseases, the objective assessment of three complementary measures of microvascular complications and the adjustments for a wide range of confounders. Our study has limitations. First, the cross-sectional design limits us from precluding reverse causation (ie, systemic microvascular complications contributing to pulmonary dysfunction). Based on the 'spill-over' theory highlighted in primary pulmonary diseases like COPD,[46] reverse causation is less likely. In the 'spill-over' theory, pulmonary dysfunction is thought to cause a 'spill-over' of inflammatory mediators into the systemic circulation, which may increase acute-phase proteins such as C reactive protein. Systemic inflammation may then lead to vascular dysfunction. Second, smoking was based on participant self-report, which could have introduced bias. Third, we did not assess exposure to inhaled toxicants from the environment. Finally, we did not assess dysfunctions of the coronary and cerebral microcirculation due to the current technical challenges associated with microvascular functional testing in these circulations. For example, coronary microcirculation is beyond the resolution of invasive or non-invasive coronary angiography.[47]

CONCLUSIONS

The current study demonstrates positive associations of lower FEV_1 and FVC with nephropathy and neuropathy, but not retinopathy, after adjustment for a wide range of conventional risk factors. Our findings provide useful insights into the possible role of pulmonary dysfunction in systemic microvascular dysfunction and provide opportunities for future research aimed at determining the mechanisms linking pulmonary dysfunction to diabetes-related microvascular complications, as well as the impact of improving pulmonary function or halting decline in pulmonary function on systemic microvascular function.

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Correction notice This article has been corrected since it was first published. Under the 'abstract' and 'method' sections, “albumin-creatinine ratio ≥3 mg/g” has been changed to “albumin-creatinine ratio ≥30 mg/g”.

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Contributors CH-B, B-JHvdB, AHM-vdZ, AGBA and CA conceived the idea. CH-B formulated the research question and study hypothesis with clinical and methodological feedback from SH, B-JHvdB, AHM-vdZ, AGBA and CA. CH-B, AGBA, KNA-A, LM, BA, PA, HWA and JAA conducted the experiment. CH-B and CA were responsible for statistical analysis. CH-B, B-JHvdB, AHM, AGBA, SH, KNA-A, JAA, PA, HWA, LM, GOA, JNA and BA were responsible for data interpretation. All authors were involved in reporting of the work/writing the manuscript. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions about the accuracy or integrity of any portion of the work are appropriately investigated and resolved. CH-B takes responsibility for the fact that this study has been reported honestly, accurately, and transparently, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained. CH-B is the author acting as guarantor.

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