Impulse oscillometry indices in relation to respiratory symptoms and spirometry in the Swedish Cardiopulmonary Bioimage Study

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Shareable abstract (@ERSpublications)
Abnormal impulse oscillometry (IOS) indices are related to increased respiratory burden in individuals with normal spirometry. This suggests that IOS might have a complementary role to identify early changes in lung function in symptomatic individuals. https://bit.ly/3nKiHwJ

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Abstract

Background Impulse oscillometry (IOS) is sensitive in detecting lung function impairment. In small studies, impaired IOS relates better to respiratory symptoms than spirometry. We studied how IOS related to spirometry and respiratory symptoms in a large population of individuals (n=10 360) in a cross-sectional analysis.

Methods Normal values for IOS and spirometry were defined in healthy, never-smoking individuals, aged 50–64 years, from the Swedish CArdioPulmonary bioImage Study (n=3664 for IOS and 3608 for spirometry). For IOS, abnormal values for resistance at 5 Hz (R_5) and at 20 Hz and area of reactance were defined using the 95th percentile. Abnormal reactance at 5 Hz for IOS and abnormal conventional spirometry indices (forced expiratory volume in 1 s (FEV_1), forced and slow vital capacity and their ratios) were defined using the 5th percentile.

Results Abnormal IOS parameters were found in 16% of individuals and were associated with increased odds ratios for nearly all respiratory symptoms when adjusted for age, gender and smoking. In individuals with normal spirometry, abnormal IOS resistance was related to cough and dyspnoea, while abnormal reactance was related to wheeze. In these individuals, the combination of abnormal R_5 with abnormal reactance resulted in approximately two-fold higher likelihood for having cough, chronic bronchitis and dyspnoea, even when further adjusting for FEV_1, expressed as % predicted.

Conclusions Abnormal IOS is related to increased respiratory burden in middle-aged individuals with normal spirometry, especially when resistance and reactance parameters are combined. The different relationships between respiratory symptoms and reactance and resistance warrant further research.

Background

The forced oscillation technique is a pulmonary function test first described >60 years ago [1]. The procedure is performed during normal tidal breathing and therefore requires only minimal cooperation from the patient. The device is connected to the patient using a mouthpiece and oscillations are superimposed on the patient's tidal breathing. Usually, these oscillations are produced by means of soundwaves generated by a loudspeaker. A variant of the forced oscillation technique is impulse oscillometry (IOS) [2]. By analysing instantaneous flow and pressure variation at different frequencies, the mechanical properties of the respiratory system (respiratory resistance and reactance) can be determined. Another advantage of the method is that it may detect changes in the function of the peripheral airways [3], a compartment that is

poorly evaluated by means of dynamic spirometry. Usually, resistance at a low frequency of 5 Hz (R_5) is considered to represent total airway resistance, whereas resistance at a higher frequency, 20 Hz (R_{20}), is considered to represent mainly central airway resistance [4]. Reactance at 5 Hz (X_5) and the area of reactance (AX) are considered to provide information from the peripheral airways, more specifically tissue elasticity. Together with the resonant frequency (f_{res}), these reactance indices are considered to reflect obstruction mainly in the peripheral airways [5].

Generally, the relationship between respiratory symptoms and lung function, assessed using spirometry, is weak to moderate [3]. For example, in patients with COPD, there is often no clear relationship between respiratory symptoms and spirometry data [6, 7]. In these patients, IOS has been shown to correlate with symptoms [8, 9] and quality of life [10]. The association between IOS parameters and spirometry is moderate at best [11]. IOS can be used for asthma diagnosis, as it may signal early obstructive changes [12], and for follow-up of asthma patients, due to its association with clinical symptoms being better than that of spirometry [13, 14]. Moreover, IOS appears to be a better predictor of loss of asthma control than spirometry [15, 16]. Small-scale studies have shown similar results for diagnosis of COPD [17, 18]. However, the clinical benefit of adding IOS parameters is more modest in patients with established COPD [19], and is questionable in cystic fibrosis [20, 21].

Abnormal IOS findings can be seen in individuals with normal spirometry and it is therefore speculated that individuals at risk of developing respiratory disease may be identified using IOS [22, 23]. There is some limited evidence that IOS is related to respiratory symptoms in individuals with normal spirometry, both in case of occupational exposures [24–26] and in systemic sclerosis [27]. However, such evidence comes from studies with relatively limited sample sizes [22–26].

Our primary aim is to use a large population-based cohort to study the relationship between IOS, spirometry and respiratory symptoms and self-reported respiratory disease. Our secondary aim is to study the relationship between IOS and respiratory morbidity in subjects with normal lung function.

Methods

Study population

The study data were collected from the Swedish CArdioPulmonary bioImage Study (SCAPIS), a national population-based study of randomly selected participants (n=30 154), aged 50–64 years, from six Swedish healthcare centres [28]. The study population for the present analyses consisted of 11 287 participants from Uppsala and Malmö, as these two centres performed IOS measurements in addition to the SCAPIS core protocol. The period of recruitment was between October 2015 and June 2018 for Uppsala and between March 2014 and March 2018 for Malmö. The participation rate in SCAPIS was 46.8% for Uppsala and 53.1% for Malmö. The present analyses are cross-sectional, based on data from the inclusion visit.

Questionnaire

The respiratory questionnaire included questions on the symptoms cough, dyspnoea, wheeze and sputum production. Chronic bronchitis was defined as self-reported expectoration of phlegm, even without simultaneous symptoms of upper respiratory tract infection, during a period of ⩾3 months per year for ⩾2 years [29].

In addition, questions covered sick leave due to respiratory problems, confirmed diagnosis and/or treatment of asthma, COPD or other respiratory disorders and smoking habits, with participants categorised as current, former or never-smokers.

Body mass index (BMI) was defined as measured weight (kg)/measured height $(m)^2$ and categorised as underweight (<18.5 $kg \cdot m^{-2}$), normal weight (18.5–24.9 $kg \cdot m^{-2}$), overweight (25–29.9 $kg \cdot m^{-2}$) and obese (⩾30 $kg \cdot m^{-2}$).

Pulmonary function testing

All pulmonary function testing was performed 15 min after inhalation of 400 µg of salbutamol administered *via* a spacer with the subject in the sitting position wearing a nose clip. During IOS, the subject used their hands to stabilise their cheeks, in line with the technical standards available at the time of testing [30].

Dynamic spirometry was performed using a Jaeger MasterScreen PFT (Vyaire, Mettawa, IL, USA) in accordance with the European Respiratory Society's standardisation of spirometry [31]. The spirometry

data consisted of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and slow vital capacity (SVC).

IOS was measured using a Jaeger MasterScreen IOS, as described previously [2]. The device propagates a train of bidirectional, harmonic sound waves, generated by a loudspeaker, along the bronchial tree. The oscillations are applied at a fixed square wave frequency of 5 Hz, from which other frequencies of interest are derived, typically multiples of 5 Hz (between 5 and 35 Hz) [4]. Reactance and resistance were expressed in $kPa \cdot s \cdot L^{-1}$ and resonant frequency (f_{res}) in Hz. The parameters of interest for the present study were R_5, R_{20}, X_5, f_{res} and AX.

The normal values for IOS parameters were defined using quantile regression stratified by gender in never-smoking participants without respiratory symptoms or respiratory disease (n=3664, 52% male) (supplementary figure S1). The reference equations were estimated for males and females separately. More specifically, the 95th percentile cut-offs (*i.e.* upper limit of normal) of R_5, R_{20}, AX, f_{res} and the 5th percentile cut-offs (*i.e.* lower limit of normal (LLN)) of X_5 were obtained using the quantile regression models, which, unlike linear regression, do not require any distributional assumptions. In the models, the dependent indices are the IOS indices, and the predictors are age, height and weight [32].

For spirometry, we applied the lambda-mu-sigma methods, according to Quanjer *et al.* [33], to the reference population from SCAPIS (n=3608, 52% male) (supplementary figure S1). By setting post-bronchodilatory lung function indices (FEV_1, FVC, SVC, FEV_1/FVC, FEV_1/SVC) as the dependent variable and the splined log-transformed age and log-transformed height as the independent variables (choosing the Box–Cox–Cole–Green power family and setting the "log" link function for the mean) we could estimate the models. The models are estimated for males and females separately.

Abnormal values were defined as below LLN, defined as the 5th percentile, for FEV_1, SVC, FVC, FEV_1/SVC and FEV_1/FVC. Normal spirometry was defined as all indices (FEV_1, SVC, FVC, FEV_1/SVC and FEV_1/FVC) being within the normal range. If any of the indices were in the abnormal range, the spirometry was defined as abnormal. Obstructive spirometry was defined as FEV_1/FVC or FEV_1/SVC being below the LLN. Predicted values of FEV_1 were obtained from these data.

The same approach was used defining abnormal and normal IOS, where abnormal values were defined as above the upper limit of normal, defined as the 95th percentile, for R_5, R_{20}, f_{res} and AX, and below the LLN, defined as the 5th percentile, for X_5. Normal IOS was defined as all indices (R_5, R_{20}, f_{res}, AX and X_5) being within the normal range. If any of the indices were in the abnormal range, IOS was defined as abnormal. In addition, resistance and reactance indices were combined in a way that abnormal R_5 in combination with any abnormal reactance indices (f_{res}, AX or X_5) was defined as abnormal.

Equations for oscillometry are presented in supplementary table S1.

Statistics

Logistic regression models were used to study associations of abnormal IOS or spirometry indices (predictor) with the presence of respiratory symptoms (outcome) in all participants and for abnormal IOS in addition in participants with normal spirometry. The relationships were adjusted for age, gender, smoking status and, in an additional model, FEV_1 (% pred). Furthermore, we tested the findings from the multiple logistic regression models for significance with BMI as an additional predictor. The confounders used in the model were selected based on characteristics previously described in the literature to be associated with the outcome (respiratory symptoms). Receiver operating characteristic analysis has been performed for the different oscillometry indices in relation to abnormal spirometry or presence of respiratory symptoms. All statistical analyses were performed using Stata/IC 15.1 (StataCorp LLC, College Station, TX, USA) with exception for generating reference values where R (version 4.2.2, R Core Team, Vienna, Austria) was used. A p-value of <0.05 was considered statistically significant.

Ethical approval

All participants gave written informed consent and SCAPIS has been approved as a multicentre study by the ethics committee at Umeå University (Dnr 2010-228-31M). The present IOS add-on analyses have been approved by the Swedish Ethical Review Authority in Uppsala (Dnr 2019-03416).

Results

The sample eligible (n=11 287) for the current study is presented in figure 1. Due to incomplete data, 927 participants were excluded from further analyses.

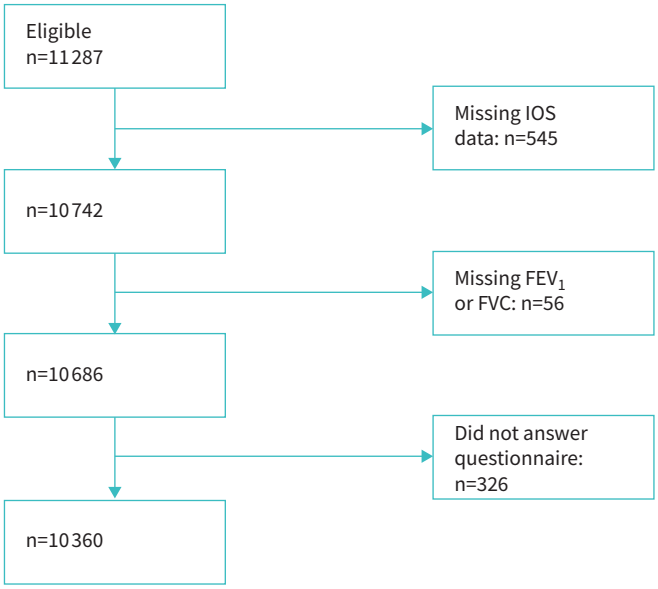

FIGURE 1 Flowchart of participants included in the study. IOS: impulse oscillometry; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Prevalence of abnormal IOS

The prevalence of abnormal IOS was 16% in the current cohort. The population characteristics, with regard to IOS, are presented in table 1. Participants with abnormal IOS appeared to have a higher prevalence of respiratory symptoms, patient-reported respiratory disease and obstructive spirometry.

Prevalence of abnormal spirometry

The prevalence of abnormal spirometry was 19% in the current cohort (n=10 247 due to missing SVC in 113 participants). The population characteristics, with regard to spirometry, are presented in supplementary table S2.

Overlap of abnormal IOS and spirometry and respiratory burden

Abnormal IOS or spirometry was found in 1616 (50%) of symptomatic participants (figure 2). This analysis was performed in 9875 participants, as SVC and/or respiratory symptoms information was missing in 485 participants. Only 32% of participants with abnormal spirometry had abnormal IOS. Looking specifically among individuals with obstructive spirometry (FEV_1/FVC or FEV_1/SVC<LLN), 30% had abnormal IOS.

Area under the curve (AUC) from receiver operating characteristic analyses have been performed for each oscillometry index in relation to abnormal spirometry and having respiratory symptoms. AUC values ranged between 0.57 and 0.64 (supplementary table S3).

Abnormal IOS and spirometry parameters in relation to respiratory burden

All abnormal parameters for IOS and spirometry were associated with increased odds ratios for all clinical outcomes except sick leave due to respiratory problems (no association with SVC) and current asthma (no association with R_{20}) (table 2).

When further adjusting for FEV_1 (% pred), abnormal resistance was associated with cough, sputum production, dyspnoea and sick leave due to respiratory problems (table 3). For abnormal reactance, the most consistent associations were with wheeze, sick leave due to respiratory problems, and current asthma. The highest adjusted odds ratios were found for sick leave due to respiratory problems both for abnormal resistance and abnormal reactance.

Abnormal IOS parameters in relation to respiratory burden when spirometry is normal

In individuals with normal spirometry, both abnormal R_5 and R_{20} were associated with cough and dyspnoea (table 4). For dyspnoea, this association remained when further adjusting for FEV_1 (% pred)

TABLE 1 Study population characteristics, grouped by impulse oscillometry (IOS) results

	Normal IOS	Abnormal IOS[#]
Subjects (n)	8697	1663
Male	48.04	47.14
Age (years)	57.43±4.33	58.06±4.35
Height (cm)	172.3±9.6	171.8±10.0
Weight (kg)	80.38±15.75	81.34±16.85
BMI (kg·m^{-2})		
Underweight <18.5	0.32	0.66
Normal weight 18.5–24.9	34.40	32.53
Overweight 25–29.9	44.45	40.83
Obese ⩾30	20.84	25.98
Smoking habits		
Never-smokers	51.12	44.79
Former smokers	36.58	35.53
Current smokers	12.30	19.67
Pack-years	22.69±28.74	33.67±39.61
Symptoms		
Cough	17.72	23.95
Chronic bronchitis	4.66	7.25
Sputum production	10.39	15.93
Wheeze	5.89	13.93
Dyspnoea	8.74	17.43
Sick leave due to respiratory problems	1.22	2.63
Reported asthma	7.28	11.12
Reported COPD	1.02	4.41
Reported other lung disease	1.42	2.18
Treated asthma past 2 weeks	3.80	6.59
Treated COPD past 2 weeks	0.46	3.11
Spirometry data		
FEV_1 (% predicted)	99.47±12.39	88.66±14.31
FEV_1/FVC <LLN	7.70	17.98

Data are presented as % or mean±SD, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal. [#]: defined as any IOS parameter being abnormal.

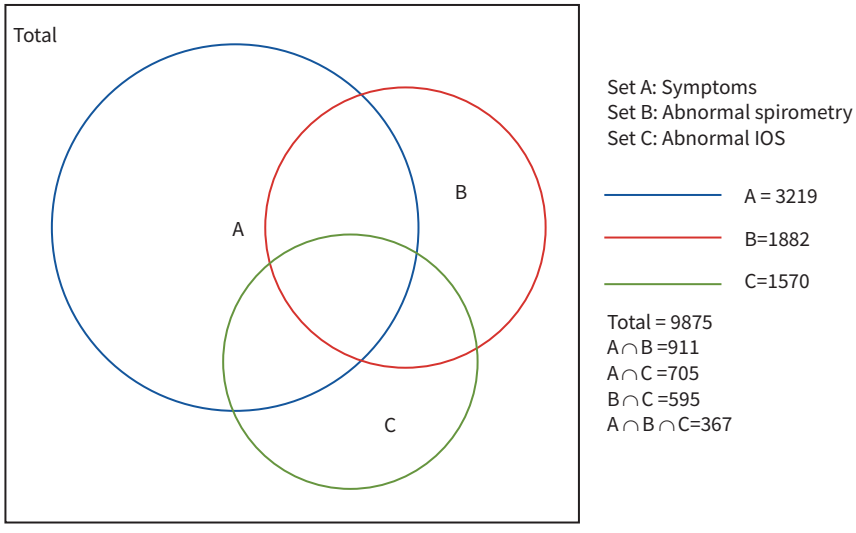

FIGURE 2 Venn diagram of participants with symptoms (any respiratory symptom), abnormal spirometry (any spirometry parameter) and abnormal impulse oscillometry (IOS) (any IOS parameter). ∩: intersection. Total study population for comparison.

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TABLE 2 Adjusted odds ratios for different respiratory symptoms with abnormal impulse oscillometry (IOS) or spirometry parameters (analyses per parameter)

	Abnormal R_5	Abnormal R_{20}	Abnormal X_5	Abnormal AX	Abnormal f_{res}	Abnormal FEV_1/SVC	Abnormal FEV_1/FVC	Abnormal FEV_1	Abnormal SVC	Abnormal FVC
Cough	**1.52 (1.27–1.82)**	**1.44 (1.18–1.75)**	**1.45 (1.22–1.73)**	**1.41 (1.19–1.69)**	**1.30 (1.08–1.57)**	**1.76 (1.51–2.07)**	**1.56 (1.34–1.83)**	**1.71 (1.46–2.00)**	**1.40 (1.15–1.71)**	**1.52 (1.26–1.83)**
Chronic bronchitis	**1.54 (1.15–2.06)**	**1.51 (1.10–2.08)**	**1.65 (1.24–2.19)**	**1.55 (1.16–2.07)**	**1.48 (1.10–2.00)**	**2.31 (1.81–2.92)**	**1.94 (1.53–2.47)**	**2.25 (1.78–2.86)**	**1.50 (1.09–2.06)**	**1.44 (1.05–1.97)**
Sputum production	**1.54 (1.25–1.91)**	**1.51 (1.20–1.91)**	**1.65 (1.35–2.03)**	**1.57 (1.28–1.93)**	**1.44 (1.16–1.79)**	**1.96 (1.64–2.35)**	**1.84 (1.54–2.20)**	**2.00 (1.67–2.40)**	**1.35 (1.07–1.71)**	**1.54 (1.24–1.93)**
Wheeze	**2.02 (1.60–2.57)**	**1.46 (1.10–1.93)**	**2.88 (2.32–3.57)**	**3.13 (2.54–3.86)**	**2.86 (2.30–3.56)**	**3.84 (3.18–4.64)**	**3.40 (2.82–4.10)**	**3.92 (3.25–4.73)**	**2.32 (1.81–2.97)**	**2.64 (2.09–3.34)**
Dyspnoea	**2.14 (1.74–2.64)**	**1.86 (1.48–2.34)**	**2.18 (1.79–2.65)**	**2.41 (1.99–2.93)**	**2.03 (1.65–2.49)**	**2.16 (1.79–2.59)**	**2.21 (1.85–2.65)**	**3.25 (2.74–3.87)**	**2.42 (1.96–3.00)**	**2.55 (2.07–3.13)**
Sick leave due to respiratory problems	**2.72 (1.72–4.31)**	**2.21 (1.32–3.69)**	**2.55 (1.62–4.00)**	**2.85 (1.85–4.38)**	**2.52 (1.59–3.98)**	**2.56 (1.69–3.88)**	**2.74 (1.83–4.11)**	**3.04 (2.03–4.55)**	1.71 (0.98–3.00)	**2.39 (1.46–3.91)**
Current asthma	**1.76 (1.32–2.34)**	1.38 (0.99–1.90)	**2.30 (1.79–2.96)**	**2.61 (2.04–3.31)**	**2.29 (1.78–2.96)**	**3.64 (2.92–4.51)**	**3.37 (2.72–4.18)**	**3.18 (2.55–3.97)**	**1.48 (1.08–2.03)**	**1.72 (1.29–2.29)**
Reported COPD	**2.71 (1.78–4.11)**	**2.00 (1.22–3.28)**	**3.37 (2.31–4.94)**	**4.04 (2.80–5.84)**	**5.26 (3.68–7.52)**	**11.13 (7.97–15.56)**	**9.70 (6.95–13.54)**	**10.19 (7.30–14.21)**	**2.13 (1.32–3.43)**	**2.47 (1.57–3.88)**

Data are presented as adjusted OR (95% CI). Odds ratios adjusted for age, gender and smoking. Results were statistically significant if the 95% confidence interval does not include 1 (shown in bold). R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; X_5: reactance at 5 Hz; AX: area of reactance; f_{res}: resonant frequency; FEV_1: forced expiratory volume in 1 s; SVC: slow vital capacity; FVC: forced vital capacity.

TABLE 3 Adjusted odds ratios for different respiratory symptoms with abnormal impulse oscillometry (IOS) parameters (analyses per parameter)

	Abnormal R_5	Abnormal R_{20}	Abnormal X_5	Abnormal AX	Abnormal f_{res}
Cough	**1.33 (1.10–1.60)**	**1.31 (1.08–1.60)**	1.18 (0.98–1.42)	1.15 (0.95–1.39)	1.07 (0.89–1.30)
Chronic bronchitis	1.19 (0.88–1.62)	1.29 (0.93–1.78)	1.14 (0.84–1.54)	1.06 (0.78–1.45)	1.06 (0.77–1.45)
Sputum production	**1.29 (1.03–1.60)**	**1.34 (1.06–1.70)**	**1.27 (1.02–1.57)**	1.20 (0.96–1.50)	1.12 (0.89–1.41)
Wheeze	1.24 (0.96–1.60)	1.04 (0.78–1.40)	**1.49 (1.17–1.89)**	**1.67 (1.33–2.11)**	**1.60 (1.26–2.03)**
Dyspnoea	**1.48 (1.19–1.84)**	**1.46 (1.15–1.85)**	1.23 (0.99–1.53)	**1.42 (1.15–1.75)**	1.22 (0.97–1.52)
Sick leave due to respiratory problems	**2.00 (1.24–3.23)**	**1.76 (1.04–2.98)**	1.63 (0.99–2.67)	**1.89 (1.18–3.03)**	**1.68 (1.03–2.75)**
Current asthma	1.27 (0.94–1.70)	1.10 (0.79–1.53)	**1.47 (1.12–1.93)**	**1.71 (1.32–2.23)**	**1.54 (1.18–2.03)**
Reported COPD	1.02 (0.63–1.64)	1.13 (0.66–1.95)	0.91 (0.58–1.44)	1.19 (0.77–1.83)	**1.86 (1.23–2.82)**

Data are presented as adjusted OR (95% CI). Odds ratios adjusted for forced expiratory volume in 1 s (% predicted), age, gender and smoking. Results were statistically significant if the 95% confidence interval does not include 1, marked in bold. R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; X_5: reactance at 5 Hz; AX: area of reactance; f_{res}: resonant frequency.

(supplementary table S4). Abnormal R_{20} was associated with cough and sputum production (table 4) and these finding were consistent after adjusting for FEV_1 (% pred) (supplementary table S4). For reactance, abnormal AX was associated with wheeze, dyspnoea and current asthma (table 4). After further adjustment for FEV_1 (% pred), associations remained for wheeze and current asthma (supplementary table S4).

Respiratory burden in relation to abnormal R_5 combined with abnormal reactance

Supplementary figure S2 presents the overlap in abnormal spirometry, abnormal R_5 and abnormal reactance. 9% of those with normal spirometry had abnormal R_5 and reactance. In table 5 we tested the combination of having both abnormal R_5 and any reactance parameter. Looking at all individuals, significant adjusted odds ratios are found for all symptoms and the majority are consistent after further adjustment for FEV_1 (% pred) (table 6). In the subgroup of individuals with normal spirometry, abnormal R_5 combined with abnormal reactance was associated with cough, chronic bronchitis, sputum production and dyspnoea. For cough, chronic bronchitis and dyspnoea, this association remained after adjustment for FEV_1 (% pred), with adjusted odds ratios of ~2 (table 6). These last results remained significant with minimal change in odds ratios after further adjustment for BMI (not presented).

Discussion

The main finding of our study was that in this large population-based material, abnormal IOS was related to respiratory symptoms in participants presenting with normal spirometry. When combining abnormal R_5 with any abnormal reactance indices, this association remained significant for many respiratory symptoms, even when adjusting for FEV_1. Interestingly, only one-third of participants with obstructive spirometry had abnormal IOS.

In line with previous studies, we found abnormal IOS in participants with normal spirometry [22–26, 34]. Our study showed that abnormal IOS was related to an increased burden of symptoms for these

TABLE 4 Adjusted odds ratios in individuals with normal spirometry for different respiratory symptoms with abnormal impulse oscillometry (IOS) parameters (analyses per parameter)

	Abnormal R_5	Abnormal R_{20}	Abnormal X_5	Abnormal AX	Abnormal f_{res}
Cough	**1.30 (1.02–1.65)**	**1.41 (1.11–1.80)**	1.24 (0.96–1.61)	1.17 (0.90–1.52)	1.03 (0.78–1.36)
Chronic bronchitis	1.35 (0.89–2.04)	**1.55 (1.03–2.33)**	1.27 (0.80–2.03)	1.02 (0.61–1.71)	0.85 (0.49–1.47)
Sputum production	1.29 (0.96–1.73)	**1.47 (1.09–1.96)**	1.30 (0.94–1.78)	1.32 (0.96–1.82)	1.00 (0.71–1.42)
Wheeze	1.28 (0.86–1.90)	1.11 (0.72–1.72)	1.27 (0.82–1.96)	**1.93 (1.32–2.80)**	**1.50 (1.00–2.25)**
Dyspnoea	**1.75 (1.31–2.35)**	**1.68 (1.24–2.28)**	1.35 (0.96–1.88)	**1.52 (1.10–2.10)**	1.17 (0.82–1.68)
Sick leave due to respiratory problems	1.37 (0.59–3.16)	1.71 (0.78–3.74)	0.47 (0.11–1.92)	0.93 (0.34–2.54)	0.72 (0.23–2.30)
Current asthma	0.82 (0.49–1.40)	0.86 (0.51–1.45)	1.25 (0.79–2.00)	**1.72 (1.14–2.59)**	1.48 (0.95–2.30)
Reported COPD	0.73 (0.18–3.05)	1.26 (0.39–4.10)	1 (omitted)	0.88 (0.21–3.66)	2.39 (0.93–6.10)

Data are presented as adjusted OR (95% CI). Odds ratios adjusted for age, gender and smoking. Results were statistically significant if the 95% confidence interval does not include 1, marked in bold. R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; X_5: reactance at 5 Hz; AX: area of reactance; f_{res}: resonant frequency.

TABLE 5 Adjusted odds ratios in all individuals and in individuals with normal spirometry for different respiratory symptoms with abnormal resistance at 5 Hz and reactance

	All individuals	Individuals with normal spirometry
Cough	**1.98 (1.56–2.51)**	**1.87 (1.33–2.65)**
Chronic bronchitis	**2.04 (1.40–2.96)**	**2.02 (1.14–3.55)**
Sputum production	**1.87 (1.41–2.48)**	**1.60 (1.04–2.47)**
Wheeze	**3.44 (2.58–4.59)**	1.72 (0.99–2.99)
Dyspnoea	**3.05 (2.35–3.97)**	**2.22 (1.47–3.36)**
Sick leave due to respiratory problems	**3.99 (2.31–6.91)**	1.07 (0.26–4.40)
Current asthma	**2.86 (2.05–4.01)**	1.23 (0.62–2.44)
Reported COPD	**5.08 (3.13–8.23)**	1.90 (0.45–8.02)

Data are presented as adjusted OR (95% CI). Odds ratios adjusted for age, gender and smoking. Results were statistically significant if the 95% confidence interval does not include 1, marked in bold.

participants. Although findings from smaller studies have suggested this [22, 35], as far as we are aware, our results are the first from a large population-based study to confirm this association. In contrast to these previous studies, focusing on participants seeking medical care due to respiratory symptoms, our study confirms this association in a larger mostly healthy population. A potential reason for this is that IOS is more sensitive than spirometry in identifying obstructive impairment [36], especially in the peripheral airways [37], and respiratory symptoms are thought to more often be related to peripheral airway function than to central airway function [8, 9]. For example, smokers who have preserved lung function but experience respiratory symptoms often exhibit impaired IOS parameters [38]. Similar findings have been described in a more unselected population of participants who underwent pulmonary function testing [35]. In this latter study, X_5 and f_{res} had the highest sensitivity for finding participants with respiratory symptoms among participants with preserved pulmonary function [35]. Moreover, looking at the individual symptoms among those with normal spirometry in our study population, cough and dyspnoea appeared to be more related to resistance, while wheeze was more related to reactance. This last finding is in contrast with findings from a study of smokers with preserved spirometry, where increased resistance was related to wheeze [38]. However, this may be due to the different populations investigated, considering a lower prevalence of current smoking and a higher age in our study population and that subjects with history of cardiac and respiratory disease were excluded in the study of Jetmalani *et al.* [38]. Furthermore, dyspnoea might have nonrespiratory causes [39]. Resistance in the large airways, R_{20}, mainly related with cough and chronic bronchitis, and this might mainly reflect inflammation in the central airway compartment due to goblet cell hyperplasia [40]. Finally, a significant part of these associations was weak or inconsistent after further adjusting for $FEV_{1,}$ expressed as % pred. However, this might be an overadjustment, as FEV_1 is related to abnormal IOS.

To further see how IOS can add information in those with normal spirometry, we defined IOS as abnormal if it contained abnormal R_5 together with any abnormal reactance indices. This combination resulted in

TABLE 6 Adjusted odds ratios in all individuals and in individuals with normal spirometry for different respiratory symptoms with abnormal resistance at 5 Hz and reactance

	All individuals	Individuals with normal spirometry
Cough	**1.60 (1.24–2.05)**	**1.77 (1.25–2.51)**
Chronic bronchitis	1.35 (0.90–2.02)	1.81 (1.02–3.22)
Sputum production	**1.43 (1.06–1.93)**	1.49 (0.96–2.32)
Wheeze	**1.74 (1.27–2.40)**	1.36 (0.78–2.39)
Dyspnoea	**1.78 (1.34–2.37)**	**1.73 (1.13–2.63)**
Sick leave due to respiratory problems	**2.61 (1.43–4.76)**	0.95 (0.23–3.96)
Current asthma	**1.84 (1.28–2.64)**	1.06 (0.53–2.12)
Reported COPD	1.36 (0.76–2.44)	1.19 (0.28–5.14)

Data are presented as adjusted OR (95% CI). Odds ratios adjusted for forced expiratory volume in 1 s (% predicted), age, gender and smoking. Results were statistically significant if the 95% confidence interval does not include 1, marked in bold.

even higher odds ratios of ∼2 for many respiratory symptoms. This probably reflects that we identify individuals with both airway obstruction and ventilation heterogeneity by requiring both parameters to be abnormal [10]. Furthermore, the highest odds ratios were noted for sick leave due to respiratory symptoms, which we could speculate that to some extent might relate to loss of asthma control [15]. When also adjusting for FEV_1, most associations remained significant with little change in odds ratios. This suggests that these associations are consistent, even when possible overadjustment is done by adjusting for a spirometry index that is related to IOS indices. These findings support the additive value of IOS in asthma management [41], as lung function, assessed using spirometry, can be preserved to a variable degree in asthma. As mentioned earlier, studies have suggested that IOS might be a complementary tool for identifying early changes in lung mechanics and could be used in early identification of patients with asthma [42] and early identification of subjects with COPD [22, 42], in cases with preserved pulmonary function.

Interestingly, only one in three participants with obstructive spirometry presented with abnormal IOS. Similar results have recently been reported in a study containing subjects with COPD, showing that not all subjects with COPD have abnormal IOS. A high proportion of subjects (60–80%) in the study had normal resistance, while one in three individuals had normal reactance despite a mean FEV_1 of ∼50% pred [19]. In addition, we know from studies of adult asthma that individuals with abnormal FEV_1 can have normal IOS [43]. This suggests that the value of IOS alone in ruling out spirometric impairment might be limited. We can only speculate on potential mechanisms. Airflow obstruction is often associated with hyperinflation and IOS measurements reflect the respiratory mechanics at functional residual capacity (FRC). Increased FRC results in reduction in resistance variables and increases in reactance [44, 45]. Therefore, hyperinflation may offset the expected changes in IOS variables.

The strengths of our study included the large number and population-based selection of participants. The prevalence of diagnosed pulmonary disease was low and the results are therefore transferrable to participants with mild symptoms and relatively preserved lung function. Another strength of our findings was that we could demonstrate that the majority of the findings with regard to impaired oscillometry and respiratory symptoms could be confirmed even when adjustments for FEV_1 were made. The narrow age range of the participants, 50–64 years, is a limitation as the results cannot be extrapolated, for example to young patients with asthma. Conversely, this age range is highly relevant for development of chronic airflow limitation and COPD. As participation rate was ∼50%, we cannot exclude a selection bias. A small portion of included participants (<5%) had minor gaps in collected data; however, neither this nor the participation rate should affect the associations found in the present study. Another limitation might be the fact that we have not differentiated patterns of abnormal spirometry. However, this was outside the scope of the present study as we wanted to investigate whether oscillometry generally adds to information from spirometry. The main spirometric abnormality is obstructive impairment and we lack statistical power to look at restrictive patterns [46] or preserved ratio impaired spirometry [47]. It has to be acknowledged that the findings of the present study are based on post-bronchodilatory spirometry and oscillometry and therefore we cannot extrapolate the findings to pre-bronchodilatory measurements. Finally, a limitation of the study is the cross-sectional nature of the study, as we only assessed lung function at one time point. Further studies should assess if our findings are consistent when multiple measurements are available and to compare persistent impaired oscillometry *versus* spirometry.

In conclusion, we have shown that abnormal IOS findings are often present in middle-aged participants with respiratory symptoms, even if spirometry is normal. Longitudinal studies are needed to show if IOS can be used to identify participants with early signs of lung disease.

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