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Cohort profile: VAScular and Chronic Obstructive Lung disease (VASCOL) - a longitudinal study on morbidity, symptoms, and quality of life among older men in Blekinge County, Sweden

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Cohort profile: VAScular and Chronic Obstructive Lung disease (VASCOL) - a longitudinal study on morbidity, symptoms, and quality of life among older men in Blekinge County, Sweden.

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ABSTRACT

Purpose: Despite data showing breathlessness to be more prevalent in older adults, we have little detail about the severity or multi-dimensional characteristics of breathlessness and other self-reported measures (such as quality of life and other cardiorespiratory-related symptoms) in this group at the population level. We also know little about the relationship between multi-dimensional breathlessness, other symptoms, co-morbidities and future clinical outcomes such as quality of life, hospitalization, and mortality. This paper reports the design and descriptive findings from the first two waves of a longitudinal prospective cohort study in older adults.

Participants: Between 2010-2011, 1900 men in a region in southern Sweden aged 65 years, were invited to attend for VASCOL baseline (Wave 1) assessments which included physiological measurements, blood sampling, and a self-report survey of lifestyle and previous medical conditions. In 2019, follow up postal survey data (Wave 2) were collected with additional self-report measures for breathlessness, other symptoms, and quality of life. At each wave, data are cross-linked with nationwide Swedish registry data of diseases, treatment, hospitalization, and cause of death.

Findings to date: 1302/1900 (68%) of invited men participated in Wave 1, which include 56% of all 65 years old men in the region. 5% reported asthma, 2% chronic obstructive pulmonary disease, 56% hypertension, 10% diabetes, and 19% had airflow limitation. The VASCOL cohort had comparable characteristics to those of similarly aged men in Sweden. By 2019, 109/1302 (8.4%) had died. 907/1193 (76%) of the remainder participated in Wave 2. Internal data completeness of 95% or more was achieved for most Wave 2 measures.

Future plans: A third wave will be conducted within four years, and the cohort will be followed through repeated follow ups planned every fourth year, as well as national registry data of diagnosis, treatments, and cause of death.

Keywords: *Older adults, breathlessness, symptoms, respiratory diseases, cardiovascular diseases, epidemiology.*

STRENGTHS AND LIMITATIONS OF THIS STUDY

- More than half (57%) of all 65 years old men in Blekinge participated in the VASCOL baseline, of which approximately 70 % also participated in the follow up.
- The VASCOL baseline, Wave 1, (n = 1302) collected a wide range of data: physiological measurements, blood samples, survey of lifestyle and self-reported conditions.

- The VASCOL follow up study, Wave 2, (n = 907) included an extensive set of validated self-report instruments of symptoms of cardiorespiratory diseases.
- Cross-linkage of data with national registries allowed prospective study of morbidity, hospitalization, and mortality in this cohort.

INTRODUCTION

Cardiorespiratory diseases, such as ischemic heart disease, heart failure and chronic obstructive pulmonary disease (COPD) are major causes of morbidity and mortality worldwide.[1,2] They often coexist with, and are worsened by, other conditions leading to poorer outcomes. Multimorbidity increases over the age of 65 years, particularly those with cardiorespiratory diseases.[3,4,5]

Cardiorespiratory diseases are associated with major adverse health effects including anxiety and depression, poorer quality of sleep and impaired physical capacity.[6 7] Symptoms of cardiorespiratory diseases includes chest pain, nausea, and fatigue, with the major 'cardinal' symptom being *chronic breathlessness*.[8] Breathlessness is also highly prevalent across the older population,[9] and the risk of developing breathlessness affecting daily life increases markedly with age.[10] People who are breathless often avoid physical activities,[11] many becoming socially isolated.[8,12] In COPD, breathlessness is a stronger predictor of mortality than the level of airflow limitation.[13] Breathlessness is also associated with impaired quality of life (QoL), worse physical capacity and higher overall mortality in people with different underlying conditions.[7,14,8]

Few population-level studies have focused on breathlessness and its relationship with other self-reported outcomes. The BOLD,[15] PLATINO,[16] and ECRHS,[17] studies assessed breathlessness mainly using the unidimensional modified Medical Research Council (mMRC) scale, which thus only assesses the level of exertion required to induce breathlessness, and not the severity of the symptom *per se.*[12] Breathlessness is a multi-dimensional symptom affecting

all domains of a person's life[18] and the intensity of both physical and affective dimensions needs to be included in measurements.[7],[18] For multi-dimensional assessment of breathlessness, the instruments Dyspnoea-12 (D12)[19] and Multidimensional Dyspnea Profile[20] (MDP) can be used. Recently, the minimal clinically important difference (MCID) was determined for both D12 and MDP in cardiorespiratory disease.[21]

Some breathlessness data from older adults at the general population level regarding prevalence and clinical outcomes are published, but details including characteristics, and severity are relatively few. We also know little about other common symptoms and co-morbidities affect clinical outcomes such as QoL, health service utilisation and survival in older adults. To date, no study has assessed the relationship between multi-dimensional breathlessness and clinical outcomes in older adults in the general population.

The VAScular and Chronic Obstructive Lung disease study (VASCOL) is an epidemiological, longitudinal, cohort study to describe the relationship between vascular diseases and COPD. Since its beginning in 2010, the scope has broaden to also focus on QoL, self-reported measures of breathlessness and other symptoms of cardiovascular diseases.

In this paper we present the VASCOL study design, including future longitudinal data collection, describe the characteristics of participants from the first two waves, (Wave 1- baseline; Wave 2 - first follow up).

Study objectives

The overall objective of the VASCOL study is to evaluate the relationship between life-style variables, morbidity due to cardiorespiratory disease, multi-dimensional breathlessness, other symptoms of cardiovascular diseases, and QoL in a population sample of men aged 65 years on cohort entry. We aim to evaluate:

- How baseline factors (diseases, lung function, lifestyle, demographics) predict the outcomes of breathlessness, QoL, diagnosed diseases, hospitalization, and mortality.
- The prevalence, characteristics, and severity of multi-dimensional breathlessness and other symptoms such as anxiety, depression, pain, nausea, and fatigue.
- The relationship between self-reported QoL and symptom burden and functional limitations.
- Contributing causes of breathlessness and other symptoms such as anxiety, depression, pain, nausea, and fatigue.
- How the presence and type of symptoms predicts future diseases.

COHORT DECRIPTION

The VASCOL study is an ongoing longitudinal epidemiological cohort study in Blekinge, Sweden. Blekinge is a county located in southern Sweden and has a total population of around 160,000, of which approximately 2300 were 65-years old men in 2010-2011. Blekinge geographically covers both urban and rural areas with good public transportations, see Figure 1.

In 2010-2011, 1900 men aged 65 years in Blekinge were invited to a screening campaign of abdominal aortic aneurysm (AAA) at a health centre in the city of Karlshamn.

The men were informed about the VASCOL study and invited to give their informed written consent to participate in the Wave 1 examinations. A self-report survey (demography, lifestyle, and previous diseases) was included with the invitation pack. Blekinge´s biggest municipality, Karlskrona, was not included in the screening campaign until 2011, resulting in approximately 80 % (1900/2300) of all 65-years-old men living in Blekinge 2010 - 2011 were invited to participate in the VASCOL study. The inclusion criteria were: men, 65-years old, living in

Blekinge (excluding Karlskrona in 2010), participating in the screening examinations, and willing to give a written consent to participate in the Wave 1 examinations. There were no exclusion criteria based on any conditions. In 2019 a follow up postal survey was sent out to the participants still alive and with a known address (Wave 2).

Wave 1: baseline data collection

At baseline, a clinical visit was performed, and data from the self-report survey collected. Nurses checked for survey data completeness, and those who omitted to bring their survey were also able to complete this during the visit. Physiological measurements and blood sampling were collected according to standard protocols by registered nurses. The blood samples were stored in a biobank for future analysis. Out of the 1900 men attending the screening, 1302 (68.5%) participated in the VASCOL baseline study. Normative values for Swedish men in the same age group were also collected from The Public Health Agency of Sweden, National Board of Health and Welfare, and Statistics Sweden.

Wave 2: Follow up survey

In 2019, the Blekinge county demographic registers were used to identify all participants who were alive with a known address (n = 1193). A new survey was sent out to all these participants. At Wave 2, 829 of the men replied to the initial survey within two weeks, and additional 78 men replied after a reminder, leading to 907/1193 (76%) of men participated in Wave 2. See Figure 2 for detailed information about data collection procedure. The postal survey consisted of questions and validated instruments regarding breathing, other cardiorespiratory-related symptoms, QoL, lifestyle, new medical conditions, and any treatments for breathlessness. Most questions and instruments pertained to the experiences during the last two weeks.

Planned data collection

Repeated waves will be conducted at four yearly intervals, to enable examination of the change in participants' breathlessness, other symptoms and QoL. Wave 3 data collection will be conducted within four years, and the procedure and survey instruments will be similar to the first two waves. Collected data will be cross-linked with nationwide Swedish registry data: Cause of Death Registry, Swedish Prescribed Drug Registry, and National Patient Registry (see table 1).

Table 1. Planned cross linkage with national registries

Data	**Source**	**Timeframe of the data**
Inpatient care including diagnoses, date for diagnoses, treatment, date for treatment, and treatment time.	Swedish National Patient Registry for In-patient Care	1987 - today
Outpatient care, diagnosis, date for diagnosis, treatment, date for treatment, and treatment time.	Swedish National Patient Registry for Out-patient Care	2001 - today
Place, date, and cause(s) of death	Causes of Death Registry	Baseline - today
Dispensed prescribed medications	Swedish Prescribed Drug Registry	July 2005 - today

Patient and Public Involvement

The follow up survey was piloted on ten people of similar age to the VASKOL study participants before the final survey was revised and administered. The pilot participants had the opportunity to add areas of research that they thought were relevant. Pilot participants also gave feedback on the layout and length of the survey as well as how the questions were asked. Minor linguistically and layout changes were done to the survey questions to fit the specific study participants.

FINDINGS TO DATE

Baseline characteristics of the VASCOL study are shown in Table 2. The majority of the participants had hypertension (56%), and approximately one fifth had airflow limitation (first second of forced expiration (FEV1) / forced vital capacity (FVC) < 0.7). Only a small proportion had self-reported asthma (5%) or COPD (2%). One tenth (10%) reported diabetes. Also, approximately one tenth of the participants (13%) were everyday smokers, and the majority (54%) were former smokers. Around half of the participants were overweight (52%) and around one third (28%) obese. Participants in the VASCOL cohort had proportions similar to Swedish reference of normative values for similarly aged men concerning everyday smokers, height, FEV1/FVC and civil status. BMI-values, educational level and proportion of former smokers were higher than the reference values.

Overall, the internal data completeness in the follow up was high, with most instruments having 95% completion or more (table 3). Men participating in Wave 2 had an overall better health, healthier lifestyle, and higher education at baseline than those who did not participate in the follow up (table 2). Wave 2 participants had a lower proportion of current smokers, and a lower average number of pack-years. Those providing data for Wave 2, had fewer co-morbidities than those who did not, but who were still alive, other than hypertension which was equally prevalent.

Table 2. Baseline characteristics

Variable	All participants Overall (n = 1302)	Non-missing observations Overall (%)	Participated in follow up (n = 907)	Did not participate in follow (n = 395)	Reference for Swedish 65-year-old men
	Self-reported data				
Married	863 (71%)	1210 (93%)	621 (73%)	242 (66%)	61%
Smoking status		1302 (100%)			
Current smoker	168 (13%)		91 (10%)	77 (19%)	13%
Former smoker	707 (54%)		514 (57%)	193 (49%)	36%
Never smoker	427 (33%)		302 (33%)	125 (32%)	51%
Pack-years of smoking	15.1±19.2	1276 (98%)	13.7±17.4	18.4±22.6	
University/college or professional school education	520 (42%)	1218 (93%)	381 (44%)	139 (38%)	25%
Hypertension	725 (56%)	1294 (99%)	507 (56%)	218 (55%)	
Diabetes	132 (10%)	1295(99)	79 (9%)	53 (13%)	
Asthma	71 (5%)	1285(99%)	47 (5%)	24 (6%)	9%*
COPD	29 (2%)	1205 (92%)	13 (1%)	16 (4%)	
	Measured data by staff				
Height	179±6.3	1285 (99%)	179±6.1	179±7	178
Body mass index (kg/m2)	28.2±4.1	1275 (98%)	28.1±4.0	28.5±4.4	26*
Underweight, BMI <18.5	1 (0.1%)		1 (0.1%)	0 (0%)	0.6%*
Normal weight, BMI 18.5–24.9	260 (20%)		184 (21%)	76 (20%)	39%*
Overweight, BMI 25–29.9	661 (52%)		470 (53%)	191 (50%)	46%*
Obesity, BMI >=30	352 (28%)		234 (26%)	118 (31%)	14%*
FEV_1, % of predicted	87.2±15.1	1278 (98%)	88.5±14.7	84.3±15.8	

VC, % of predicted	85.4±13.1	1278 (98%)	86.3±13.0	83.4± 13.1	
FEV_1 / FVC < 0.7	242 (19%)	1295 (99%)	157 (17%)	85 (22%)	18.2%**

Data are presented as mean±SD or frequency (rounded percentage). Normative values were collected from the public available databases of The Public Health Agency of Sweden (www.folkhalsomyndigheten.se), and Statistics Sweden (www.scb.se). The following variables are collected but not included in the table: **Self-reported:** *exercise habits, alcohol consumption, tiredness, blood pressure medication, myocardial infarction, stroke, tia, angina pectoris, apnoea, snoring, osteoporosis, fractures, back pain, femur, radius, glaucoma, cataract, intermittent claudication.* ***Measured by staff****:* blood pressure, pulse, weight, waist, swab measure, number of teeth, *aortic diameter*. **Blood sample:** *Hb, HbA1C (% and later mmol), P-cystatin C, p-glucose, PT-GFR(CC estimate), S-CA, S-Na, S-K, S-creatinine, S-total cholesterol, ApoA1, ApoB.*

**Reference based on available self-reported data for men 65 years or older*

***Reference based on available data for men 40 years or older[22]*

Table 3. Follow up survey data collected

Measurements and analyses	**Description**	**Non-missing observations, %**
Modified Medical Research Council (mMRC) breathlessness scale [23]	Functional impact of breathlessness (yes or no at each item)	97
mMRC-scale	Intensity of functional impact of breathlessness (0-10 at each item)	97
Dyspnoea-12 (D-12)[24]	Multidimensional breathlessness	95
Multidimensional Dyspnea Profile (MDP) total[20]	Multidimensional breathlessness	77
MDP A1 unpleasantness	Breathing unpleasantness	91
MDP perception score	MDP A1 and five perception descriptors	79
MDP emotional response score	Five emotional descriptors	89
Short form 12 item (version 2) Health survey[14]	Quality of life	98
Edmonton Symptom Assessment System. Revised (ESAS-r) [25]	Associated symptoms	98
FACIT-Fatigue[26]	Pathological tiredness	98

Hospital Anxiety and Depression Scale (HADS)[27]	Anxiety and depression	94
World Health Organization Performance Status 0-4[28]	Performance Status	97
Custom items		
Global impression of change (GIC)[29] in breathlessness since baseline	7 categories from *very much better* to *very much worse*	99
Global impression of change (GIC)[29] in health since baseline	7 categories from *very much better* to *very much worse*	98
Activities given up because of breathlessness	What activities have the participant giving up doe to breathlessness	91
Breathlessness unpleasantness	Likert scale, 4 categories from *mild* to *severe*.	93
Breathlessness duration	How many years the participant have experience breathlessness.	89
Proportion of awake time experiencing breathlessness	5 categories from none to whole time awake	91
Experiences temporary worsening breathlessness (how often, how long, when, causative factors).	4-6 categories at each question	94
Self-reported treatments of breathlessness	8 different possible treatments for breathlessness, and free text	89
Smoking status	4 categories (*everyday*, *sometimes*, *former*, and *never smoker*)	98
Smoking frequency	Years of smoking, and number of cigarettes per day	92
Alcohol use	Amount of wine, beer, and strong spirit a week	84
Quality and duration of sleep	Quality: 5 categories. Duration: 7 categories.	99
Physical activity frequency	4 categories, from daily to never	99
Physical activity intensity	4 categories, from sedentary to intensity	97
Self-reported conditions	19 different possible diseases and conditions	95
Self-reported height and weight now	cm and kg	99
Recall of height and weight at the age of 20	cm and kg	92

Statistical methodology

A detailed statistical analysis plan will be prepared before each analysis. Relevant characteristics for each studies objective will be tabulated and compared using standard descriptive methods. Associations will be evaluated using regression models including logistic regression for categorical outcomes, and linear regression for continuous outcomes. Kaplan-Meier, Cox proportional hazards regression and Fine-Grey regression (accounting for competing events) will be used for time-to-event analyses.

Sample size/Power

The participants in the first follow up of the VASCOL study (Wave 2) covers 45 % of the population of men in the age group (n = 2013) in Blekinge in 2019. Statistical power will be specified for each analysis.

STRENGTHS AND LIMITATIONS

Strengths of the VASCOL study includes that it covers a large proportion of the eligible men in Blekinge. Over half (1302/2300) of all 65-year-old men in Blekinge county participated in the VASCOL baseline. The quality of the data was good, with a high data completeness. The cohort is similar to men aged 65 in Sweden as a whole, which gives confidence regarding generalisability for men, although inherently not so for women or younger men. A limitation is the fact that nearly one-quarters (30%) of the participants did not participate in the follow up (Wave 2). However, all participants in VASCOL baseline can be followed through the national registries, which can give some insight about the participants who did not participate in the follow up (Wave 2). Participants in the follow up study (Wave 2) was overall healthier at baseline than those not participating which might be explained by lower motivation to

participate in studies among those with poorer health or that less healthy participants have deceased between the baseline and follow up study.

The VASCOL study is to our knowledge, the most detailed prospective population-based study of breathlessness and other symptoms of cardiorespiratory diseases linked to registries with key information regarding health service utilisation and survival. Also, there are, to our knowledge, few population studies of older men's symptoms and quality of life. The VASCOL data are rich and consists of physiological measurements, blood samples, and extensive survey data which makes it possible to study many aspects of different symptoms and conditions. Sweden has a rich set of health-related registry data that can be cross-linked with the VASCOL data, and the variables collected in the VASCOL study can be studied as risk factors for outcomes such as morbidity, hospitalization, and mortality. The set of variables of the VASCOL data also enables studies of different conditions long term effect on breathlessness and other symptoms. The symptom data mostly consist of validated instruments, which enables comparison with other studies.

A limitation of the collected data is that former workplaces was not recorded, and pollution from dusty workplaces could possibly be a confounder of breathlessness. We therefore plan to include questions about former workplaces in future follow ups. Breathlessness was not assessed at baseline so the *Global impression of change (GIC) of breathlessness* was used in Wave 2. This introduces the risk of recall bias in studies of changed breathlessness between Waves 1 and 2, and an inherently unknown baseline measurement error, but nevertheless is accepted as a valid approach. Further, for future VASCOL waves, the repeated self-report breathlessness measures will enable longitudinal examination from Wave 2.

Cardiorespiratory diseases, as well as breathlessness are common in the older population,[3,9] and we believe that the VASCOL study can add valuable knowledge of the symptoms in the

population. We will add knowledge regarding which symptoms predict worse clinical outcomes to identify people with a higher risk of mortality and morbidity, and as a potential therapeutic target.

COLLABORATION

We welcome researchers from different disciplines and fields for collaboration over the collected data from the VASCOL study, including suggested additional data collection. Interested researchers should submit a study proposal to the corresponding author. All study proposals will be reviewed by the VASCOL research group. All additional objectives not included in this paper must also be approved by the Sweden's national ethical review board.

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FURTHER DETAILS

Author Contributions: Conception and design: ME; Data collection: MO, ME; Analysis: MO, ME; Interpretation: All authors; First draft: MO, ME; Revisions and acceptance of the version to publish: All authors.

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Competing Interests Statement: None declared

Ethics approval: The baseline study was approved by the regional ethical review board at Lund University (reference number: 2008/676). The first follow up study and the registry data cross linkage was approved by the national ethical review board (reference number: 2019-00134).

Data sharing statement: The VASCOL research group will consider requests for using de-identified data from the VASCOL study by external collaborators. Also, all requests must be approved by the Sweden's national ethical review board.

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FIGURE LEGENDS

Figure 1- Location of Blekinge in Sweden, Blekinge's municipalities and main cities.

Figure 2 - Flow chart of the recruitment for the VASCOL study

Figure 1 - Location of Blekinge in Sweden, Blekinge's municipalities and main cities.

57x46mm (300 x 300 DPI)

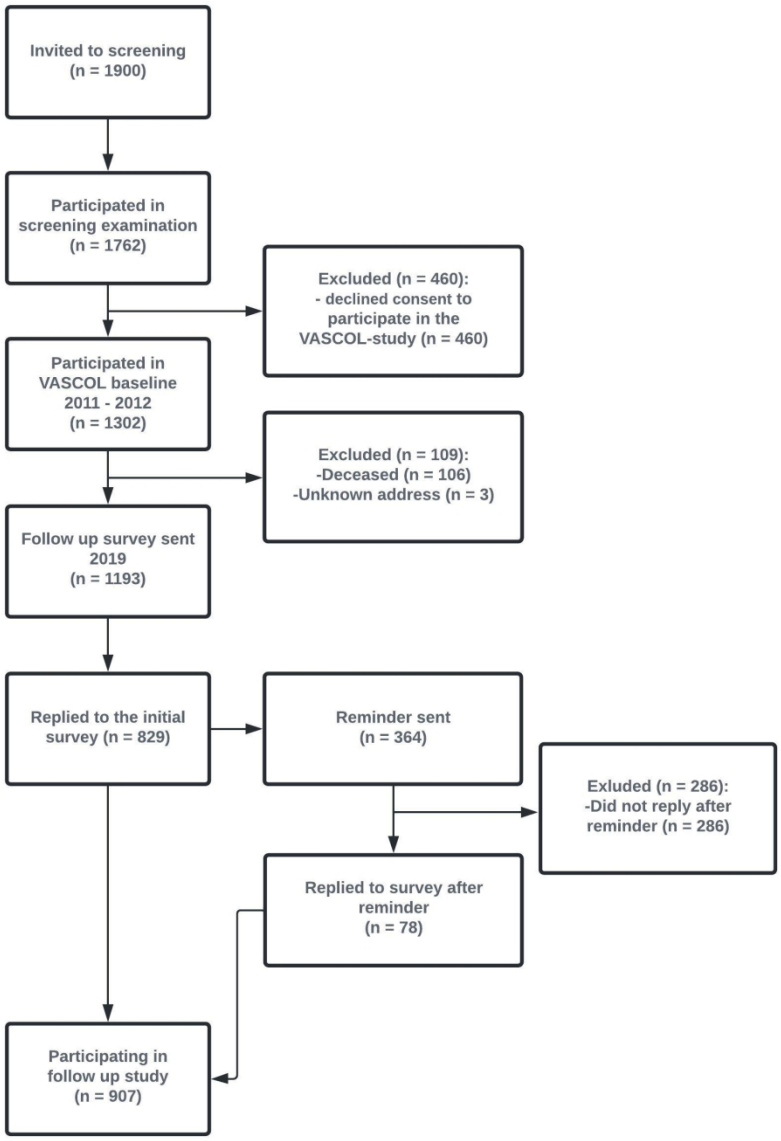

Figure 2 - Flow chart of the recruitment for the VASCOL study

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BMJ Open

Cohort profile: VAScular and Chronic Obstructive Lung disease (VASCOL) - a longitudinal study on morbidity, symptoms, and quality of life among older men in Blekinge County, Sweden

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Running title: Morbidity, symptoms, and quality of life among older men

Cohort profile: VAScular and Chronic Obstructive Lung disease (VASCOL) - a longitudinal study on morbidity, symptoms, and quality of life among older men in Blekinge County, Sweden.

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ABSTRACT

Purpose: Despite data showing breathlessness to be more prevalent in older adults, we have little detail about the severity or multi-dimensional characteristics of breathlessness and other self-reported measures (such as quality of life and other cardiorespiratory-related symptoms) in this group at the population level. We also know little about the relationship between multi-dimensional breathlessness, other symptoms, co-morbidities and future clinical outcomes such as quality of life, hospitalization, and mortality. This paper reports the design and descriptive findings from the first two waves of a longitudinal prospective cohort study in older adults.

Participants: Between 2010-2011, 1900 men in a region in southern Sweden aged 65 years, were invited to attend for VASCOL baseline (Wave 1) assessments which included physiological measurements, blood sampling, and a self-report survey of lifestyle and previous medical conditions. In 2019, follow up postal survey data (Wave 2) were collected with additional self-report measures for breathlessness, other symptoms, and quality of life. At each wave, data are cross-linked with nationwide Swedish registry data of diseases, treatment, hospitalization, and cause of death.

Findings to date: 1302/1900 (68%) of invited men participated in Wave 1, which include 56% of all 65 years old men in the region. 5% reported asthma, 2% chronic obstructive pulmonary disease, 56% hypertension, 10% diabetes, and 19% had airflow limitation. The VASCOL cohort had comparable characteristics to those of similarly aged men in Sweden. By 2019, 109/1302 (8.4%) had died. 907/1193 (76%) of the remainder participated in Wave 2. Internal data completeness of 95% or more was achieved for most Wave 2 measures.

Future plans: A third wave will be conducted within four years, and the cohort will be followed through repeated follow ups planned every fourth year, as well as national registry data of diagnosis, treatments, and cause of death.

Keywords: *Older adults, breathlessness, symptoms, respiratory diseases, cardiovascular diseases, epidemiology.*

STRENGTHS AND LIMITATIONS OF THIS STUDY

- More than half (57%) of all 65 years old men in Blekinge participated in the VASCOL baseline, of which approximately 70 % also participated in the follow up.

- The VASCOL baseline, Wave 1, (n = 1302) collected a wide range of data: physiological measurements, blood samples, survey of lifestyle and self-reported conditions.
- The VASCOL follow up study, Wave 2, (n = 907) included an extensive set of validated self-report instruments of symptoms of cardiorespiratory diseases.
- Cross-linkage of data with national registries allowed prospective study of morbidity, hospitalization, and mortality in this cohort.

INTRODUCTION

Cardiorespiratory diseases, such as ischemic heart disease, heart failure and chronic obstructive pulmonary disease (COPD) are major causes of morbidity and mortality worldwide.[1,2] They often coexist with, and are worsened by, other conditions leading to poorer outcomes. Multimorbidity increases over the age of 65 years, particularly those with cardiorespiratory diseases.[3,4,5]

Cardiorespiratory diseases are associated with major adverse health effects including anxiety and depression, poorer quality of sleep and impaired physical capacity.[6 7] Symptoms of cardiorespiratory diseases includes chest pain, nausea, and fatigue, with the major 'cardinal' symptom being *chronic breathlessness*.[8] Breathlessness is also highly prevalent across the older population,[9] and the risk of developing breathlessness affecting daily life increases markedly with age.[10] People who are breathless often avoid physical activities,[11] many becoming socially isolated.[8,12] In COPD, breathlessness is a stronger predictor of mortality than the level of airflow limitation.[13] Breathlessness is also associated with impaired quality of life (QoL), worse physical capacity and higher overall mortality in people with different underlying conditions.[7,14,8]

Few population-level studies have focused on breathlessness and its relationship with other self-reported outcomes. The BOLD,[15] PLATINO,[16] and ECRHS,[17] studies assessed breathlessness mainly using the unidimensional modified Medical Research Council (mMRC)

scale, which thus only assesses the level of exertion required to induce breathlessness, and not the severity of the symptom *per se.*[12] Breathlessness is a multi-dimensional symptom affecting all domains of a person's life[18] and the intensity of both physical and affective dimensions needs to be included in measurements.[7],[18] For multi-dimensional assessment of breathlessness, the instruments Dyspnoea-12 (D12)[19] and Multidimensional Dyspnea Profile[20] (MDP) can be used. Recently, the minimal clinically important difference (MCID) was determined for both D12 and MDP in cardiorespiratory disease.[21]

Some breathlessness data from older adults at the general population level regarding prevalence and clinical outcomes are published, but details including characteristics, and severity are relatively few. We also know little about other common symptoms and co-morbidities affect clinical outcomes such as QoL, health service utilisation and survival in older adults. To date, no study has assessed the relationship between multi-dimensional breathlessness and clinical outcomes in older adults in the general population.

The VAScular and Chronic Obstructive Lung disease study (VASCOL) is an epidemiological, longitudinal, cohort study to describe the relationship between vascular diseases and COPD. Since its beginning in 2010, the scope has broaden to also focus on QoL, self-reported measures of breathlessness and other symptoms of cardiovascular diseases.

In this paper we present the VASCOL study design, including future longitudinal data collection, describe the characteristics of participants from the first two waves, (Wave 1- baseline; Wave 2 - first follow up).

Study objectives

The overall objective of the VASCOL study is to evaluate the relationship between life-style variables, morbidity due to cardiorespiratory disease, multi-dimensional breathlessness, other

symptoms of cardiovascular diseases, and QoL in a population sample of men aged 65 years on cohort entry. We aim to evaluate:

- How baseline factors (diseases, lung function, lifestyle, demographics) predict the outcomes of breathlessness, QoL, diagnosed diseases, hospitalization, and mortality.
- The prevalence, characteristics, and severity of multi-dimensional breathlessness and other symptoms such as anxiety, depression, pain, nausea, and fatigue.
- The relationship between self-reported QoL and symptom burden and functional limitations.
- Contributing causes of breathlessness and other symptoms such as anxiety, depression, pain, nausea, and fatigue.
- How the presence and type of symptoms predicts future diseases.

COHORT DECRIPTION

The VASCOL study is an ongoing longitudinal epidemiological cohort study in Blekinge, Sweden. Blekinge is a county located in southern Sweden and has a total population of around 160,000, of which approximately 2300 were 65-years old men in 2010-2011. Blekinge geographically covers both urban and rural areas with good public transportations, see Figure 1.

In 2010-2011, 1900 men aged 65 years in Blekinge were invited to a screening campaign of abdominal aortic aneurysm (AAA) at a health centre in the city of Karlshamn.

The men were informed about the VASCOL study and invited to give their informed written consent to participate in the Wave 1 examinations. A self-report survey (demography, lifestyle, and previous diseases) was included with the invitation pack. Blekinge´s biggest municipality, Karlskrona, was not included in the screening campaign until 2011, resulting in approximately

80 % (1900/2300) of all 65-years-old men living in Blekinge 2010 - 2011 were invited to participate in the VASCOL study. The inclusion criteria were: men, 65-years old, living in Blekinge (excluding Karlskrona in 2010), participating in the screening examinations, and willing to give a written consent to participate in the Wave 1 examinations. There were no exclusion criteria based on any conditions. In 2019 a follow up postal survey was sent out to the participants still alive and with a known address (Wave 2).

Wave 1: baseline data collection

At baseline, a clinical visit was performed, and data from the self-report survey collected. Nurses checked for survey data completeness, and those who omitted to bring their survey were also able to complete this during the visit. Physiological measurements and blood sampling were collected according to standard protocols by registered nurses. The blood samples were stored in a biobank for future analysis. Out of the 1900 men attending the screening, 1302 (68.5%) participated in the VASCOL baseline study. Normative values for Swedish men in the same age group were also collected from The Public Health Agency of Sweden, National Board of Health and Welfare, and Statistics Sweden.

Wave 2: Follow up survey

In 2019, the Blekinge county demographic registers were used to identify all participants who were alive with a known address (n = 1193). A new survey was sent out to all these participants. At Wave 2, 829 of the men replied to the initial survey within two weeks, and additional 78 men replied after a reminder, leading to 907/1193 (76%) of men participated in Wave 2. See Figure 2 for detailed information about data collection procedure. The postal survey consisted of questions and validated instruments regarding breathing, other cardiorespiratory-related symptoms, QoL, lifestyle, new medical conditions, and any treatments for breathlessness. Most questions and instruments pertained to the experiences during the last two weeks.

Planned data collection

Repeated waves will be conducted at four yearly intervals, to enable examination of the change in participants' breathlessness, other symptoms and QoL. Wave 3 data collection will be conducted within four years, and the procedure and survey instruments will be similar to the first two waves. To broaden the VASCOL study and reach a bigger sample size, future data collections should also invite women to participate. Collected data will be cross-linked with nationwide Swedish registry data: Cause of Death Registry, Swedish Prescribed Drug Registry, and National Patient Registry (see table 1). The Swedish registry databases have high coverage and completeness, but are limited in that they are not including any (or very limited) physiologic variables and no symptoms or other patient reported outcomes. The VACSCOL study and the registry databases will therefore complete each other.

Table 1. Planned cross linkage with national registries

Data	**Source**	**Timeframe of the data**
Inpatient care including diagnoses, date for diagnoses, treatment, date for treatment, and treatment time.	Swedish National Patient Registry for In-patient Care	1987 - today
Outpatient care, diagnosis, date for diagnosis, treatment, date for treatment, and treatment time.	Swedish National Patient Registry for Out-patient Care	2001 - today
Place, date, and cause(s) of death	Causes of Death Registry	Baseline - today
Dispensed prescribed medications	Swedish Prescribed Drug Registry	July 2005 - today

Patient and Public Involvement

The follow up survey was piloted on ten people of similar age to the VASKOL study participants before the final survey was revised and administered. The pilot participants had the opportunity to add areas of research that they thought were relevant. Pilot participants also gave feedback on the layout and length of the survey as well as how the questions were asked. Minor linguistically and layout changes were done to the survey questions to fit the specific study participants.

FINDINGS TO DATE

Baseline characteristics of the VASCOL study are shown in Table 2. The majority of the participants had hypertension (56%), and approximately one fifth had airflow limitation (first second of forced expiration (FEV1) / forced vital capacity (FVC) < 0.7). Only a small proportion had self-reported asthma (5%) or COPD (2%). One tenth (10%) reported diabetes. Also, approximately one tenth of the participants (13%) were everyday smokers, and the majority (54%) were former smokers. Around half of the participants were overweight (52%) and around one third (28%) obese. Participants in the VASCOL cohort had proportions similar to Swedish reference of normative values for similarly aged men concerning everyday smokers, height, FEV1/FVC and civil status. BMI-values, educational level and proportion of former smokers were higher than the reference values.

Overall, the internal data completeness in the follow up was high, with most instruments having 95% completion or more (table 3). Men participating in Wave 2 had an overall better health, healthier lifestyle, and higher education at baseline than those who did not participate in the follow up (table 2). Wave 2 participants had a lower proportion of current smokers, and a lower average number of pack-years. Those providing data for Wave 2, had fewer co-morbidities than those who did not, but who were still alive, other than hypertension which was equally prevalent.

Variable	All participants Overall (n = 1302)	Non-missing observations Overall (%)	Participated in follow up (n = 907)	Did not participate in follow (n = 395)	Reference for Swedish 65-year-old men
	Self-reported data				
Married	863 (71%)	1210 (93%)	621 (73%)	242 (66%)	61%
Smoking status		1302 (100%)			
Current smoker	168 (13%)		91 (10%)	77 (19%)	13%
Former smoker	707 (54%)		514 (57%)	193 (49%)	36%
Never smoker	427 (33%)		302 (33%)	125 (32%)	51%
Pack-years of smoking	15.1±19.2	1276 (98%)	13.7±17.4	18.4±22.6	
University/college or professional school education	520 (42%)	1218 (93%)	381 (44%)	139 (38%)	25%
Hypertension	725 (56%)	1294 (99%)	507 (56%)	218 (55%)	
Diabetes	132 (10%)	1295(99)	79 (9%)	53 (13%)	
Asthma	71 (5%)	1285(99%)	47 (5%)	24 (6%)	9%*
COPD	29 (2%)	1205 (92%)	13 (1%)	16 (4%)	
	Measured data by staff				
Height	179±6.3	1285 (99%)	179±6.1	179±7	178
Body mass index (kg/m2)	28.2±4.1	1275 (98%)	28.1±4.0	28.5±4.4	26*
Underweight, BMI <18.5	1 (0.1%)		1 (0.1%)	0 (0%)	0.6%*
Normal weight, BMI 18.5–24.9	260 (20%)		184 (21%)	76 (20%)	39%*
Overweight, BMI 25–29.9	661 (52%)		470 (53%)	191 (50%)	46%*
Obesity, BMI >=30	352 (28%)		234 (26%)	118 (31%)	14%*

Table 2. Baseline characteristics

FEV_1, % of predicted	87.2±15.1	1278 (98%)	88.5±14.7	84.3±15.8	
VC, % of predicted	85.4±13.1	1278 (98%)	86.3±13.0	83.4± 13.1	
FEV_1 / FVC < 0.7	242 (19%)	1295 (99%)	157 (17%)	85 (22%)	18.2%**

Data are presented as mean±SD or frequency (rounded percentage). Normative values were collected from the public available databases of The Public Health Agency of Sweden (www.folkhalsomyndigheten.se), and Statistics Sweden (www.scb.se). The following variables are collected but not included in the table: **Self-reported:** *exercise habits, alcohol consumption, tiredness, blood pressure medication, myocardial infarction, stroke, tia, angina pectoris, apnoea, snoring, osteoporosis, fractures, back pain, femur, radius, glaucoma, cataract, intermittent claudication.* ***Measured by staff****:* blood pressure, pulse, weight, waist, swab measure, number of teeth, *aortic diameter*. **Blood sample:** *Hb, HbA1C (% and later mmol), P-cystatin C, p-glucose, PT-GFR(CC estimate), S-CA, S-Na, S-K, S-creatinine, S-total cholesterol, ApoA1, ApoB.*

**Reference based on available self-reported data for men 65 years or older*

***Reference based on available data for men 40 years or older*[22]

Table 3. Follow up survey data collected

Measurements and analyses	**Description**	**Non-missing observations, %**
Modified Medical Research Council (mMRC) breathlessness scale [23]	Functional impact of breathlessness (yes or no at each item)	97
mMRC-scale	Intensity of functional impact of breathlessness (0-10 at each item)	97
Dyspnoea-12 (D-12)[24]	Multidimensional breathlessness	95
Multidimensional Dyspnea Profile (MDP) total[20]	Multidimensional breathlessness	77
MDP A1 unpleasantness	Breathing unpleasantness	91
MDP perception score	MDP A1 and five perception descriptors	79
MDP emotional response score	Five emotional descriptors	89
Short form 12 item (version 2) Health survey[14]	Quality of life	98
Edmonton Symptom Assessment System. Revised (ESAS-r) [25]	Associated symptoms	98

FACIT-Fatigue[26]	Pathological tiredness	98
Hospital Anxiety and Depression Scale (HADS)[27]	Anxiety and depression	94
World Health Organization Performance Status 0-4[28]	Performance Status	97
Custom items		
Global impression of change (GIC)[29] in breathlessness since baseline	7 categories from *very much better* to *very much worse*	99
Global impression of change (GIC)[29] in health since baseline	7 categories from *very much better* to *very much worse*	98
Activities given up because of breathlessness	What activities have the participant giving up doe to breathlessness	91
Breathlessness unpleasantness	Likert scale, 4 categories from *mild* to *severe*.	93
Breathlessness duration	How many years the participant have experience breathlessness.	89
Proportion of awake time experiencing breathlessness	5 categories from none to whole time awake	91
Experiences temporary worsening breathlessness (how often, how long, when, causative factors).	4-6 categories at each question	94
Self-reported treatments of breathlessness	8 different possible treatments for breathlessness, and free text	89
Smoking status	4 categories (*everyday*, *sometimes*, *former*, and *never smoker*)	98
Smoking frequency	Years of smoking, and number of cigarettes per day	92
Alcohol use	Amount of wine, beer, and strong spirit a week	84
Quality and duration of sleep	Quality: 5 categories. Duration: 7 categories.	99
Physical activity frequency	4 categories, from daily to never	99
Physical activity intensity	4 categories, from sedentary to intensity	97
Self-reported conditions	19 different possible diseases and conditions	95
Self-reported height and weight now	cm and kg	99

Recall of height and weight at the age of 20	cm and kg	92

Statistical methodology

A detailed statistical analysis plan will be prepared before each analysis. Relevant characteristics for each studies objective will be tabulated and compared using standard descriptive methods. Associations will be evaluated using regression models including logistic regression for categorical outcomes, and linear regression for continuous outcomes. Kaplan-Meier, Cox proportional hazards regression and Fine-Grey regression (accounting for competing events) will be used for time-to-event analyses.

Sample size/Power

The participants in the first follow up of the VASCOL study (Wave 2) covers 45 % of the population of men in the age group (n = 2013) in Blekinge in 2019. Statistical power will be specified for each analysis.

STRENGTHS AND LIMITATIONS

Strengths of the VASCOL study includes that it covers a large proportion of the eligible men in Blekinge. Over half (1302/2300) of all 65-year-old men in Blekinge county participated in the VASCOL baseline. The quality of the data was good, with a high data completeness. The cohort is similar to men aged 65 in Sweden as a whole, which gives confidence regarding generalisability for men. However, a limitation is that we cannot generalise for women or younger men and future data collections should therefore include these groups. A limitation is the fact that nearly one-quarters (30%) of the participants did not participate in the follow up (Wave 2). However, all participants in VASCOL baseline can be followed through the national registries, which can give some insight about the participants who did not participate in the

follow up (Wave 2). Participants in the follow up study (Wave 2) was overall healthier at baseline than those not participating which might be explained by lower motivation to participate in studies among those with poorer health or that less healthy participants have deceased between the baseline and follow up study.

The VASCOL study is to our knowledge, the most detailed prospective population-based study of breathlessness and other symptoms of cardiorespiratory diseases linked to registries with key information regarding health service utilisation and survival. Also, there are, to our knowledge, few population studies of older men's symptoms and quality of life. The VASCOL data are rich and consists of physiological measurements, blood samples, and extensive survey data which makes it possible to study many aspects of different symptoms and conditions. Sweden has a rich set of health-related registry data that can be cross-linked with the VASCOL data, and the variables collected in the VASCOL study can be studied as risk factors for outcomes such as morbidity, hospitalization, and mortality. The set of variables of the VASCOL data also enables studies of different conditions long term effect on breathlessness and other symptoms. The symptom data mostly consist of validated instruments, which enables comparison with other studies.

A limitation of the collected data is that former workplaces was not recorded, and pollution from dusty workplaces could possibly be a confounder of breathlessness. Also, cough was not measured, which is a common symptom of COPD. We therefore plan to include questions about former workplaces and cough in future follow ups. Breathlessness was not assessed at baseline so the *Global impression of change (GIC) of breathlessness* was used in Wave 2. This introduces the risk of recall bias in studies of changed breathlessness between Waves 1 and 2, and an inherently unknown baseline measurement error, but nevertheless is accepted as a valid approach. Further, for future VASCOL waves, the repeated self-report breathlessness measures will enable longitudinal examination from Wave 2.

Cardiorespiratory diseases, as well as breathlessness are common in the older population,[3],[9] and we believe that the VASCOL study can add valuable knowledge of the symptoms in the population. We will add knowledge regarding which symptoms predict worse clinical outcomes to identify people with a higher risk of mortality and morbidity, and as a potential therapeutic target.

COLLABORATION

We welcome researchers from different disciplines and fields for collaboration over the collected data from the VASCOL study, including suggested additional data collection. Interested researchers should submit a study proposal to the corresponding author. All study proposals will be reviewed by the VASCOL research group. All additional objectives not included in this paper must also be approved by the Sweden's national ethical review board.

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FURTHER DETAILS

Contributors: ME was responsible for the conceptualisation of the wave 2 study and will take the role as principal investigator. Kerstin Ström was responsible for the wave 1 data collection. ME and MO conducted wave 2 data collection and will collect the data for wave 3 as well as cross-linking data with national registries. MO, ME wrote the first draft of this cohort profile. GE, DC, MJ, and JS contributed with their research experience and medical knowledge in

interpretation of the findings, review, and revision of the manuscript draft. All authors approved the final version.

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Competing Interests Statement: None declared

Ethics approval: The baseline study was approved by the regional ethical review board at Lund University (reference number: 2008/676). The first follow up study and the registry data cross linkage was approved by the national ethical review board (reference number: 2019-00134).

Data sharing statement: The VASCOL research group will consider requests for using de-identified data from the VASCOL study by external collaborators. Also, all requests must be approved by the Sweden's national ethical review board.

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FIGURE LEGENDS

Figure 1- Location of Blekinge in Sweden, Blekinge's municipalities and main cities.

Figure 2 - Flow chart of the recruitment for the VASCOL study

Figure 1 - Location of Blekinge in Sweden, Blekinge's municipalities and main cities.

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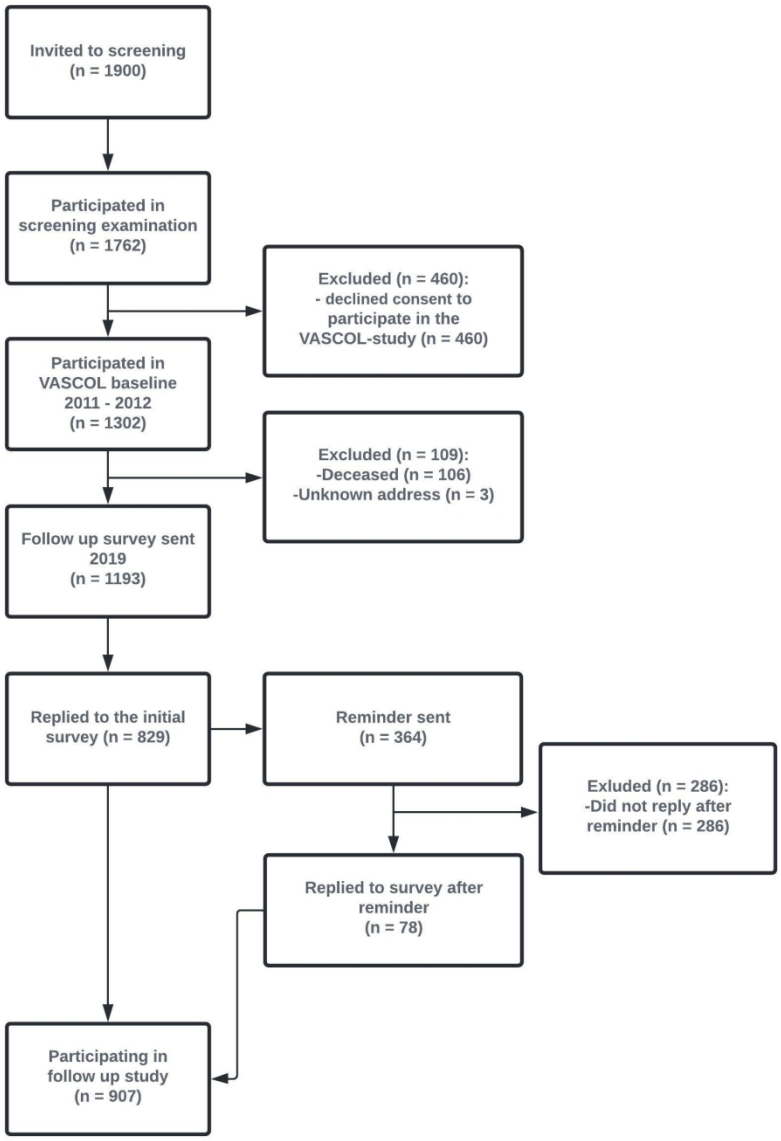

Figure 2 - Flow chart of the recruitment for the VASCOL study

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